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**Appendix II:
Individual Review of In-vitro Studies**

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STUDY 030508A– INDUCTION POTENTIAL OF CYTOCHROME P450 1A2, CYTOCHROME P450 2C9 AND CYTOCHROME P450 3A4 BY THE TEST ARTICLE CLEVIDIPINE (H324/38) IN PRIMARY CULTURED HUMAN HEPATOCYTES.

PRINCIPAL INVESTIGATOR: _____

SITE: _____

REPORT # 030508A

EDR MODULE 4

STUDY DATE: October 30, 2003 – April 21, 2004

OBJECTIVE:

The purpose of this study was to determine the induction potential of clevidipine (H324/38) in freshly plated human hepatocytes. Induction was measured by the catalytic activity assay selective for various cytochrome P450 (CYP) isoforms.

STUDY DESIGN:

Hepatocytes were exposed to clevidipine (H324/38) for a total of 3 days. Freshly isolated hepatocytes were plated in collagen I-coated 24-well plates. Samples for P450 induction were analyzed by measuring the P450 specific probe substrate catalytic activity using HPLC analysis with absorbance detection.

Hepatocytes from a total of five donor livers (three female and two male) were tested in the study. Each isoform of P450 was tested with three donors.

The use of solvent vehicle control and/or blanks, as well as triplicate samples, provided a control for bias.

Final clevidipine concentrations were 1, 10, and 100 μ M. the substrates, final substrate concentration, the enzyme tested, and the reaction catalyzed are shown below.

Table 1. Marker enzyme assay parameters

Probe substrate	P450 isoform	Reaction	Assay concentration
Testosterone	CYP3A4	6 β -Hydroxylase	200 μ M
Phenacetin	CYP1A2	O-Deethylase	100 μ M
Diclofenac	CYP2C9	4'-Hydroxylase	100 μ M

The cells were incubated with substrate at 37°C for various times (e.g. 30 min for testosterone, 60 min for phenacetin and diclofenac). The reaction was stopped by removing the sample medium and combining an aliquot (175 μ l for CYP1A2 and 300 μ l for CYP2C9 and 3A4) with stop solution organic solvent and/or acid as shown below.

Table 2. Stop solution and volumes

P450 Substrate	Stop Solution	Volume Stop Solution/ml Incubation Volume
Testosterone	100% Acetonitrile	500 μ l
Phenacetin	70% Perchloric Acid	125 μ l
Diclofenac	6% Acetic Acid/94% Acetonitrile	300 μ l

Positive control inducers for hepatocyte P450 enzymes, the concentration and the solvent used for delivery are shown in Table 3. These were tested in triplicate under the same conditions as used above.

Table 3. Positive control inducer chemicals

Enzyme	Positive control inducer	Final concentration	Solvent for delivery
CYP1A2	β -Naphthoflavone	20 μ M	DMSO
CYP2C9	Rifampicin	20 μ M	DMSO
CYP3A4	Rifampicin	20 μ M	DMSO

RESULTS:

Inhibitory effect of clevidipine at 100 μ M on CYP 1A2, 2C9, and 3A4 activity in hepatocytes from three donors' hepatocytes is shown below:

Donors	CYP 1A2 Inhibition (%)	CYP 2C9 Inhibition (%)	CYP 3A4 Inhibition (%)
*1	24	82	0.4
2	3.6	0.57	13
3	-4.8	3.0	12

Donor 1 refers to HM018 for CYP1A2 and 2C9 and HH136 for CYP3A4;

Donor 2 refers to HH137 for CYP1A2 and 2C9 and HM017 for CYP3A4;

Donor 3 refers to HH138 for CYP1A2 and 2C9 and HH137 for CYP3A4.

Summary of effect of clevidipine and positive control β -naphthoflavone (BNF) on CYP1A2-catalyzed phenacetin O-deethylase activity and protein content in hepatocytes of 3 donors' hepatocytes – means of 3 donors (HM018, HH137, and HH138)

Treatment	Activity (μ mol/mg/min)	Fold induction	Protein (mg/well)
0 μ M (DMSO vehicle)	4.7 \pm 2.5	-	0.314 \pm 0.095
1 μ M clevidipine	5.2 \pm 2.1	1.2 \pm 0.23	0.300 \pm 0.088
10 μ M clevidipine	4.4 \pm 3.1	0.86 \pm 0.18	0.337 \pm 0.129
100 μ M clevidipine	4.1 \pm 2.6	0.82 \pm 0.23	0.325 \pm 0.094
20 μ M RIF	135 \pm 37	39 \pm 30	0.311 \pm 0.096

Data are the mean \pm standard deviation from three donors in each group.

Summary of effect of clevidipine and positive control rifampicin (RIF) on CYP2C9-catalyzed diclofenac 4'-hydroxylase and protein content in hepatocytes of 3 donors' hepatocytes – means of 3 donors (HM018, HH137, and HH138)

Treatment	Activity (pmol/mg/min)	Fold induction	Protein (mg/well)
0 μ M (DMSO vehicle)	32 \pm 16	-	0.314 \pm 0.067
1 μ M clevidipine	56 \pm 39*	2.0 \pm 1.9	0.296 \pm 0.067
10 μ M clevidipine	18 \pm 10	0.57 \pm 0.12	0.296 \pm 0.067
100 μ M clevidipine	23 \pm 15	0.67 \pm 0.23	0.302 \pm 0.078
20 μ M RIF	177 \pm 90	5.4 \pm 0.21	0.319 \pm 0.093

Data are the mean \pm standard deviation from three donors in each group. * Significantly different from controls ($p \leq 0.05$)

Summary of effect of clevidipine and positive control rifampicin (RIF) on CYP3A4-catalyzed testosterone 6 β -hydroxylase and protein content in hepatocytes of 3 donors' hepatocytes – means of 3 donors (HH136, HM017, and HH137)

Treatment	Activity (pmol/mg/min)	Fold induction	Protein (mg/well)
0 μ M (DMSO vehicle)	36 \pm 46	-	0.375 \pm 0.052
1 μ M clevidipine	33 \pm 41	0.95 \pm 0.10	0.372 \pm 0.046
10 μ M clevidipine	42 \pm 52*	1.2 \pm 0.07	0.380 \pm 0.048
100 μ M clevidipine	225 \pm 235*	7.3 \pm 2.6	0.402 \pm 0.063
20 μ M RIF	1099 \pm 414	77 \pm 56	0.407 \pm 0.066

Data are the mean \pm standard deviation from three donors in each group. * Significantly different from controls ($p \leq 0.05$)

CONCLUSIONS:

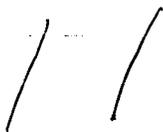
- 1) Clevidipine was found to be a statistically significant inducer of CYP3A4 but not CYP1A2 or 2C9 at the 10 μ M and 100 μ M concentrations of clevidipine tested. These data suggest that clevidipine has the potential to induce this enzyme.
- 2) Clevidipine caused a moderate decrease in CYP 2C9 activity in all three donors tested though it was not statistically significant. Additional donors would be required in order to make a conclusion as whether clevidipine has the potential to down-regulate.
- 3) In general, the qualitative and quantitative induction/down-regulation or direct inhibition response was not always uniform among the three donors. This suggests that there may be some donor characteristics (age, sex, other genetic factors) that may contribute to the non-uniform response.
- 4) There is an induction response for CYP3A4 to clevidipine.

REVIEWER'S COMMENT:

1. Clevidipine seems to be an inducer of CYP 3A4, CYP 1A2 and CYP 2C9.

STUDY 030508D – INDUCTION POTENTIAL OF CYTOCHROME P450 ISOFORMS 1A2, CYTOCHROME P450 2C9, AND CYTOCHROME P450 3A4 BY THE PRIMARY METABOLITE (H152/81) OF CLEVIDIPINE IN PRIMARY CULTURED HUMAN HEPATOCYTES.

INVESTIGATOR:



SITE:

REPORT # 030508D

EDR MODULE 4

RELEASE DATE: October 30, 2003 – April 21, 2004

OBJECTIVES:

The purpose of this study was to determine the induction potential of the primary metabolite (H152/81) of clevidipine in freshly plated human hepatocytes. Induction was measured by the catalytic activity assay selective for various cytochrome P450 (CYP) isoforms.

STUDY DESIGN:

Hepatocytes were exposed to H152/81 for a total of 3 days. Freshly isolated hepatocytes were plated in collagen I-coated 24-well plates. Samples for P450 induction were analyzed by measuring the P450 specific probe substrate catalytic activity using HPLC analysis with absorbance detection.

Hepatocytes from a total of five donor livers (three female and two male) were tested in the study. Each isoform of P450 was tested with three donors.

The use of solvent vehicle control and/or blanks, as well as triplicate samples, provided a control for bias.

Final H152/81 concentrations were 1, 10, and 100 μM . DMSO at a concentration of 0.08 % served as solvent vehicle control for both the test article and positive controls. Each H152/81 concentration (including the 0 μM) was tested in triplicate incubations in accordance with the methods below:

The substrates, final substrate concentration, the enzyme tested and the reaction catalyzed are shown below:

Table 1. Marker enzyme assay parameters

Probe substrate	P450 isoform	Reaction	Assay concentration
Testosterone	CYP3A4	6 β -Hydroxylase	200 μM
Phenacetin	CYP1A2	O-Deethylase	100 μM
Diclofenac	CYP2C9	4'-Hydroxylase	100 μM

The cells were incubated with substrate at 37°C for various times (e.g. 30 min for testosterone, 60 min for phenacetin and diclofenac). The reaction was stopped by removing the sample medium and combining an aliquot (175 µl for CYP1A2 and 300 µl for CYP2C9 and 3A4) with stop solution organic solvent and/or acid as shown below:

Table 2. Stop solution and volumes

P450 Substrate	Stop Solution	Volume Stop Solution/ml Incubation Volume
Testosterone	100% Acetonitrile	500 µl
Phenacetin	70% Perchloric Acid	125 µl
Diclofenac	6% Acetic Acid/94% Acetonitrile	300 µl

Positive control inducers for hepatocyte P450 enzymes, the concentration and the solvent used for delivery are depicted below:

Table 3. Positive control inducer chemicals

Enzyme	Positive control inducer	Final concentration	Solvent for delivery
CYP1A2	β-Naphthoflavone	20 µM	DMSO
CYP2C9	Rifampicin	20 µM	DMSO
CYP3A4	Rifampicin	20 µM	DMSO

RESULTS:

Below is the summary of effect of H152/81 and positive control β-naphthoflavone (BNF) on CYP1A2-catalyzed phenacetin O-deethylase activity and protein content in hepatocytes of 3 donors hepatocytes – means of three donors (HM018, HH137, and HH138).

Treatment	Activity (pmol/mg/min)	Fold induction	Protein (mg/well)
0 µM (DMSO vehicle)	6.0 ± 3.3	-	0.321 ± 0.109
1 µM H152/81	6.1 ± 4.2	0.94 ± 0.43	0.286 ± 0.055
10 µM H152/81	5.5 ± 2.9	0.94 ± 0.042	0.303 ± 0.054
100 µM H152/81	5.0 ± 2.9	0.81 ± 0.21	0.326 ± 0.049
20 µM BNF	151 ± 28	34 ± 23	0.338 ± 0.064

Data are the mean ± standard deviation from three donors in each group.

Summary of effect of H152/81 and positive control rifampicin (RIF) on CYP2C9-catalyzed diclofenac 4'-hydroxylase and protein content in hepatocytes of 3 donors hepatocytes – means of three donors (HM018, HH137, and HH138).

Treatment	Activity (pmol/mg/min)	Fold induction	Protein (mg/well)
0 µM (DMSO vehicle)	33 ± 23	-	0.331 ± 0.092
1 µM H152/81	31 ± 19	0.97 ± 0.11	0.310 ± 0.068
10 µM H152/81	18 ± 13*	0.54 ± 0.18	0.356 ± 0.030
100 µM H152/81	23 ± 22*	0.63 ± 0.29	0.365 ± 0.050
20 µM RIF	167 ± 128	4.9 ± 0.76	0.369 ± 0.055

Data are the mean ± standard deviation from three donors in each group. *

Significantly different from controls (p ≤ 0.05)

Below is the summary of effect of H152/81 and positive control rifampicin (RIF) on CYP3A4-catalyzed testosterone 6β-hydroxylase and protein content in hepatocytes of 3 donors hepatocytes – means of three donors (HH136, HM017, and HH137)

Treatment	Activity ($\mu\text{mol}/\text{mg}/\text{min}$)	Fold induction	Protein (mg/well)
0 μM (DMSO vehicle)	39 \pm 49	-	0.326 \pm 0.047
1 μM H152/81	39 \pm 51	0.96 \pm 0.037	0.332 \pm 0.044
10 μM H152/81	50 \pm 65	1.2 \pm 0.22	0.337 \pm 0.053
100 μM H152/81	294 \pm 316*	8.7 \pm 5.0	0.350 \pm 0.067
20 μM RIF	1235 \pm 322	82 \pm 60	0.354 \pm 0.076

Data are the mean \pm standard deviation from three donors in each group. * Significantly different from controls ($p \leq 0.05$)

Inhibitory effect of H152/81 at 100 μM on CYP1A2, 2C9, and 3A4 activity in hepatocytes from 3 donors hepatocytes

Donors	CYP 1A2 Inhibition (%)	CYP 2C9 Inhibition (%)	CYP 3A4 Inhibition (%)
*1	-5.2	18	-1.5
2	5.9	-25	-0.48
3	5.4	9.7	3.7

Donor 1 refers to HM018 for CYP1A2 and 2C9 and HH136 for CYP3A4;

Donor 2 refers to HH137 for CYP1A2 and 2C9 and HM017 for CYP3A4;

Donor 3 refers to HH138 for CYP1A2 and 2C9 and HH137 for CYP3A4.

CONCLUSIONS:

- 1) H152/81 was found to be a statistically significant inducer of CYP3A4 but not CYP1A2 or 2C9 at 100 μM concentration of H152/81 tested. These data suggest that H152/81 has the potential to induce CYP3A4.
- 2) H152/81 caused a moderate but statistically significant decrease in CYP 2C9 activity in all three donors tested. These data suggest that H152/81 has the potential to down-regulate this enzyme.
- 3) In general, the qualitative and quantitative induction/down-regulation or direct inhibition/activation response was not always uniform among the three donors. This suggests that there may be some donor characteristics (age, sex, other genetic factors) that may contribute to the non-uniform response. Additional donors would need to be examined to determine whether those factors influence induction and/or down-regulation and inhibition/activation response.
- 4) Induction response for CYP3A4 to H152/81 was always less than that from the positive control inducer. One parameter of induction response is the potency index (PI), expressed as a ratio of induction response of H152/81 to the induction response of the gold-standard inducer. Using this approach with H152/81 (100 μM), the PI was about 21% from an average of three donors.

REVIEWER'S COMMENT:

1. There was an induction response for CYP 3A4, CYP 1A2 and CYP 2C9 to clevidipine. It seems it is an inducer of all three cytochromes.

STUDY 030512A—INHIBITION OF CYTOCHROME P450 1A2, CYTOCHROME P450 2C9, CYTOCHROME P450 2C19, CYTOCHROME P450 2D6, CYTOCHROME P450 2E1 AND CYTOCHROME P450 3A4 CATALYTIC ACTIVITIES.

INVESTIGATOR:

SITE:

REPORT #030512A

EDR Module 4

STUDY DATE: October 30, 2003 – January 15, 2004

OBJECTIVES:

The purpose of this study was to determine whether H324/38 (clevidipine) inhibits human cytochrome P450 catalytic activity. The cytochromes P450 (CYP) examined, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are involved in many drug-drug interactions. Inhibition of these enzymes was measured using the model substrates and cDNA-derived enzymes in microsomes prepared from human lymphoblastoid cell lines or baculovirus-infected insect cells.

STUDY DESIGN:

The inhibition study consisted of the determination of a 50% inhibitory concentration (IC₅₀) for H324/38 and each enzyme. A single concentration of each model substrate (near the apparent K_m) and several concentrations of H324/38 were tested in duplicate. Metabolism of the model substrates was assayed by the production of a metabolite. The metabolites were detected via HPLC separation with absorbance, fluorescence or scintillation detection. Control microsomes (without cDNA-expressed cytochrome P450) were added if needed to standardize microsomal protein concentration.

The use of negative controls or blanks, as well as duplicate samples, provided a control for bias.

Table 2 provides a list of the names of enzymes examined, the model substrates used and the catalog number of the microsomes used as a source of each enzyme.

Table 2. Names of Enzymes, Substrates and Catalog Numbers of Microsomes.

Enzyme	Substrate	Catalog Number
CYP1A2	Phenacetin	
CYP2C9	Diclofenac	
CYP2C19	(S)-Mephenytoin	
CYP2D6	Bufuralol	
CYP2E1	p-Nitrophenol	
CYP3A4	Testosterone	
Control Microsomes	Added to standardize protein concentration	

Final concentrations of H324/38 (clevidipine) were 300, 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01 and 0 μ M. Each test substance concentration was tested in duplicate incubations in accordance with the methods below.

Each test concentration was tested in duplicate incubations in accordance with the methods described in Part E above.

Table 3. Positive Controls used.

Enzyme	Positive Control	Concentrations
CYP1A2	7,8-Benzoflavone	0.3 μ M
CYP2C9	Sulfaphenazole	3 μ M
CYP2C19	Tranylcypromine	100 μ M
CYP2D6	Quinidine	1 μ M
CYP2E1	4-Methylpyrazole	50 μ M
CYP3A4	Ketoconazole	1 μ M

RESULTS:

Table 4. Summary of IC₅₀ results for H324/38 using cDNA-expressed cytochrome P450s as an enzyme source.

Isoform of Cytochrome P450	IC ₅₀ (μ M)
CYP1A2	>300
CYP2C9	4.4
CYP2C19	2.5
CYP2D6	72
CYP2E1	>300
CYP3A4	8.4

CONCLUSIONS:

The test compound, H324/38, was tested for inhibition potential towards the major human cytochrome P450 isozymes involved in drug metabolism using cDNA-expressed enzymes. H324/38 inhibited CYP 2C9 (diclofenac 4'-hydroxylase), 2C19 [(S)-mephenytoin 4'-hydroxylase], 2D6 (bufuralol 1'-hydroxylase), and 3A4 (testosterone 6 β -hydroxylase) catalytic activity with an IC₅₀ value of 4.4 μ M, 2.5 μ M, 72 μ M, and 8.4 μ M, respectively. The catalytic activities of CYP 1A2 -(phenacetin hydroxylase), and 2E1 (p-nitrophenol hydroxylase) were inhibited by less than 50% at concentrations of up to 300 μ M.

REVIEWER'S COMMENT:

Clevidipine seems to inhibit CYP 2C9, 2C19, and 3A4.

STUDY 030512B – INHIBITION OF CYTOCHROME P450 1A2, CYTOCHROME P450 2C9, CYTOCHROME P450 2C19, CYTOCHROME P450 2D6, CYTOCHROME P450 2E1 AND CYTOCHROME P450 3A4 CATALYTIC ACTIVITIES BY H152/81

INVESTIGATOR AND SITE:

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REPORT #030512B

EDR Module 4

STUDY DATE: October 30, 2003 – January 13, 2004

OBJECTIVES:

The purpose of this study was to determine whether H152/81, the primary metabolite of clevidipine, inhibited human cytochrome P450 catalytic activity. The cytochromes P450 (CYP) examined, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are involved in many drug-drug interactions. Inhibition of these enzymes was measured using the model substrates and cDNA-derived enzymes in microsomes prepared from human lymphoblastoid cell lines or baculovirus-infected insect cells.

STUDY DESIGN:

The inhibition study consisted of the determination of a 50% inhibitory concentration (IC₅₀) for H152/81 and each enzyme. A single concentration of each model substrate (near the apparent K_m) and several concentrations of H152/81 were tested in duplicate. Metabolism of the model substrates was assayed by the production of a metabolite. The metabolites were detected via HPLC separation with absorbance, fluorescence or scintillation detection. Control microsomes (without cDNA-expressed cytochrome P450) were added if needed to standardize microsomal protein concentration.

The use of negative controls or blanks, as well as duplicate samples, provided a control for bias.

Table 2. Names of Enzymes, Substrates and Catalog Numbers of Microsomes.

Enzyme	Substrate	Catalog Number
CYP1A2	Phenacetin	
CYP2C9	Diclofenac	
CYP2C19	(S)-Mephenytoin	
CYP2D6	Bufuralol	
CYP2E1	p-Nitrophenol	
CYP3A4	Testosterone	
Control Microsomes	Added to standardize protein concentration	

Final concentrations of H152/81 was 300, 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01 and 0 μM . Each test substance concentration was tested in duplicate incubations in accordance with the methods below.

Table 3. Positive Controls Used.

Enzyme	Positive Control	Concentrations
CYP1A2	7,8-Benzoflavone	0.3 μM
CYP2C9	Sulfaphenazole	3 μM
CYP2C19	Tranlycypromine	100 μM
CYP2D6	Quinidine	1 μM
CYP2E1	4-Methylpyrazole	50 μM
CYP3A4	Ketoconazole	1 μM

RESULTS:

The catalytic activity of CYP2C9, CYP2C19, and CYP3A4 was inhibited (50%) by H152/81 at 92 μM , 69 μM , and 198 μM , respectively. The IC_{50} values for CYP1A2, CYP2D6, and CYP2E1 were not determined, since inhibition by H152/81 was less than 50% at the highest concentration (300 μM).

Table 4. Summary of IC_{50} results for H152/81 using cDNA-expressed cytochrome P450s as an enzyme source.

Isoform of Cytochrome P450	IC_{50} (μM)
CYP1A2	>300
CYP2C9	92
CYP2C19	69
CYP2D6	>300
CYP2E1	>300
CYP3A4	198

CONCLUSIONS:

H152/81 does not inhibit CYP 2C9 -(diclofenac 4'-hydroxylase), 2C19 -[(S)-mephenytoin 4'-hydroxylase]], and CYP3A4-(testosterone 6 β -hydroxylase) catalytic activity with an IC_{50} value of 92 μM , 69 μM , and 198 μM , respectively. The catalytic activities of CYP1A2-(phenacetin hydroxylase), CYP2D6 (bufuralol 1'-hydroxylase), and CYP2E1 (p-nitrophenol hydroxylase) were either not inhibited or inhibited by less than 50 % at concentrations of up to 300 μM .

REVIEWER'S COMMENT:

Reviewer concurs.

STUDY 030512C – INHIBITION OF CYTOCHROME P450 2C9, CYTOCHROME P450 2C19, AND CYTOCHROME P450 3A4 CATALYTIC ACTIVITIES BY H324/38. DETERMINATION OF KI VALUES.

INVESTIGATOR AND SITE:

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REPORT # 030512C

EDR MODULE 4

Release Date: January 7 – April 2, 2004

OBJECTIVES:

The purpose of this study was to determine whether the test substance, H324/38 (Clevidipine) inhibits human cytochrome P450 (CYP) catalytic activity. Inhibition was measured using model substrates and cDNA-derived enzymes in microsomes prepared from human lymphoblastoid cell lines or baculovirus-infected insect cells.

STUDY DESIGN:

The data obtained from the IC₅₀ study (030512a) was used to design an inhibition study to determine apparent K_i. In this study, three substrate concentrations were utilized and were incubated with and without three linearly spaced concentrations of the test substance (H324/38). Triplicate incubations were performed for each condition. Substrate metabolism was assayed by the production of a metabolite. The metabolite was quantified by HPLC separation with absorbance or radiometric detection. The apparent K_i was calculated using standard methods.

The use of blanks, as well as triplicate samples, provided a control for bias.

Below is a list of the names of the enzymes examined and the model substrate used.

Enzyme	Substrate
CYP2C9	Diclofenac
CYP2C19	(S)-Mephenytoin
CYP3A4	Testosterone
Control Microsomes	Added to standardize protein concentration

Test substance concentrations were based on the data obtained from the IC₅₀ determinations (Study 030512a). Each test concentration was tested in triplicate incubations.

Positive controls:

The test compound served as its own positive control.

RESULTS:

Diclofenac (P450 2C9)

Calculated K_i Values

Test Substance	3 μ M vs 6 μ M	3 μ M vs 20 μ M	6 μ M vs 20 μ M
	Diclofenac	Diclofenac	Diclofenac
H324/38	1.18 μ M	1.53 μ M	2.19 μ M

$K_i = 1.6 \mu$ M

(S)-Mephenytoin (P450 2C19)

Calculated K_i Values

Test Substance	15 μ M vs 30 μ M	15 μ M vs 100 μ M	30 μ M vs 100 μ M
	(S)-Mephenytoin	(S)-Mephenytoin	(S)-Mephenytoin
H324/38	4.50 μ M	3.95 μ M	3.51 μ M

$K_i = 4.0 \mu$ M

Testosterone (P450 3A4)

Calculated K_i Values

Test Substance	40 μ M vs 80 μ M	40 μ M vs 200 μ M	80 μ M vs 200 μ M
	Testosterone	Testosterone	Testosterone
H324/38	5.65 μ M	6.13 μ M	7.66 μ M

$K_i = 6.5 \mu$ M

CONCLUSIONS:

Based on these experiments, the apparent K_i for CYP2C9, CYP2C19 and CYP3A4 was calculated to be 1.6, 4.0, and 6.5 μ M, respectively.

REVIEWER'S COMMENT:

Reviewer concurs with findings since the therapeutic concentration of clevidipine given at 3.2 μ g/kg/min (16 mg/hr) is about 50 nM. However, if the dose were to be doubled, as is allowed in the labeling one could assume a therapeutic concentration for clevidipine reaching approximately 100 nM. This scenario could potentially close in on inhibitory concentrations for CYP P450 2C9. As a result,

STUDY 1327 – IN VITRO PROTEIN BINDING OF CLEVIDIPINE AND ITS ENANTIOMERS IN PLASMA FROM DIFFERENT ANIMAL SPECIES AND HUMANS

INVESTIGATOR AND SITE:

Astra Hässle AB, S-431
83 Mölndal, Sweden

REPORT # 1327

EDR MODULE 4

STUDY DATES: February 3 – July 2, 1997

OBJECTIVES:

The objective of this study was to determine the plasma protein binding of clevidipine in different animal species and in human plasma. In addition, the protein binding of the enantiomers of clevidipine, H 190/90 and H 190/91, was determined in human plasma.

Note: Only results in human will be reported in this review.

STUDY DESIGN:

The test system was plasma from 6 healthy human subjects (3 males and 3 females), 3 rats (males), 3 dogs (1 male and 2 females), 3 rabbits (2 males and 1 female) and 3 pigs (females).

The blood was pooled to give separate male and female samples.

Human samples

The protein binding of clevidipine was determined at three different concentrations 25, 100 and 250 nM. The protein binding of the enantiomers of clevidipine was determined at 100 nM.

To control the linearity, different volumes (50, 100, 150 and 200 µl) of diluted plasma were injected onto the column. The dilution of the plasma was selected to give peak linearity for added plasma volumes between 50 and 200 µl. When linearity was established, the mean value for the 100 and 150 µl injections was calculated and reported. Between 9 and 14 injections were performed at each concentration and for each animal species studied.

Validation of the method

The liquid chromatography method was validated by comparing the results obtained for a reference compound, felodipine, with those obtained by equilibrium dialysis (ref. 3). Plasma was injected twenty-nine times onto the column. The mobile phase consisted of _____

RESULTS:

Clevidipine was extensively bound to plasma from all species studied. The mean protein binding of clevidipine in male and female humans was 99.71 and 99.66%, respectively. The corresponding values of clevidipines enantiomers, H 190/90 and H 190/91, were 99.57 and 99.68%, respectively, in pooled plasma from both genders. The results show that the free fraction is slightly different for the two enantiomers, 0.43 and 0.32%, respectively. However, *in vivo* results in essential hypertensive patients have shown that the pharmacokinetic parameters derived for the separate enantiomers after clevidipine administration are virtually identical, suggesting that the minor difference in protein binding has no influence on the pharmacokinetics (ref. 4).

Individual and mean protein binding of clevidipine at different concentrations in pooled plasma from male and female humans at 37°.

Injection No.	Human male Clevidipine nM			Human female Clevidipine nM		
	25	100	250	25	100	250
1	99.74	99.67	99.73	99.57	99.67	99.61
2	99.77	99.65	99.67	99.68	99.66	99.65
3	99.75	99.68	99.68	99.65	99.63	99.64
4	99.76	99.71	99.65	99.64	99.64	99.66
5	99.73	99.70	99.67	99.65	99.64	99.67
6	99.76	99.71	99.68	99.65	99.67	99.65
7	99.77	99.69	99.71	99.65	99.68	99.66
8	99.75	99.70	99.70	99.59	99.72	99.70
9	99.76	99.68	99.72	99.64	99.70	99.67
10	99.75	99.70	99.71		99.68	99.70
Mean	99.75	99.69	99.69	99.64	99.67	99.66
SD	0.01	0.02	0.03	0.03	0.03	0.03
n	10	10	10	9	10	10

The individual and mean protein binding of the enantiomers of clevidipine, H190/90 and H190/91, at 100 nM in pooled plasma from male and female humans at 37°.

Injection No.	H 190/90	H 190/91
	100 nM	
1	99.60	99.65
2	99.60	99.67
3	99.62	99.69
4	99.60	99.68
5	99.52	99.73
6	99.55	99.70
7	99.60	99.68
8	99.56	99.68
9	99.54	99.66
10	99.58	99.67
11	99.51	99.71
12		99.61
Mean	99.57	99.68
SD	0.04	0.03
n	11	12

CONCLUSIONS:

- There is no concentration-dependent binding of clevidipine in the concentration range studied, 25-250 nM.
- The free fraction of the enantiomers of clevidipine in man was 0.43 and 0.32%, respectively. This difference does not seem to have any influence on the *in vivo* pharmacokinetics of the separate enantiomers.
- Clevidipine and its enantiomers are > 99.5% bound to plasma proteins.

REVIEWER'S COMMENT:

The reviewer concurs with study findings

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**Appendix III:
Individual Review of Clinical Pharmacokinetic Studies**

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STUDY SH-SAD-0002 – PHARMACOKINETICS OF H 324/38 IN HEALTHY MALE SUBJECTS AFTER INTRAVENOUS INFUSION.

STUDY INVESTIGATOR AND SITE:
Metabolism Portion of Study:

Astra Hässle Human Pharmacology
Sahlgrenska hospital
S-400 36 GÖTEBORG, Sweden

Mass Balance Part of Study:

REPORT # Sh-SAD-0002

EDR VOLUME 5

STUDY DATES: October 10 - November 6, 1995

OBJECTIVES

Primary objectives of this study were to evaluate the pharmacokinetics, metabolism and rates and routes of excretion of H 324/38 in healthy male subjects after intravenous administration of H 324/38-³H.

FORMULATION: (Expiration dates not provided.)

H 324/38 emulsion for intravenous infusion 1 mg/ml

Batch H 1153-1-1-2 (vials containing 100 ml)

H 324/38-³H emulsion for intravenous infusion 0.5 mg/ml, 1.1 Mbq/ml

Batch H 1198-1-2-1 (vials containing 12 ml)

H 324/38 was manufactured and bottled by _____ and labelled and distributed by Astra Hässle AB, Mölndal, Sweden.

The study drug was mixed as follows:

- 40 ml H 324/38 emulsion 1 mg/ml was drawn into a 50 ml syringe.
- 5 ml H 324/38-³H 0.5 mg/ml 1.1 Mbq/ml was drawn into a 5 ml syringe.
- The 5 ml H 324/38-³H 0.5 mg/ml was flushed into the 50 ml syringe. The emulsion was mixed thoroughly by turning the syringe up side down 10 times (not shaken). The contents of the syringe was then 45 ml emulsion of H 324/38, 0.94 mg/ml (2.06 µmol/ml) and a radioactivity of 0.12 Mbq/ml.
- The subject was then to receive 30 ml i.v. infusion during 60 minutes which was equivalent to 1030 nmol/min.

After termination of the infusion the remaining emulsion (appr. 10 ml) was transferred into another vial which was given subject no and date of infusion. This vial was then kept in a refrigerator until analysis by Product analysis at Astra Hässle, AB, Mölndal, Sweden.

STUDY DESIGN

The study was performed as an open single dose study. The subjects received 12 nmol/kg/min H 324/38 containing a trace amount of H 324/38-³H during 1 hour as a constant i.v. infusion. All subjects were medically examined within 14 days before the actual study day (including a physical examination, ECG, blood pressure (BP), heart rate (HR) and a laboratory check). The same was also done at the follow-up visit. On the study day the subject arrived at the laboratory in the morning after a 10-hour overnight fast. Indwelling plastic cannulas were inserted into a forearm vein on both arms. One of these cannulas was used for the infusion of the study drug and the cannula on the other arm was used for blood sampling. Frequent blood samples were taken for estimation of drug blood concentrations before infusion and up to 32 hours after start of infusion. Urine and faeces were collected up to 168 hours after start of infusion. ECG, BP and HR were followed before, during and after the infusion. Standardized meals were served during the study day. The subjects stayed for 32 hours. Adverse events were registered throughout the study.

Eight male subjects between the ages of 20 to 40 years were enrolled. Duration of treatment was one hour.

The dose to be used was based upon results from the tolerability study SH-SAD-0001. Consequently, the dose was decided to be 1030 nmol/min (containing 3.7 Mbq). This was specified in Amendment no 1, dated September 25, 1995.

The subjects were instructed to have dinner no later than 7 p.m. and abstain from all food and drink after 10 p.m. on the evening before the study day. Standardized meals were served at the following time points after start of infusion.

- 3 hours, breakfast
- 5 hours, lunch
- 7 hours, snack
- 10 hours, dinner
- 13 hours, snack
- 24 hours, breakfast
- 28 hours, lunch
- 31 hours, snack

No alcohol or over-the-counter drugs were permitted for two days before the study day. Neither should the subjects have taken any prescribed medicine for two weeks before study start. Tobacco (smoking, snuff, nicotine chewing gum or nicotine plaster) was not allowed during the study day or during the fasting period before study drug infusion.

ANALYTICAL METHODS:

The blood samples were analysed at Bioanalytical Chemistry, Astra Hässle AB, Mölndal, method BA-272. Values below limit of quantitation (LOQ) 5 nmol/l could not be accurately determined and were set to nondeterminable (nd) and not used in the calculations.

However, during the course of the study the method to analyse the blood samples was improved so that the limit of quantitation was set to 1 nmol/l. Consequently, key blood samples taken up to 30 min after stop of infusion were analysed using the lower limit of quantitation. These values were used when calculating the pharmacokinetic variables and they were also used in the statistical analysis.

Two methods were used for the determination of clevidipine and its metabolite:

Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
GC-MS	H 324/38	BA272: 5.5-111	92.8% (BA286)	BA272: 3.1%, 4.3%	102.5% (91.8-116.9%) (BA272)	Linear ^B	5 nmol/L ^C (BA272)
		BA286: 1.2-125	86.0% (BA286)	BA286: 2.7-3.1%			0.5 nmol/L ^C (BA286)
LC-Fluor	H 152/81	BA272: 217-31200	85% (BA272)	BA272: 1.5% 2.2% 4.7%	97.6% (86.0-104.4%) (BA286)		50 nmol/L ^C (BA272)

B = Linearity defined as a maximum deviation of 15% from nominal conc. (Accuracy 85–115%).

C = LOQ is the lowest conc. Where precision is better than 20% and the accuracy is within 85–155%.

Limit of quantitation

The limit of quantitation (LOQ), was 5.0 nmol/l for clevidipine and 50.0 nmol/l for H 152/81. LOQ is the lowest concentration where, routinely, precision is better than 20 % and accuracy within 85–115 %. LOQ for the modified analytical method was 1.0 nmol/l for clevidipine.

Excretion

Urine and faeces were collected for 168 hours after start of infusion and total radioactivity in urine and faeces was determined by liquid scintillation counting at:

Analytical report for urine and faecal bioanalysis was not provided.

PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood samples (1.5 ml) for the analyses of H 324/38 and the metabolite H 152/81 were collected as follows:

-15 (predose), at 0.5, 1, 1.5, 2, 5, 10, 20, 40, 50, 60 (stop of infusion), 60.5, 60.75, 61, 62, 63, 65, 68, 70, 90 minutes and at 2, 3, 4.5, 6, 9, 12, 24 and 32 hours after start of infusion

The blood samples (10 ml) for determination of metabolic pattern of H 324/38 in plasma were collected at 1.5, 2, 3, 4.5, 6, 9, 12, 24 and 32 hours after start of infusion.

Urine collection

Before the administration of H 324/38 the subject was to empty his bladder at the laboratory. Approximately 50 ml of this blank sample was kept for analysis. Urine was collected up to 168 h after start of infusion at the following sampling intervals:

Urine sampling intervals (11):

predose and at 0-3, 3-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h after start of infusion.

Faeces collection

Eight fractions of faeces were collected over a time period of 7 days. The sampling intervals are listed below.

Faeces sampling intervals (8):

predose, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h after start of infusion.

Supine systolic and diastolic blood pressure, mean arterial pressure and heart rate (SBP, DBP, MAP and HR) were recorded during the study day. The pharmacokinetic variables for the 8 subjects were analysed using 95% confidence intervals for the mean effects. The between subject variation was estimated. In these calculations Student's t-distribution was used. Pharmacodynamic and adverse event data were presented descriptively.

The pharmacokinetic parameters of H 324/38 were determined with non-compartmental and compartmental analysis. For the inactive metabolite, H 152/81, only compartmental analysis was performed. All analyses were performed with the computer programme WinNonlin (ver. 1.0, Scientific Consulting Inc., Apex, North Carolina, U.S.).

RESULTS:

SAFETY:

ECG (12-lead): predose, and at 15, 30, 45, 60 minutes after start of infusion.

Moreover, ECG was run continuously on an oscilloscope for 120 minutes.

BP (by sphygmomanometer) and HR (by palpation): predose and at 15, 30, 45, 60, 75, 90 minutes and at 2, 3, 4, 5, 6, 7, 8 hours after start of infusion.

Haematology, blood chemistry, urine analysis, and adverse events were monitored before the study, during, and at follow-up. There were no withdrawals due to adverse events and no deaths occurred during the study.

The most frequently reported adverse event was flushing and were all mild in nature; but one that was classified as severe.

Following a one-hour infusion of H 324/38, the average effects on blood pressure and heart rate were back to pre-dose values 15 minutes after the infusion was terminated

H 324/38 is safe and well-tolerated by healthy male subjects in the dose used.

PHARMACOKINETICS:

Non-compartmental analysis of H 324/38

Subject	AUC _{0-x} (nmol*min/L)	AUC _{0-∞} (nmol*min/L)	CL (L/min/kg)	C _∞ (nmol/L)	t _{1/2λz} (min)	V _∞ (L/kg)
N	8	8	8	8	8	8
Mean	5539.5	5571.8	0.136	97.35	11.646	0.746
SD	1257.0	1271.1	0.033	23.81	2.791	0.415
Max	7243.7	7306.8	0.172	133.00	15.484	1.651
Median	5993.1	6027.3	0.144	95.05	11.259	0.638
Min	3433.0	3451.6	0.090	72.83	8.478	0.185

Compartmental analysis of H 324/38

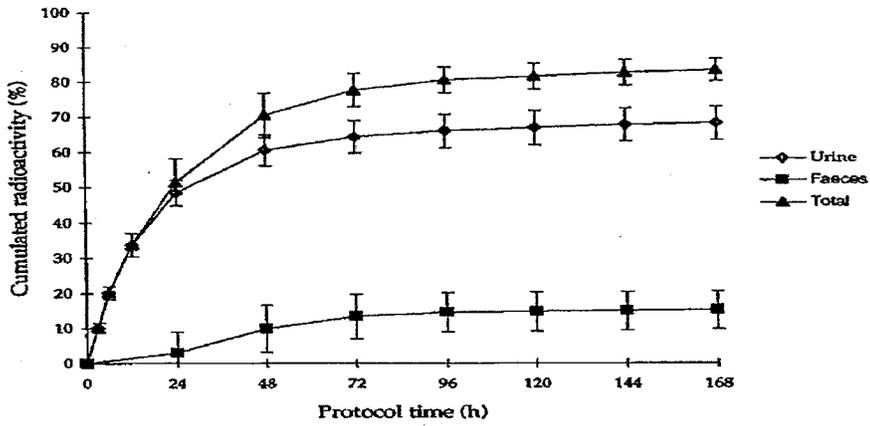
Subject	AUC _{λ1}	CL (L/min/kg)	t _{1/2λz1} (min)	t _{1/2λz} (min)	V ₁ (L/kg)	V _∞ (L/kg)	t _∞ (min)
N	8	8	8	8	8	8	8
Mean	0.870	0.149	1.027	11.970	0.250	0.504	0.810
SD	0.038	0.039	0.266	2.948	0.092	0.129	0.637
Max	0.906	0.205	1.380	16.053	0.416	0.671	1.785
Median	0.882	0.140	0.967	11.631	0.259	0.526	0.956
Min	0.807	0.098	0.711	8.300	0.122	0.325	0.000

Compartmental analysis of H 152/81

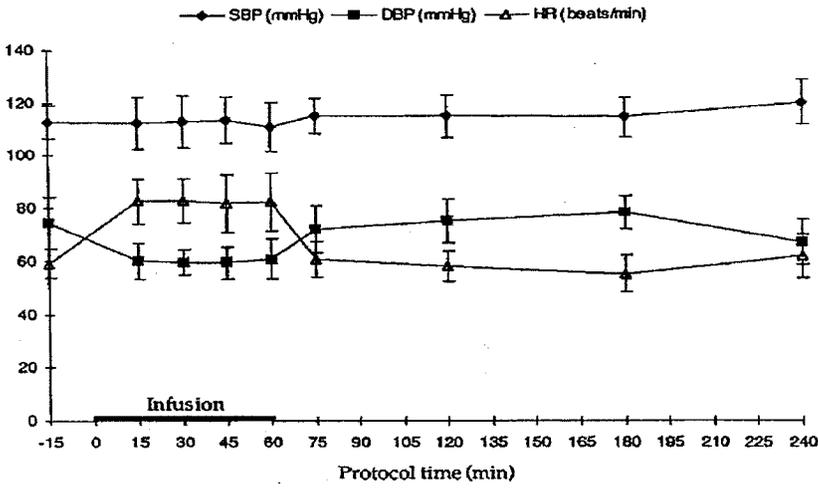
Subject	CL (L/h/kg)	C _∞ (nmol/L)	t _∞ (h)	t _{1/2λz} (h)	V _{λz} (L/kg)
N	8	8	8	8	8
Mean	0.0306	3362.50	1.0359	9.1859	0.4041
SD	0.0034	218.55	0.0232	0.7715	0.0468
Max	0.0363	3730.00	1.0833	10.5126	0.4574
Median	0.0305	3330.00	1.0333	8.9586	0.4197
Min	0.0247	2990.00	1.0083	8.3195	0.3423

The mean cumulative amounts of radioactivity excreted in urine and faeces over a 7-day period, expressed as percentage of given dose, are shown in the figure below. Most of the radioactivity was found in urine, 67.7% ± 4.9%. The recovery in faeces was 15.1 ± 5.4% resulting in a total recovery of 82.9 ± 3.2%. More than 90% of the recovered dose was excreted within 72 hours. No unchanged compound was detected in plasma, urine or faeces, indicating extensive metabolism of the parent compound in man. Recovery of a portion of the administered radioactivity in faeces suggests that biliary elimination was likely to be involved in the excretion of the IV dose given.

Metabolites were formed via by mainly four routes of metabolism: ester hydrolysis, oxidation of the dihydropyridine ring to the corresponding pyridine, glucuronidation and decarboxylation. Clevidipine was completely metabolized to the primary metabolite M1, which was the predominant peak in plasma. The main metabolites in urine were M3a and M3b, which were identified as the diastereomeric pair of M1 glucuronides. The predominant peak in the samples of faeces was the decarboxylated pyridine M5.

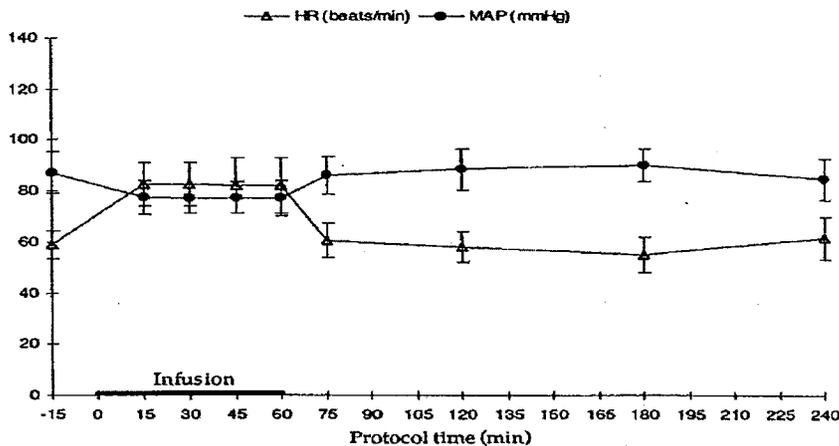


Urine, faeces, and total cumulated radioactivity, mean and SD (n=8). The total is calculated assuming no radioactivity in faeces during 0-12 hours.



Systolic blood pressure, Diastolic blood pressure and Heart rate vs. protocol time, mean and SD

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Heart rate and Mean arterial blood pressure vs. protocol time, mean and SD

CONCLUSIONS:

H 324/38 is a high clearance compound rapidly metabolised to the corresponding acid, H 152/81. The high clearance value (0.14 L/min/kg) for H 324/38 indicates metabolism by hepatic and extrahepatic tissues.

The half-life of the initial phase of the blood concentration vs. time curve representing >80% of the total area under the curve is approximately 1 minute. The half-life of the terminal phase is approximately 12 minutes.

The total recovery of radioactivity following administration of H 324/38-³H after 168 hours was 83%. Most of the dose was recovered in urine (68%). More than 90% of the recovered dose was excreted within 72 hours.

A small portion of urinary radioactivity was volatile (<0.5% of the dose) suggesting that there was very little metabolic exchange of the tritium label with water. There were no measurable volatile components excreted in faeces.

REVIEWER'S COMMENT:

The reviewer concurs.

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ON ORIGINAL**

STUDY SH-SAD-0001 – TOLERABILITY AND SAFETY ON H 324/38 AFTER ADMINISTRATION OF GRADUALLY INCREASING IV DOSES TO HEALTHY SUBJECTS.

STUDY INVESTIGATOR AND SITE:

Human Pharmacology
Astra Hässle AB
Department 40
Sahlgrenska Hospital
S-413 45 Göteborg, Sweden

REPORT # SH-SAD-0001

VOLUME in EDR, Section 5

STUDY DATES: August 9 – September 19, 1995

OBJECTIVES

The primary objective of this study was to investigate the tolerability and safety of H 324/38 after administration of gradually increasing intravenous doses to healthy subjects.

The secondary objective was to obtain a preliminary assessment of the pharmacokinetics of the drug in healthy volunteers.

FORMULATION:

H324/38 The concentration of the investigational drug, H 324/38, was planned to be 1 mg/ml. However, the analysis showed that the concentration was 0.94 mg/ml (Appendix 2, page 1). The formulation consisted of H 324/38 fat emulsion for (i.v.) infusion (Batch No. H 1153-1-1-2).

The solution was diluted with 20% Intralipid® (batch # H 622-2-2-1) to a conc of 0.05 mg/mL H324/38 for the first four dose steps.

Placebo 20 % Intralipid® was used as placebo solution (Batch No. H 662-2-2-1).

NOTE: Both placebo and H324/38 were in 100 mL vials. An opened bottle had to be used within 12 hours.

H 324/38 was manufactured and bottled by _____
_____ and placebo was manufactured and bottled by _____
_____. All drugs were packed and labelled at Astra Hässle AB, S-431 83 Mölndal, Sweden.

Expiration dates were not provided.

Overall study design

This was a single-blind tolerability and safety study of short-term (20 min) i.v. infusions of H 324/38 at increasing doses. H 324/38 was administered to three subjects (two active + one placebo) for each of the first two dose steps and to five subjects (four active + one placebo) for each of the following consecutive dose steps. The study was designed to include 11 dose steps in a total of 51 healthy subjects.

H 324/38 was to be administered in the following increasing dose steps: 1/50, 1/25, 1/12, 1/4, 1/2, 1, 2, 4, 6, 8 and 10 times the assumed therapeutic dose, which was 6 nmol/kg/min, corresponding to 2.7 µg/kg/min of H 324/38 (MW= 456.3 g/mol). The planned dose regimen is given in

the table below over a minute IV infusion.

Part of the estimated therapeutic dose 2.7(38) µg/kg/min	Dose µg/kg/min	Dose nmol/kg/min
1/50	0.055	0.12
1/25	0.110	0.24
1/12	0.228	0.50
1/4	0.685	1.50
1/2	1.369	3.00
1	2.738	6.00
2	5.476	12.00
4	10.952	24.00
6	16.428	36.00
8	21.904	48.00
10	27.378	60.00

The subjects were instructed not to have dinner later than 7 p.m. and abstain from all food and drink after 10 p.m. the evening before the study day. Standardised food was served during the study day.

No alcohol was permitted for two days before the drug was taken or during the study day. Tobacco (smoking, snuff, nicotine chewing-gum or nicotine plaster) was not allowed during the day at the laboratory or during the fasting period before drug intake.

The subjects were administered the drug over a period of 20 minutes. Each subject could be included twice with at least a three-day wash-out period in-between. These subjects received a unique subject number each time they were included. If a subject participated more than once in the study, the physical examination, ECG and laboratory investigation from the follow-up visit in the preceding part of the study were used as pre-treatment values for the next part, provided that the follow-up visit took place within 14 days before the second study day.

Over-the-counter drugs were not permitted for two days before the drug was given or during the study day. Neither were the subjects allowed to take any prescribed medicine for two weeks before the study commenced. Other medication which was considered necessary for the subject's welfare might be given at the discretion of the investigator. The administration of all such drugs had to be recorded in the appropriate section of the Case Report Form (CRF). If such an action was taken, the subject had, however, to be withdrawn from the study.

ANALYTICAL METHODS:

The samples were analysed for H 324/38 by a gas chromatography-mass-spectrometry method and the metabolite H 152/81 by a liquid chromatography method (BA-272) at Astra Hässle AB, Mölndal, Sweden. The limit of quantitation (LOQ) was 5 nmol/L for H 324/38 and 50 nmol/L for the metabolite. Values below LOQ were set to non-determinable (-).

Validation report no.	Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
1312-316 SAD 0001	GC-MS	H32438	5.0-300	See 1312-316	3.9%-11.4% (low standards) 0.7%-7.5% (high standards)	100.2% (94.6-104.4%)	Linear ^c	50 nmol/L ^c
	LC-Fluor	H5281	50-65000	See 1312-316	1.4%-4.0%	99.1% (96.3-101.8%)		50.0 nmol/L ^c

B = Linearity defined as a maximum deviation of 15% from nominal conc. (Accuracy 85–115%).

C = LOQ is the lowest conc. Where precision is better than 20% and the accuracy is within 85–155%.

Limit of quantitation

The limit of quantitation (LOQ), was 5.0 nmol/l for clevidipine and 50.0 nmol/l for H 152/81. LOQ is the lowest concentration where, routinely, precision is better than 20 % and accuracy within 85-115 %. LOQ for the modified analytical method was 1.0 nmol/l for clevidipine.

PHARMACOKINETICS, PHARMACODYNAMICS, AND STATISTICAL ANALYSIS:

During the two first dose steps, 1/50 and 1/25 of the estimated therapeutic dose, no blood samples were collected.

Blood samples for determination of H 324/38 were collected at the following times:

Dose step 1/12 and 1/4 of estimated therapeutic dose: -15 (pre-dose), 10, 15 and 19 minutes after start of infusion.

Dose step 1/2 of estimated therapeutic dose: -15 (pre-dose), 10, 15, 19, 20.25, 20.5, 20.75, 21, 25, 30, 45 and 60 minutes after start of infusion.

Dose step 1 of estimated therapeutic dose and above: -15 (pre-dose), 10, 15, 19, 20.25, 20.5, 20.75, 21, 25, 30, 45, 120, 240, 480 and 720 minutes after the start of infusion.

For subject numbers 38 to 46 (dose level 6, 36 nmol/kg/min) the blood sampling times were changed to the following: -15 (pre-dose), 10, 15, 19, 20.5, 20.75, 21, 23, 25, 30, 45, 120, 240, 480 and 720 minutes after start of infusion (changes made above were due to amendments to the protocol).

The samples collected at 15 and 19 minutes after the start of infusion from each subject were analysed. If no drug was detected in these samples, no more samples from that subject were analysed for drug concentration.

Blood samples from dose-step 1 were also analysed for the metabolite H 152/81.

The total blood clearance (CL) and the steady state concentration (C_{ss}) of H 324/38 were calculated. For the inactive metabolite, H 152/81, the pharmacokinetic parameters were calculated by non-compartmental analysis performed with the computer program WinNonlin (ver. 1.0, Scientific Consulting Inc., Apex, NC, U.S.).

Values below the LOQ were set to non-determinable (nd) and not used in the calculations. Actual sampling times were used for calculation.

A linear regression analysis was used in order to estimate the intercept and the slope of the line fitted for the relationship between the steady state concentration and the dose rate.

Descriptive statistics were used in the evaluation of data.

All pharmacodynamic variables (BP and HR) were listed in tables and summarised using descriptive statistics. The pharmacodynamic variables were also described graphically versus time and versus blood concentrations.

A simple E_{\max} -model was fitted to the reduction in MAP/HR from pre-dose values and blood concentrations by the computer program WinNonlin (ver. 10 Scientific consulting Inc., Apex, NC, U.S.).

$$\text{Effect} = 100 \cdot (E_{\max} \times C) / (EC_{50} + C)$$

where E_{\max} is the maximum reduction in MAP/HR in relation to pre-dose value (expressed as %) and EC_{50} is the concentration that reduces E_{\max} by 50%.

RESULTS:

Twenty-five individuals were enrolled in the study, twenty-one of them were included twice, which gives a total of forty-six study entries (each study entry gives an unique subject number) in the study. On forty-four occasions the infusion was completed per protocol and could be included in the pharmacokinetic, pharmacodynamic and statistical evaluation. One subject (No. 46) discontinued due to an endpoint, and another subject (No.32) was given too low a dose. For each of the first two dose steps, three subjects (two active + one placebo) were included, and for each of the following consecutive dose steps five subjects (four active + one placebo) were included.

The infusion rate was changed after 8 minutes and 34 seconds in subject No. 32 due to a drop in mean arterial pressure (MAP). He will be excluded from the descriptive statistics. Subject No. 19 received 2.9 nmol/kg/min instead of 3.0 nmol/kg/min, and subject No. 40 received 36.4 nmol/kg/min instead of 36.0 nmol/kg/min. They are included in the descriptive statistics as the deviations are small.

Subject no. 46 discontinued the study after 2.5 minutes' infusion because he reached an endpoint, HR > 120 beats/min. He will only be included in the safety report.

The following dose levels were administered to the subjects: 1/50, 1/25, 1/12, 1/4, 1/2, 1, 2, 4, 6 and 8 times the assumed therapeutic dose, which was 6 nmol/kg/min. Subjects 42, 43 and 46 reached the endpoint, i.e. HR above 120 beats/minute at a dose level 8 times the estimated dose (48 nmol/kg min), and therefore the study was stopped. Subjects 42 and 43 reached the endpoint between two listed measurements (maximum HR for both 122 beats/min) and then HR decreased again. Therefore HR >120 beats/min is not listed in the HR table for the individuals.

All subjects that participated in the study were male Caucasians. Subjects with identical identity are listed below:

1, 22	6, 17	13, 31	21, 30	37, 44
2, 23	7, 20	14, 32	27, 38	41
3, 24	8, 19	15, 35	28, 40	43
4, 12	9, 26	16, 25	29, 39	45
5, 11	10, 33	18, 34	36, 42	46

Below are the subjects' allocation at the different dose steps:

Dose step	Dose H 324/38 (nmol/kg/min)	Subjects
1/50	0.12	1, 3
1/25	0.24	4, 5
1/12	0.5	8, 9, 10, 11
1/4	1.5	12, 13, 14, 16
1/2	3	17, 18, 19, 20
1	6	22, 24, 25, 26
2	12	27, 28, 29, 30
4	24	32, 33, 34, 35
6	36	37, 39, 40, 41
8	48	42, 43, 44, 46
placebo (Intralipid®)	-	2, 6, 7, 15, 21, 23, 31, 36, 38, 45

Thirteen of the subjects were administered H 324/38 twice.

Sections described below are from the original application study report.

Two of the subjects are excluded from the descriptive analysis, subject 32 (see section 5.1.2.) and subject 46 (see section 5.1.3.)

In the pharmacokinetic analysis of H324/38, subjects were included that received infusion rates ranging from 1.5 to 48 nmol/min/kg, and of H 152/81 ranging from 6 to 48 nmol/min/kg. Subject 46 (see section 5.1.3.) was excluded from the calculations, and only the elimination half-life of H 152/81 was calculated for subject 32 (see section 5.1.2.).

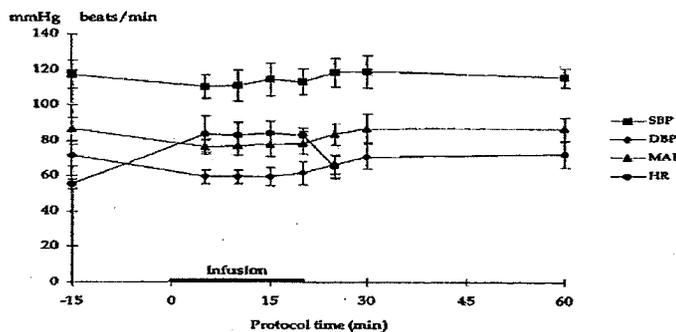


Figure 1. SBP, DBP, MAP and HR at dose 12 nmol/kg/min, mean and SD, n=4 (pat. No. 27-30).

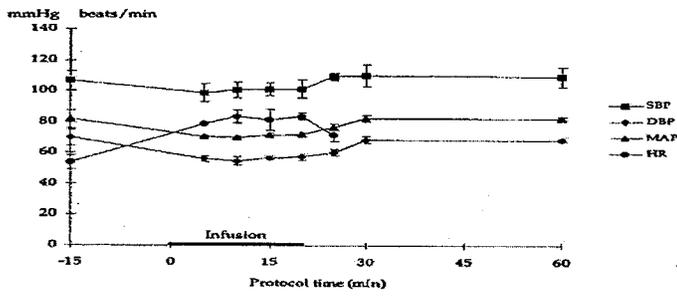


Figure 2. SBP, DBP, MAP and HR at dose 24 nmol/kg/min, mean and SD, n=3 (pat. No. 33-35).

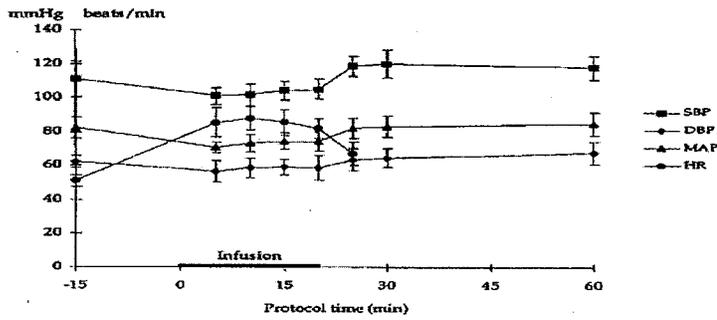


Figure 3. SBP, DBP, MAP and HR at dose 36 nmol/kg/min, mean and SD, n=4 (pat. No. 37, 39-41).

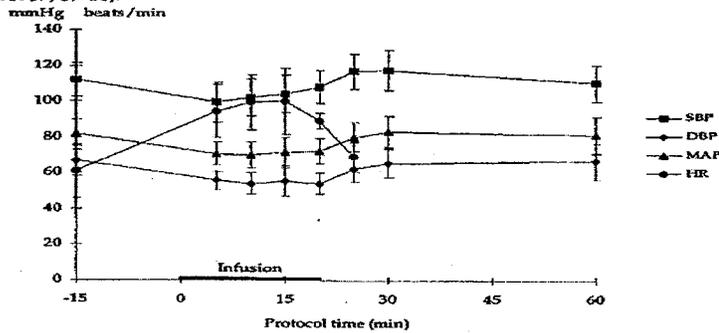


Figure 4. SBP, DBP, MAP and HR at dose 48 nmol/kg/min, mean and SD, n=3 (pat. No. 42-44).

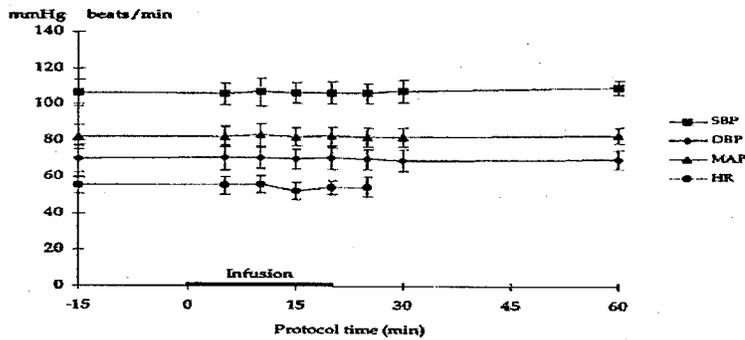


Figure 5. SBP, DBP, MAP and HR, mean and SD, placebo, n=10 (pat. Nos. 2, 6, 7, 15, 21, 23, 31, 36, 38 and 45).

Figures 6 and 7 are not depicted since they did not add to the pharmacokinetic findings.

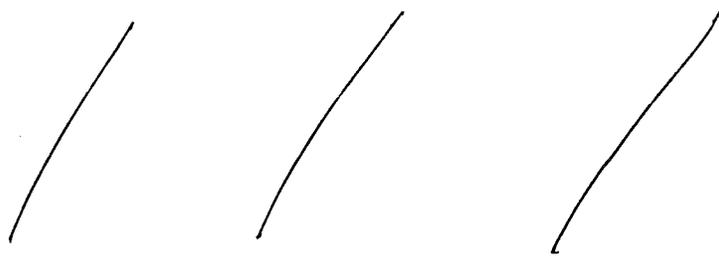


Figure 8. Blood concentration of H 324/38 vs. protocol time, dose 12 nmol/kg/min, the right panel lin scale and the left panel log scale.

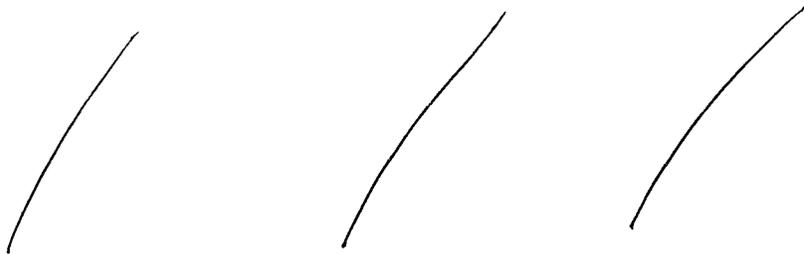


Figure 9. Blood concentration of H 324/38 vs. protocol time, dose 24 nmol/kg/min, the right panel lin scale and the left panel log scale.

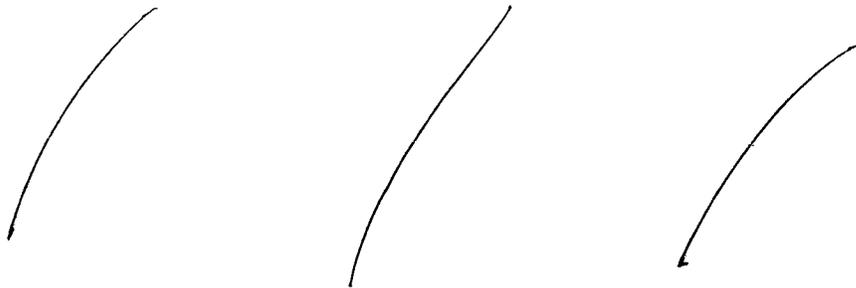


Figure 10. Blood concentration of H 324/38 vs. protocol time, dose 36 nmol/kg/min, the right panel lin scale and the left panel log scale.

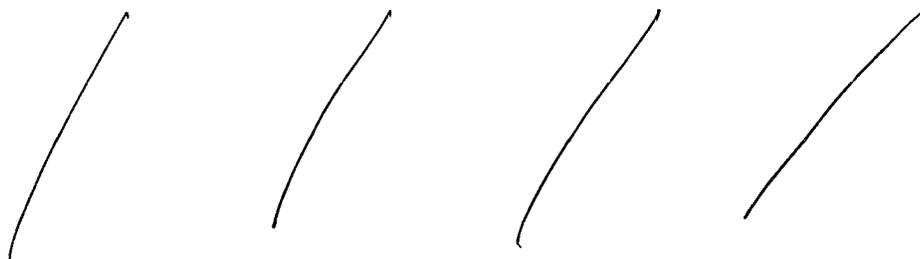


Figure 11. Blood concentration of H 324/38 vs. protocol time, dose 48 nmol/kg/min, the right panel lin scale and the left panel log scale.

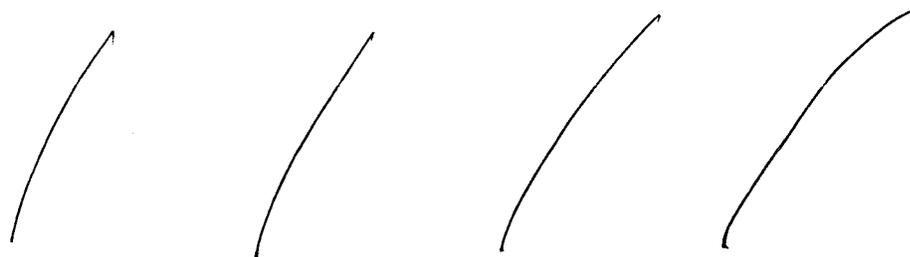


Figure 12. Blood concentration of H 152/38 vs. protocol time, dose 36 nmol/kg/min, the right panel lin scale and the left panel log scale.

The CL and C_{ss} were calculated for H 324/38 and are depicted in Figure 13. Clearance was approximately constant in the subjects receiving infusion at rates ranging from 1.5 to 48 nmol/kg/min, with a linear relationship between C_{ss} and infusion rates in the same range (Figure 14).

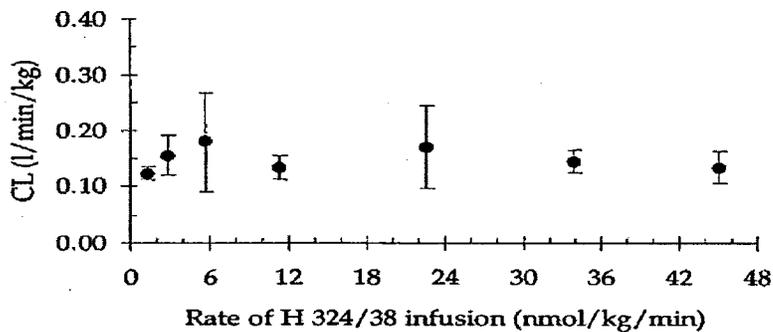


Figure 13. Clearance of H 324/38 vs. rate of infusion (actual rates of infusion are depicted). Mean and SD (1.5 nmol/kg/min $n=4$, 3 nmol/kg/min $n=4$, 6 nmol/kg/min $n=4$, 12 nmol/kg/min $n=4$, 24 nmol/kg/min $n=3$, 36 nmol/kg/min $n=4$, 48 nmol/kg/min $n=3$).

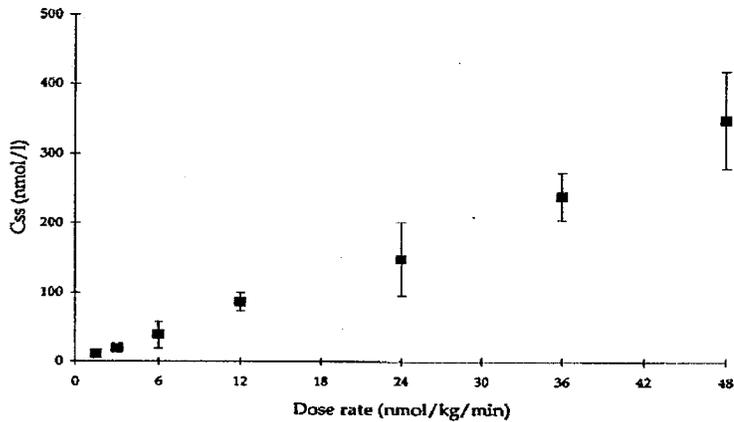


Figure 14. Blood concentration during steady state (mean of 10, 15 and 19 minutes) vs. dose rate, mean and SD (1.5 nmol/kg/min n=4, 3 nmol/kg/min n=4, 6 nmol/kg/min n=4, 12 nmol/kg/min n=4, 24 nmol/kg/min n=3, 36 nmol/kg/min n=4, 48 nmol/kg/min n=3).

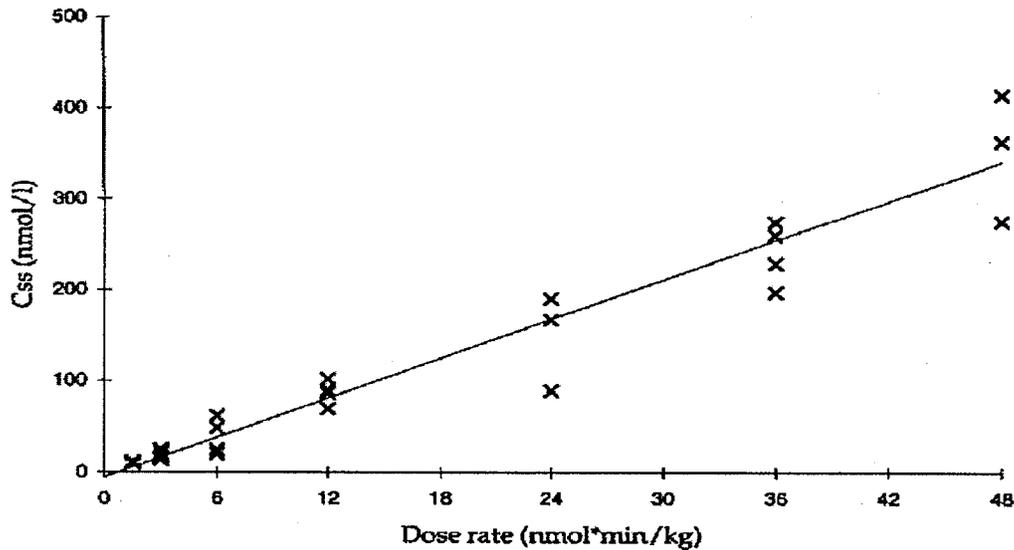


Figure 15. Blood concentration during steady state vs. dose rate calculated by a linear regression analysis.

The clearance, volume of distribution (V_{d2}) and terminal half-life of the inactive metabolite H 152/81 were about 0.03 l/h/kg, 0.4 l/kg and 8 h, respectively.

No relationship between blood concentration and MAP or DBP could be found by the Emax model.

Blood concentration (nmol/L)

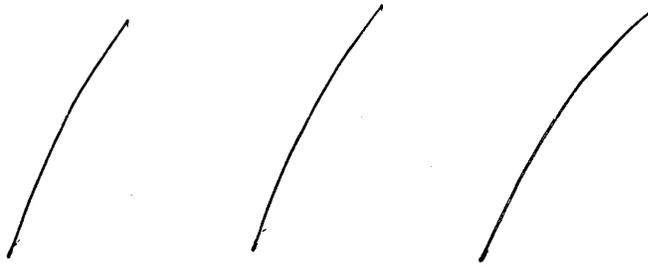


Figure 16. Relationship between blood concentration and effect expressed as reduction in the ratio MAP/HR.

SAFETY:

There were no serious adverse events. The most common adverse event was flushing.

CONCLUSIONS:

Clearance seems to be independent dose rate. A large variation in blood concentration at each dose level was observed and may be due to technical difficulties in rapid blood sampling; which was required to enable complete inhibition of blood esterases that will hydrolyse H324/38 in vitro.

REVIEWER'S COMMENT:

1. The reviewer concurs. However, summary data should have been included for the inactive metabolite (H152/81). All that was provided was individual data.

**APPEARS THIS WAY
ON ORIGINAL**

STUDY SH-SAD-0018 –PHARMACOKINETICS OF CLEVIDIPINE IN HEALTHY MALE SUBJECTS DURING AND AFTER A 24-HOUR AND A 20-MINUTE IV INFUSION.

STUDY INVESTIGATOR AND SITE:

Clinical Pharmacology
Astra Hässle AB
Department 40
Sahlgrenska Hospital
S-413 45 Göteborg, Sweden

REPORT # SH-SAD-0018

VOLUME in EDR, Section 5

STUDY DATES: March 10 – May 5, 1997

OBJECTIVES:

The **primary objectives** in this study were to:

- determine the pharmacokinetic parameters of clevidipine during and after a 20-minute and a 24-hour infusion, respectively, in healthy volunteers
- establish the dose/blood concentration (arterial and venous) - response relationships of clevidipine

The **secondary objective** was to:

- study the tolerability and safety of clevidipine following a 20-minute and a 24-hour infusion, respectively

FORMULATION:

The clevidipine infusion was administered at two different concentrations of the formulations. The formulations contained 0.3 mg/ml (Batch No. H 1153-01-01-05) and 1 mg/ml (Batch No. H 1239-01-01-02) of the substance clevidipine, respectively, in a 20 per cent lipid emulsion for (i.v.) infusion.

Both formulations were manufactured and bottled by _____
_____. The drug was packed and labelled at Astra Hässle AB, S-431 83 Mölndal, Sweden.

NOTE: a 100 mL vial was opened for each subject and had to be used within 12 hours.

Overall study design

This was a randomised, open single-dose study. Twelve (12) healthy male volunteers were planned to receive clevidipine over a period of 20 minutes or 24 hours as a constant i.v. infusion.

Four subjects were planned to receive the drug at a final infusion rate of 2 nmol/kg/min (0.91 µg/kg/min) over 24 hours - low infusion rate group. An infusion escalation was started with dose steps from 0.5 nmol/kg/min (0.23 µg/kg/min) up to 4 nmol/kg/min (1.8 µg/kg/min), each step lasting for 15 minutes. After 120 minutes the infusion was decreased to 2 nmol/kg/min (0.91 µg/kg/min), and this final infusion rate was kept constant for a total infusion time of 24 hours. See Figure 1.

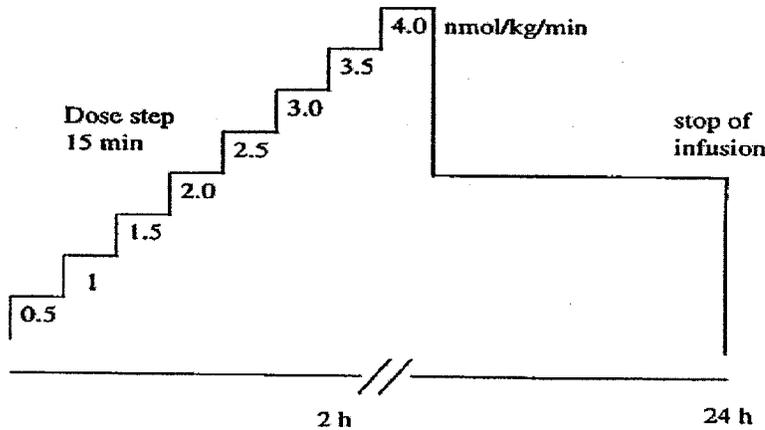


Figure 1. Study design, 24-hour infusion, final dose rate of 2 nmol/kg/min (0.91 µg/kg/min).

Four subjects were planned to receive the drug at a final infusion rate of 7 nmol/kg/min (3.2 µg/kg/min) over 24 hours - high infusion rate group. An infusion escalation was started with dose steps from 0.5 nmol/kg/min (0.23 µg/kg/min) up to 7 nmol/kg/min (3.2 µg/kg/min), each step lasting for 10 minutes. The final infusion rate was 7 nmol/kg/min (3.2 µg/kg/min), and this infusion rate was kept constant for a total infusion time of 24 hours. See Figure 2.

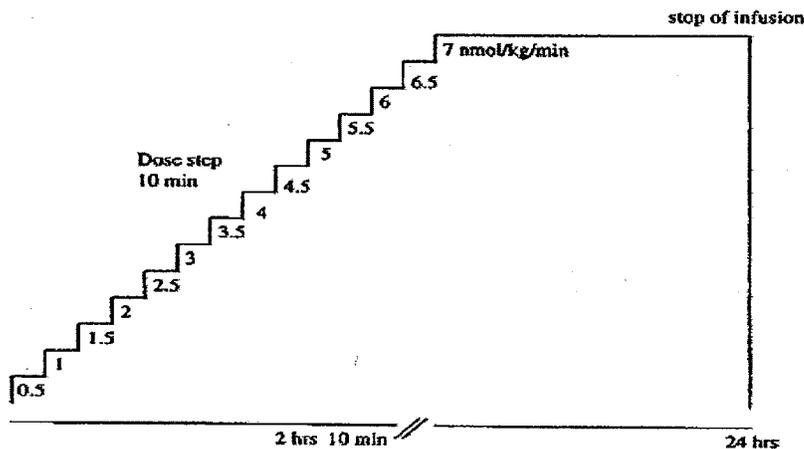


Figure 2. Study design, 24-hour infusion, final dose rate of 7 nmol/kg/min (3.2 µg/kg/min).

Four subjects were planned to receive clevidipine for 20 minutes at a dose rate of 7 nmol/kg/min (3.2 µg/kg/min) – short infusion time group.

The subjects were instructed not to have dinner later than 7 p.m. and to abstain from all food and drink after 10 p.m. the evening before the study day. Standardised food was served during the study day. If the subject needed more to drink, for his comfort, he was allowed to drink water. The amount of water was recorded in the CRF.

Neither coffee, tea, coke, alcohol nor over-the-counter drugs were permitted for two days before the study day. The subjects were not allowed to take any prescribed medicine for two weeks before the study commenced. Tobacco (smoking, snuff, nicotine chewing-gum or nicotine plaster) was not allowed during the days at the laboratory or during the fasting period before drug intake.

ANALYTICAL METHODS:

The samples were analysed for clevidipine by gas chromatography-mass-spectrometry (BA-286) and the metabolite H 152/81 by liquid chromatography with fluorescence detection (BA-272) at Astra Hässle AB, Mölndal, Sweden. The limit of quantitation (LOQ) was 0.5 nmol/L for clevidipine and 50 nmol/L for the metabolite. Values below LOQ were regarded as to non-determinable (-). However, during the course of the study the sensitivity to analyse clevidipine was improved, so that the LOQ was set to 0.1 nmol/l. Consequently, all blood samples below LOQ drawn after the final dose rate was reached were re-analysed using the improved method. These values were used both when calculating the pharmacokinetic parameters and when performing the statistical analysis.

Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
GC-MS	H 324/38	0.5-350	See 1312-424	22%-12.0% (low standards) 0.9%-5.4% (high standards)	98.5% (87.0-105.4%)	Linear ^B	0.5 nmol/L ^C

Limit of quantification

The limit of quantification (LOQ), was 0.5 nmol/l. LOQ is the lowest concentration where, routinely, precision is better than 20 % and accuracy within 85-115 %. LOQ for the modified analytical method was 0.1 nmol/l for clevidipine.

PHARMACOKINETICS, PHARMACODYNAMICS AND STATISTICAL ANALYSIS:

H 152/81:

Mean blood concentrations of H 152/81 were determined.

Lower Dose Level:

At the lower dose level, blood samples for determination of clevidipine were drawn from cannulas in a forearm vein at baseline and at dose steps 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 nmol/kg/min at time points: 3, 10 and 14 minutes after the start of each dose step. Blood samples were also drawn from the radial artery at dose steps 1, 2, 3 and 4 nmol/kg/min at the same time points. After the last sample at dose step 4 nmol/kg/min, the infusion rate (120 minutes after start of infusion) was decreased to 2 nmol/kg/min and blood samples from both the vein and artery catheters were drawn at 122, 124, 127, 130, 135, 140, 145, and 150 minutes after the start of infusion.

The radial artery cannula was then withdrawn. Additional blood samples were drawn from the cannula in the forearm vein at the following time points: 3, 4, 8, 12, 16 and 20 hours after the start of infusion.

At 23 hours after the start of infusion a new cannula was inserted into the radial artery. Blood samples (two different tubes) for determination of both clevidipine and the metabolite H 152/81 were drawn from the forearm vein at the following time points: 23 hours and 30 mins, 23 hours and 45 mins and 23 hours and 59 mins after the start of infusion. Blood samples for determination of clevidipine were also drawn from the radial artery at the same time points. After 24 hours the infusion was stopped. The following blood samples were then drawn from the radial artery and forearm vein at: 0.5, 1, 1.5, 2, 3, 5, 8, 12, 17, 25, 35, 45, 60 minutes after the end of infusion. After this the arterial line was withdrawn. Additional blood samples from the vein were drawn after 75, 90 and 120 minutes.

Higher Dose Level:

At the higher dose level, blood samples for determination of clevidipine were drawn from cannulas in a forearm vein at baseline and at dose steps 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5 and 7 nmol/kg/min at time points: 7 and 9 minutes after the start of each dose step. Blood samples were also drawn from the radial artery at dose steps 1, 2, 3, 4, 5, 6 and 7 nmol/kg/min at the same time points. After the 9-minute sample (2 hours and 19 minutes after the start of infusion) at dose step 7 nmol/kg/min, an additional blood sample was drawn at 2.5 hours after the start of infusion.

Thereafter the procedure for blood sampling was the same in both 24 hours infusions, but additional blood samples from the vein were drawn after 150, 180 and 240 minutes after the end of infusion at the higher dose level.

20-Minute-Infusion:

Before the start of the 20-minute-infusion a baseline blood sample was drawn from the forearm vein. After the start of the infusion blood samples were drawn from both the radial artery and the forearm vein at the following time points: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 and 19.5 minutes after the start of infusion. After the end of infusion, blood samples were collected at 20.5, 21, 21.5, 22, 23, 24, 25, 27, 29, 30, 32, 35, 37, 40, 45, 50, 55, 60, 65, 70 and 80 minutes after the start of infusion. Thereafter the catheter in the radial artery was withdrawn and blood samples from the vein were collected at 90 and 120 minutes.

Pharmacokinetic parameters

The following pharmacokinetic parameters of clevidipine were estimated for each patient:

The fractional constants A, B and C, blood clearance (CL_b), half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$), initial volume of distribution (V_1) and volume of distribution at steady state (V_{ss}).

Statistical Analysis

An open two- or three-compartment model was fitted to each individual's blood concentrations of clevidipine during and after the infusion of clevidipine. The actual sampling times were used in the analyses. Weighted least squares non-linear regression analysis was used to fit the model to the data of each subject.

Pharmacodynamics, pharmacokinetics and laboratory values

All pharmacokinetic, pharmacodynamic and laboratory values were summarised using descriptive statistics. Moving averages were used in plotting MAP and HR.

Pharmacodynamics:

The relationships between blood concentrations of clevidipine and hemodynamic effect (MAP, HR or MAP/HR, expressed as the percentage (%) reduction from baseline value) were analysed by visual inspections of the plots of the effect *vs* arterial and venous blood concentrations, respectively, after the short infusion of clevidipine.

An effect compartment model (Link-model) was fitted to each individual's reduction in MAP/HR from baseline value after the short infusion by non linear regression analysis (WinNonlin®). The pharmacokinetic model was first fitted to the arterial blood concentrations and then fixed and used to drive the dynamics. The sigmoid E_{max} model was used to describe the arterial blood concentration-effect relationship. The following pharmacodynamic parameters were estimated for each subject: The maximal effect (E_{max}), the concentration for 50 % maximal effect (EC_{50}), the steepness of the curve (γ), and the parameter used to characterise the delay between the peak blood concentration and peak effect ($t_{1/2}k_{e0}$)

RESULTS:

NUMBER OF PATIENTS

Fourteen subjects were administered clevidipine of which 12 were possible to evaluate. Four subjects received the low infusion rate, 4 received the high infusion rate and 4 received the short time infusion.

All subjects were Caucasian.

Two of the subjects were occasional smokers, and one of them was a former smoker. Two of the subjects used snuff.

The subjects were randomised to three different treatment groups. When a subject discontinued or was found not evaluable, the subject was replaced with a new subject who received the first available subject number within the same treatment group. Subjects Nos. 1 and 8 were replaced with subject Nos. 14 and 16, respectively.

Subject No. 1 received the clevidipine infusion but will be excluded from the analysis because the — recording did not work properly and difficulty in inserting the arterial catheter caused the subject pain. In addition, the body weight of the subject was below the inclusion criteria.

Subject No. 08 (male, aged 33), with no relevant medical history, randomised to the low infusion rate of clevidipine experienced transient dizziness, nausea and vomiting after 1 hour's constant infusion (total infusion time; 3 h.), at a dose rate of 0.90 µg/kg/min, which resolved during the infusion. However, it was decided to stop the infusion with clevidipine due to the latter two conditions.

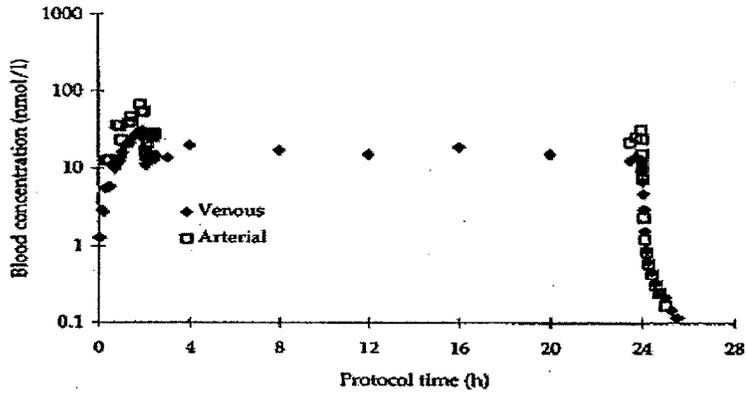
Treatment	Subject
Low infusion rate	1*, 5, 8*, 11, 14, 16
High infusion rate	2, 4, 9, 12
Short infusion time	3, 6, 7, 10

* Only included in the safety analysis.

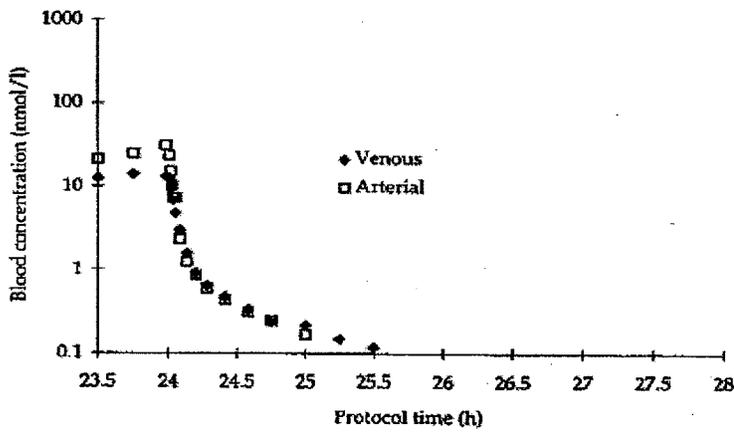
Pharmacokinetic Results:

Low Infusion

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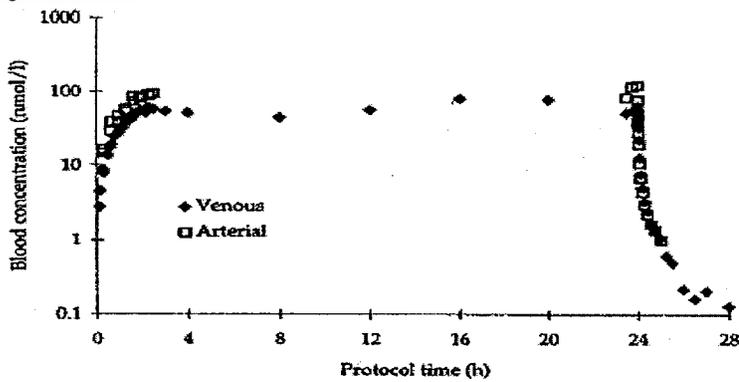


Mean conc. of clevidipine in arterial and venous blood vs. protocol time above (n=4).

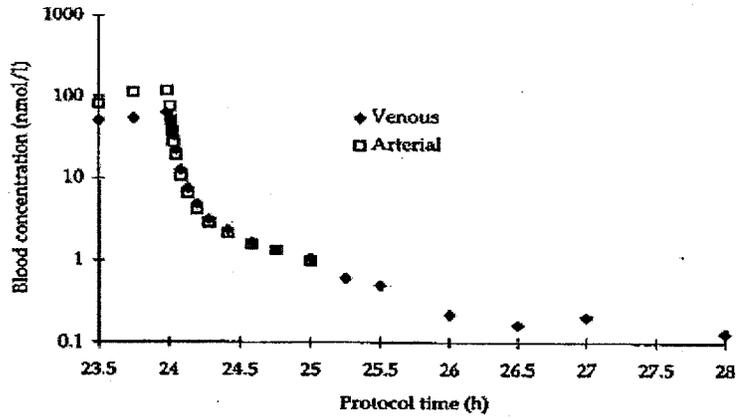


Mean terminal blood conc. of clevidipine in arterial and venous blood vs. protocol time using an expanded scale above (n=4).

High Infusion



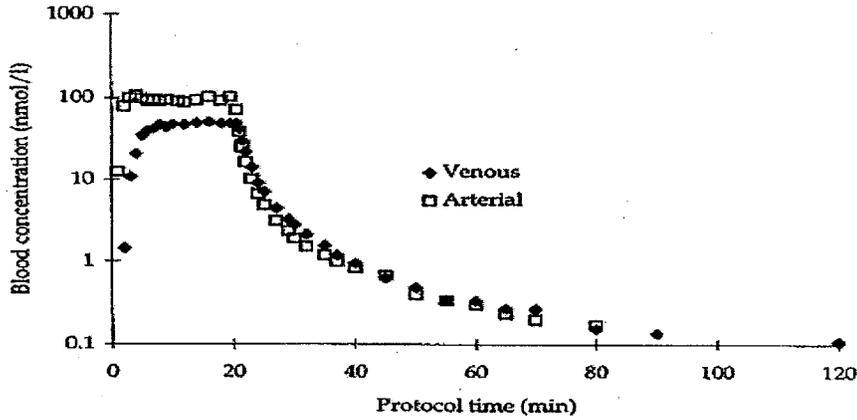
Mean conc. of clevidipine in arterial and venous blood vs. protocol time above (n=4).



Mean terminal blood conc. of clevidipine in arterial and venous blood vs. protocol time using an expanded scale above (n=4).

Short Infusion

Below is the mean conc. Of clevidipine in arterial and venous blood vs. protocol time (n=4).



Venous blood descriptive PK statistics:

		Low infusion rate	High infusion rate	Short infusion time
Cl (l/min/kg)	Mean	0.139	0.104	0.147
	SD	0.043	0.010	0.032
	Median	0.136	0.109	0.150
V ₁ (l/kg)	Mean	0.45	0.31	0.39
	SD	0.21	0.15	0.11
	Median	0.47	0.28	0.38
V _{ss} (l/kg)	Mean	0.81	0.61	0.67
	SD	0.41	0.20	0.08
	Median	0.83	0.62	0.69
t _{1/2α1} (min)	Mean	2.1	1.7	1.6
	SD	0.4	1.0	0.4
	Median	2.1	1.6	1.6
t _{1/2β1} (min)	Mean	.*	9.5	4.3
	SD	.	2.7	0.5
	Median	.	9.8	4.4
t _{1/2β2} (min)	Mean	37.5	59.1	25.6
	SD	9.6	9.5	12.1
	Median	40.8	55.8	24.1

Arterial blood descriptive PK statistics:

		Low infusion rate	High infusion rate	Short infusion time
Cl (l/min/kg)	Mean	0.072	0.066	0.070
	SD	0.007	0.005	0.006
	Median	0.072	0.068	0.072
V ₁ (l/kg)	Mean	0.10	0.08	0.07
	SD	0.02	0.02	0.01
	Median	0.10	0.09	0.07
V _{ss} (l/kg)	Mean	0.20	0.22	0.14
	SD	0.03	0.08	0.02
	Median	0.20	0.20	0.13
t _{1/2α1} (min)	Mean	0.7	0.8	0.6
	SD	0.1	0.3	0.1
	Median	0.7	0.7	0.6
t _{1/2α2} (min)	Mean	2.2	2.3	2.3
	SD	0.2	0.1	1.0
	Median	2.2	2.3	2.0
t _{1/2αz} (min)	Mean	18.4	21.7	16.3
	SD	2.8	1.6	2.8
	Median	18.0	21.1	15.6

Metabolite H152/81

Mean blood conc. Values during the low infusion is below:

Subject	Protocol time (min)		
	23.5	23.75	23.98
N	4	4	4
Mean	3225	3220	3213
SD	264	257	236
Min	2980	3020	3050
Median	3165	3140	3125
Max	3590	3580	3550

Mean blood conc. Values during the low infusion is below:

Subject	Protocol time (min)		
	23.5	23.75	23.98
N	4	4	4
Mean	10413	10218	10200
SD	1893	1718	1617
Min	8680	8590	8740
Median	10435	10240	10230
Max	12100	11800	11600

A three-compartment model was fitted to the individual blood concentrations. However, for the venous blood concentrations during and after the low infusion rate, a two-compartment model was fitted to the data.

A clear difference in arterio-venous blood concentrations was obtained for blood concentrations during ongoing infusion. The arterial concentration was approximately twice as high as the venous blood concentration following constant infusion to steady state blood levels. After the clevidipine infusion was stopped, the blood concentrations declined rapidly, and after a short time the arterial and venous blood concentrations merged into a common concentration-time profile.

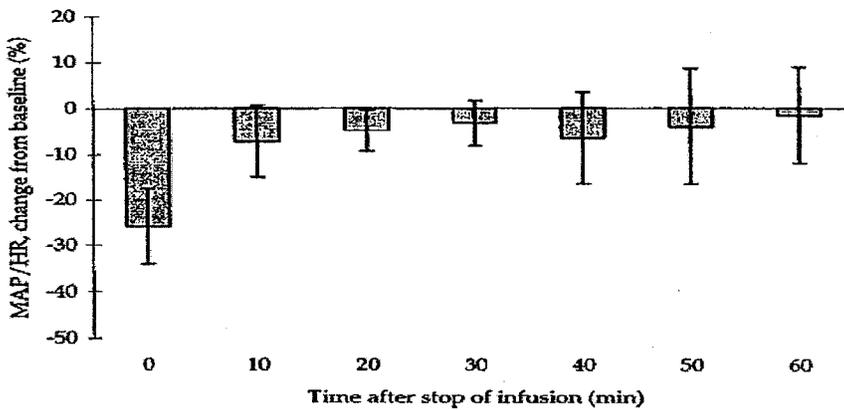
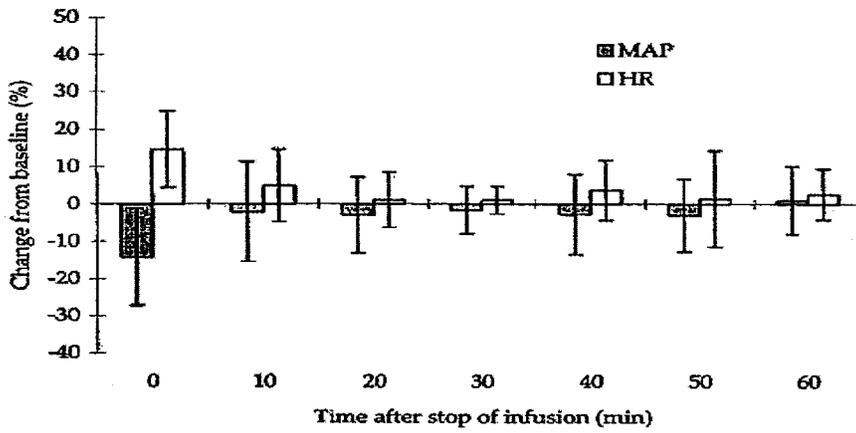
The clearance and volume of distribution calculated from venous and arterial blood concentrations were different. The clearance value obtained from arterial blood concentrations was about half of that obtained from venous blood concentrations. The volume of distribution determined from arterial blood concentrations was lower than the corresponding volume determined from venous blood concentrations. The half-lives determined from venous blood concentrations were somewhat longer in the venous blood. At least to some extent this was probably an effect of that blood samples were drawn over a longer period of time. Both venous and arterial blood concentrations predict a terminal half-life longer than has previously been reported (1,2). When transforming the data to a unit i.v. bolus dose, the magnitude of the extrapolated terminal intercept is less than 0.3% of the initial concentration, which indicates a negligible contribution of this phase to reach steady state. This is in agreement with the finding in this study where the arterial blood concentration is close to steady state within 2 minutes. The differences between arterial and venous blood concentrations indicate an extensive and very rapid metabolism of clevidipine in the blood and in the tissues.

Pharmacodynamic Results:

Low Infusion

Below is the change in % of baseline in MAP and HR, mean \pm SD at and after the end of infusion (n=4, baseline MAP=90.9 \pm 5.0, baseline HR=59.4 \pm 2.4).

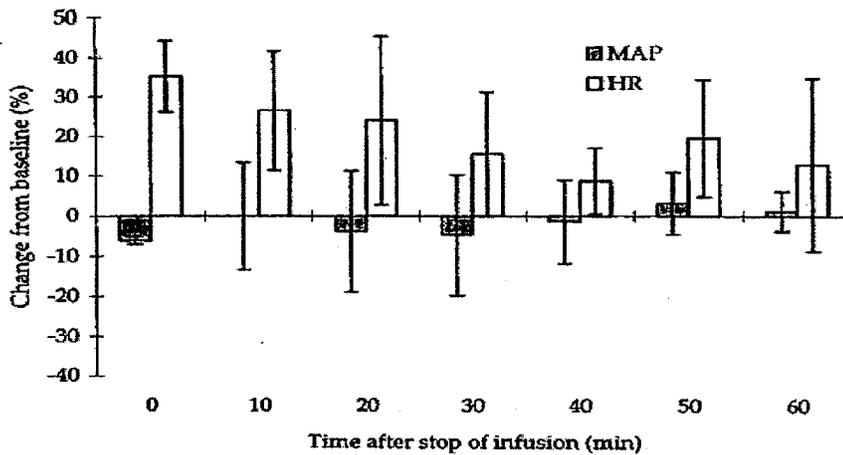
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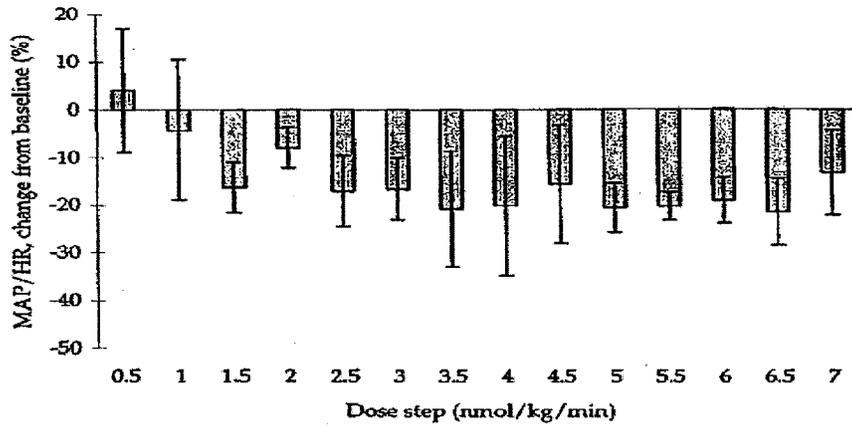


Above is the change in % baseline in MAP/HR, mean \pm SD at and after the end of the infusion (n=4, baseline MAP/HR=1.6 \pm 0.1).

High Infusion

Change in % of baseline in MAP and HR, mean \pm SD at and after the end of infusion (n=4, baseline MAP=85.3 \pm 12.7, baseline HR=56.9 \pm 11.3) below:

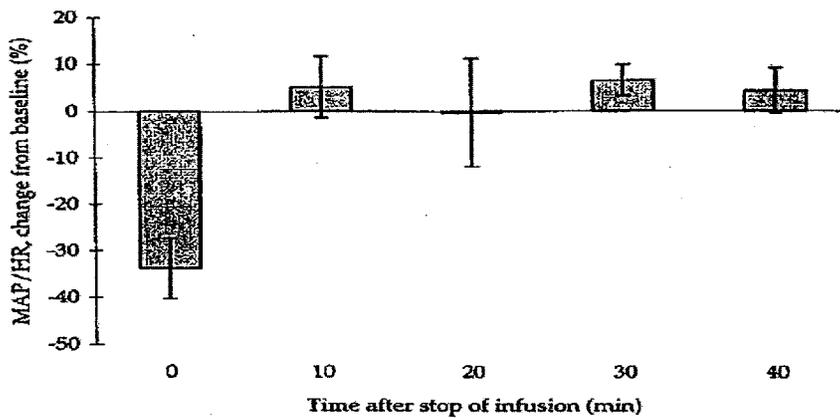
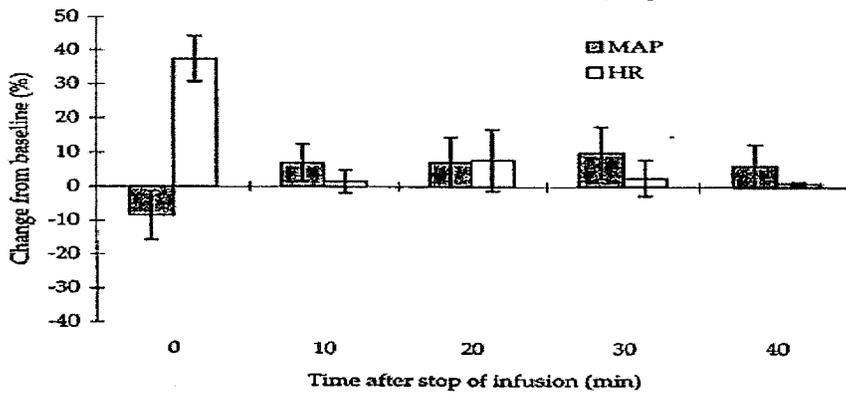




Above is the change in % of baseline in MAP/HR, mean \pm SD at and after the end of infusion (n=4, baseline MAP/HR=1.4 \pm 0.2).

Short Infusion (20 minutes)

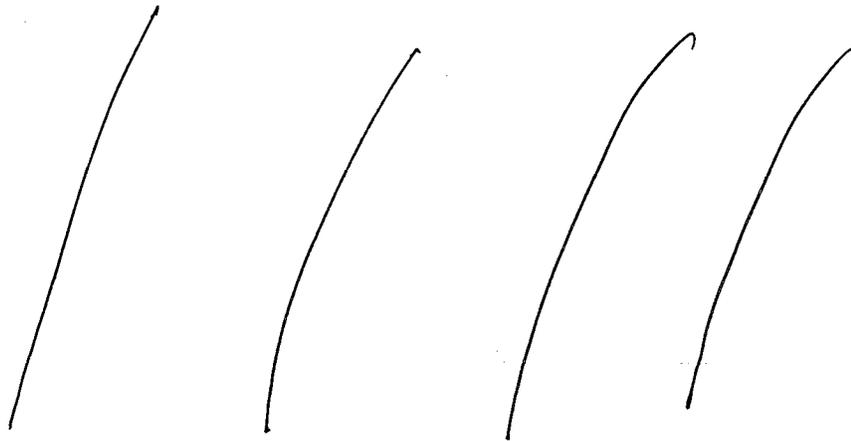
Change in % of baseline in MAP and HR, mean \pm SD at and after the stop of the short infusion (n=4, baseline MAP=88.6 \pm 10.3, baseline HR=52.9 \pm 3.8) depicted below:



Above is the change in % of baseline in MAP/HR, mean \pm SD at and after the infusion (n=4, baseline MAP/HR=1.7 \pm 0.1).

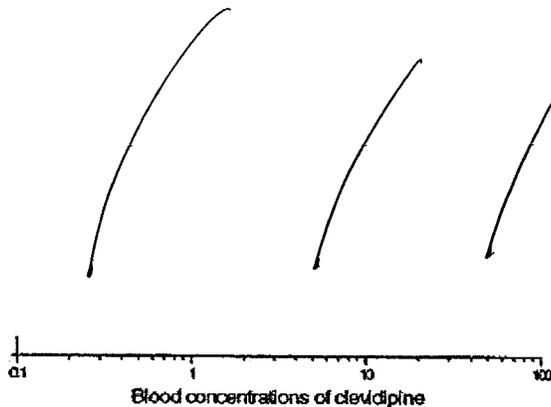
PK/PD

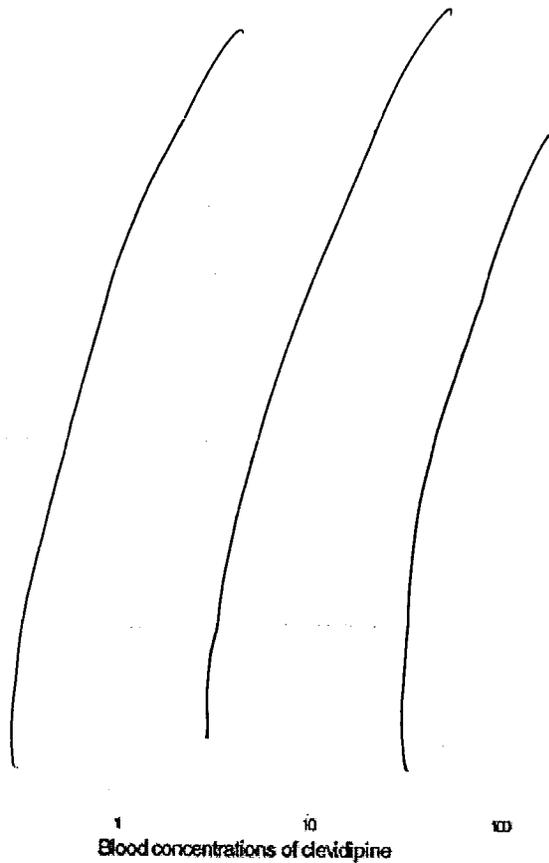
Arterial and Venous blood conc. Of CLE and the PD responses (MAP, HR, and MAP/HR) during and after the short infusion for subject #3.



The figure shows that the time course of the arterial blood concentrations are in close agreement with the onset of responses, with a very short time delay between the maximal arterial blood concentrations and the maximal responses. After the clevidipine infusion was stopped, the arterial and venous blood concentrations declined rapidly, with a more rapid initial decline of the arterial blood concentrations, and after a short time the difference between the arterial and venous concentration was small.

The responses (MAP, HR and MAP/HR) expressed as the percentage change from baseline values vs arterial and venous blood concentrations of clevidipine are shown in the three figures below. The blood concentration is plotted in time order, according to the directions shown by the arrows, and the numbers refer to the time after the start of infusion. The infusion of clevidipine lasted for 20 minutes, and each dynamic observation is the average from the recorded effect 20 seconds before and 20 seconds after each collection of blood.





No determination of the reduction in systemic vascular resistance (SVR) was made since no measurements of cardiac output (CO) were performed. Therefore, the change in the ratio MAP/HR was used as an indirect measurement of the SVR. There was a close correlation between the changes in MAP/HR and the arterial blood concentrations with a short delay between the concentrations and effect, during and after the short infusion. Plotting the effect *vs* arterial blood concentrations in time order resulted in an anticlockwise hysteresis, indicating that an effect-compartment model could be used to account for the delay in the onset of the response. The $t_{1/2k_{ew}}$, the parameter used to characterise the delay between the peak blood concentration and peak effect by means of a theoretical effect compartment, was determined to 1.1 minutes, when using MAP/HR as a measure of effect. The maximal reduction in MAP/HR (E_{max}) was 42 per cent and the arterial blood concentration producing 50 per cent of maximal effect (EC_{50}) was 40 nmol/l.

The time for maximum effect on MAP/HR was also determined by visual inspection of the change *vs* time, after the short infusion of clevidipine, and found to be between 3 and 5 minutes. The offset of this effect was rapid, less than 10 minutes. The return of the effect to baseline values after the 24-hour infusion was difficult to determine. However, after 30 minutes the effect on MAP/HR were restored to 90 per cent of the initial baseline value after infusion at the low dose rate. The effect on MAP/HR was restored to 70 per cent of the initial baseline value within 40 minutes after the high dose rate.

SAFETY:

The total amount of blood drawn from each subject during the study did not exceed 250 ml (including health examination and follow-up).

Summary of AEs during study drug infusion:

Drug	During infusion Clevidipine		
	low rate (n=6)	high rate (n=4)	short time (n=4)
Any AE	6	4	3
Serious AE	0	0	0
Drug stopped due to AE	1	0	0

Summary of AEs during follow-up after study drug infusion:

Follow up after	Clevidipine		
	low rate (n=6)	high rate (n=4)	short time (n=4)
Any AE	4	1	2
Serious AE	0	0	0

There were no serious AEs. Flushing and headache was the most reported AE.

**APPEARS THIS WAY
ON ORIGINAL**

CONCLUSIONS:

From this study in healthy volunteers with clevidipine the main results and conclusions are:

- a clear arterio-venous blood concentration difference exists during ongoing infusion
- the differences in the derived pharmacokinetic parameters after a short and long term infusion are small
- there is a close correlation between the arterial blood concentrations and dynamic responses during and after the short infusion of clevidipine
- arterial blood levels were at steady state at approximately 2 minutes
- the maximal reduction in MAP/HR after a short infusion is 42 per cent and the concentration producing 50 per cent of maximal effect is 40 nmol/l
- the delay between arterial peak blood concentration and peak effect (MAP/HR) is 1.1 min ($t_{1/2 k_{e0}}$)
- clevidipine was safe and well tolerated at the dose rates studied

REVIEWER'S COMMENT:

The reviewer concurs.

**APPEARS THIS WAY
ON ORIGINAL**

STUDY SH-SAD-0010 – THE PHARMACOKINETICS AND PHARMACODYNAMICS OF CLEVIDIPINE IN PATIENTS WITH ESSENTIAL HYPERTENSION. A PLACEBO CONTROLLED, SINGLE BLIND STUDY.

STUDY INVESTIGATOR AND SITE:

///

REPORT # SH-SAD-0010

EDR VOLUME 5

STUDY DATES: June 15 – October 31, 1996

OBJECTIVES

To investigate the pharmacokinetic parameters of clevidipine and its enantiomers, H 190/90 and H 190/91, in moderately hypertensive patients during the steady-state and post-infusion periods of clevidipine administration. Furthermore, the dose rate-haemodynamic response and the blood concentration- haemodynamic response relationships were studied as well as the tolerability of the drug.

Formulation:

The clevidipine stock formulation consisted of 1 mg/ml of the substance clevidipine in a 20% lipid emulsion with the same ingredients as Intralipid® 20%, which was used as placebo solution.

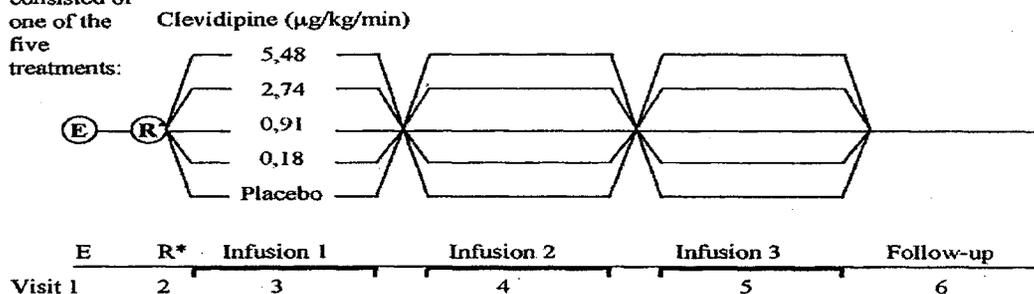
Clevidipine: H 1153-01-01-02, Placebo: H 0662-02-02-02

Clevidipine and placebo were manufactured and bottled by _____
Clevidipine was provided in 100 ml glass bottles.

STUDY DESIGN

In this randomised, placebo-controlled, single-blind, five-arm, three-way cross-over study in essential hypertensive patients, each patient received three out of five possible infusion rates of clevidipine or placebo on three separate study days. The target dose rates for clevidipine were 0.18, 0.91, 2.74 and 5.48 µg/kg/min, respectively. Five days after the last study day, the patient visited the clinic for follow-up.

Each period consisted of one of the five treatments:



* Randomisation seated SBP/DBP ≥ 160/100mmHg

E=enrolled

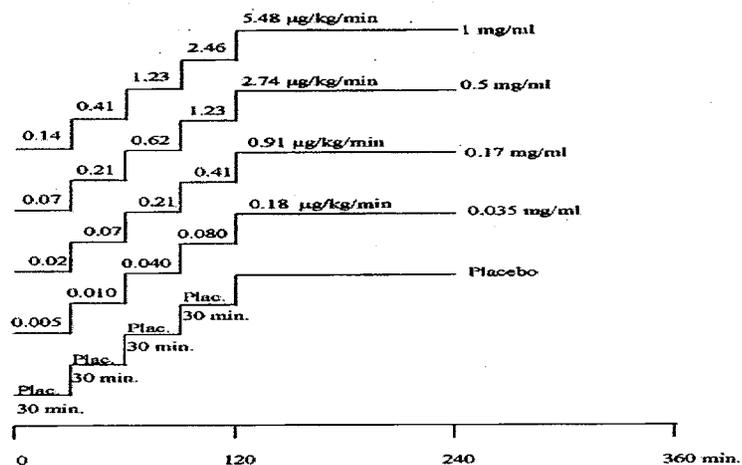
Cross-over was done within 2 to 7 days of end of the following treatment arm.

Each infusion assessment consisted of three different phases with frequent blood sampling and dose-effect recording: i.e. firstly a dose titration phase of 120 minutes, secondly the target dose rate phase of 120 minutes and, after the infusion was stopped at 240 minutes, a follow-up phase of a further 120 minutes, i.e. a total assessment time of 360 minutes.

Twenty-three patients with essential hypertension, aged 45 to 73 years, were enrolled into the study, and twenty-one patients, 16 male and 5 female, were randomised.

Dosage of Clevidipine for each titration step ($\mu\text{g}/\text{kg}/\text{min}$). Each titration step of 30 min. duration.

Concentration (mg/ml) of Clevidipine solution used for each dosage arm.



ANALYTICAL METHODS:

The samples were analysed for the enantiomers H 190/90 and H 190/91 by a liquid chromatography-mass spectrometry method (BA-253) at Astra Hässle AB, Mölndal, Sweden. The limit of quantification (LOQ) was 0.5 nmol/l for each enantiomer. Values below LOQ were set to non-determinable (-). In cases where two consecutive samples, taken after steady state had been reached, indicated blood concentrations below the limit of quantitation, the following samples were not analysed. The clevidipine concentrations were calculated as the sum of the enantiomers.

Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
LC-MS	H 190/91	0.3-700	See 1312-378	1.7%-18.1% (low standards) 0.9%-3.2% (high standards)	97.1% (92.8-104.0%)	Linear ^e	0.5 nmol/L ^c
	H 190/90		See 1312-378	1.6%-18.5% (low standards) 1.2%-2.8% (high standards)	95.9% (90.7-101.0%)		

PHARMACOKINETICS, PHARMACODYNAMICS, AND STATISTICAL ANALYSIS:

Pharmacokinetics

Venous blood samples for determination of clevidipine and its enantiomers were collected at the following times:

Prior to infusion and at 135, 150, 165, 180, 200, 220 and 239 min during constant rate infusion and at times 241, 241.5, 242, 243, 245, 252, 256, 260, 270 and 300 min after the start of infusion.

In order to investigate whether steady state could be concluded, the relative difference between the estimated value at 240 minutes and the estimated values at 150 and 135 minutes, respectively, was calculated: to be able to conclude steady state, the true relative difference should be within $\pm 10\%$ (0.10).

A one-compartment model was fitted to each individual's blood concentrations obtained during the target dose rates of 0.18 and 0.91 $\mu\text{g}/\text{kg}/\text{min}$, and a two-compartment model was fitted to each individual's blood concentrations obtained after the target dose rates of 2.74 and 5.48 $\mu\text{g}/\text{kg}/\text{min}$, respectively. An additional non-compartmental analysis was also performed to determine blood clearance (CL_b) and the steady state concentration of clevidipine (C_{ss}).

Pharmacodynamics

The maximal achievable effect of clevidipine (E_{max}) on MAP or on MAP/HR, both expressed as the percentage (%) reduction from the baseline value, and the blood concentration and dose rates mediating half the maximal effect (EC_{50} and ED_{50}) were estimated from pooled data obtained from target dose rates (C_{ss}) of study drug by fitting an E_{max} model to the data. The following equation was used:

$$E = \frac{E_{max} \times C_{ss}^{\gamma}}{EC_{50}^{\gamma} + C_{ss}^{\gamma}}$$

The shape factor, γ , was set to 1, since neither statistical criteria (Akaike or Schwartz) nor visual inspection gave priority to a more complex sigmoid E_{max} model. The computer program WinNonlin[®] (ver. 1.1, Scientific Consulting Inc., Apex, North Carolina, U.S.) was used.

Statistics

It was calculated that, with 12 measurements of the slope (beta parameter) from the linear regression of the blood concentrations for each dose level, it would be possible to demonstrate steady state. The calculation was based on an expected standard deviation for beta of 0.22. This value was a bootstrap estimate of the standard deviation based on preliminary data from a study in healthy volunteers (3). The expected loss of patients at each dose level was 8%, the expected beta value was zero, and the significance level was set to 0.05.

RESULTS:

Twenty-one patients, 16 male and 5 female, were randomised into the study. They all had a blood pressure $\geq 160/100$, 1-4 weeks after their ordinary antihypertensive therapy was had been withdrawn. Two patients never received the study drug at the highest dose rate; one was discontinued beforehand, and infusion was stopped in the other because of a rapid decline in SBP.

Outcome of treatment allocation:

Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	Patient no.
placebo	3, 4, 6, 7, 10, 11, 13, 14, 15, 17, 19, 20, 27
0.18	1, 3, 5, 6, 8, 9, 12, 14, 15, 17, 18, 20
0.91	1, 2, 3, 4, 9, 10, 11, 12, 14, 16, 18, 19, 27
2.74	1, 2, 5, 7, 8, 10, 13, 15, 16, 18, 19, 20, 27
5.48	2, 4, 5, 6, 7, 8, 9, 11, 12, 13, 16, 17

Patient no. 11 had the clevidipine emulsion at visit 4 incorrectly diluted to 0.5 mg/ml (intended dose rate; 2.74 $\mu\text{g}/\text{kg}/\text{min}$ instead of 1 mg/ml (intended dose rate; 5.48 $\mu\text{g}/\text{kg}/\text{min}$). Patient no. 1 had the clevidipine emulsion at visit 5 incorrectly diluted to 0.07 mg/ml (intended dose rate; 0.36 $\mu\text{g}/\text{kg}/\text{min}$) instead of 0.035 mg/ml (intended dose rate; 0.18 $\mu\text{g}/\text{kg}/\text{min}$).

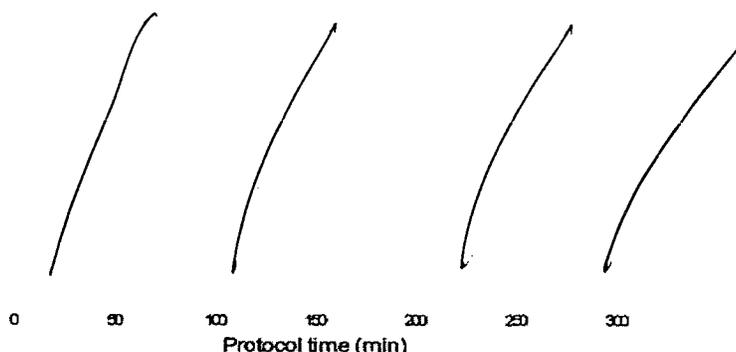
Patient no 5 experienced AEs during the follow-up phase (120 min.) after the study drug infusion at the dose rate 2.74 $\mu\text{g}/\text{kg}/\text{min}$. The decision was taken not to administer the drug at the highest dose rate for this patient. For patient no. 9, the infusion of clevidipine 5.48 $\mu\text{g}/\text{kg}/\text{min}$ was stopped as the SBP declined rapidly during study drug infusion.

Pharmacokinetics:

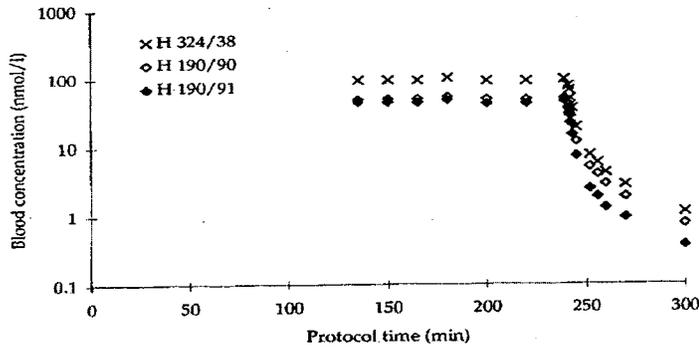
Below:

Blood concentrations of the enantiomers and of clevidipine in patient no. 5.

The dose rate during the target infusion rate was 2.74 $\mu\text{g}/\text{kg}/\text{min}$. The solid lines show the fit of the two-compartment model to the data.



The mean blood concentrations of clevidipine did not increase during the 15 minutes following achievement of target dose rates. Therefore, steady state was assumed to be reached 15 minutes after initiation of the target dose rates (below).



Mean blood concentrations (log scale) of clevidipine and its enantiomers vs Above: protocol time for the dose rate of 5.48 $\mu\text{g}/\text{kg}/\text{min}$.

It was not possible to conclude steady state in accordance with the selected criteria defined in the protocol, as none of the confidence intervals was entirely within the interval (-0.10; 0.10) for the standardised variable. In spite of this, the blood levels recorded during infusion of the target rate were used in the calculation of the mean C_{ss} and CL_b by the non-compartmental analysis.

Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	Estimate	Lower	Upper	p-value
0.18	0.1219	-0.0127	0.2565	0.1333
0.91	-0.0894	-0.2204	0.0415	0.2499
2.74	-0.0792	-0.2110	0.0526	0.3088
5.48	-0.0121	-0.1606	0.1364	0.8883

Non-compartmental analysis for C_{ss} and CL_b

Dose rate 0.18 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

Dose rate 0.91 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	0.09*	0.09*	0.18	0.46*	0.46*	0.91
R_o ($\mu\text{g}/\text{kg}/\text{min}$)						
Mean	0.22	0.22	0.44	0.97	0.97	1.95
C_{ss} (nmol/l)						
Mean	2.4	2.2	4.6	9.9	9.2	19.4
SD	1.4	1.2	2.5	3.4	3.4	6.4
Median	2.0	1.9	3.9	9.4	9.1	18.5
CL_b (l/min/kg)						
Mean	0.102	0.112	0.107	0.111	0.124	0.112
SD	0.037	0.043	0.040	0.046	0.056	0.039
Median	0.098	0.104	0.101	0.105	0.108	0.106

Dose rate 2.74 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

Dose rate 5.48 $\mu\text{g}/\text{kg}/\text{min}$ (N=8)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	1.37*	1.37*	2.74	2.74*	2.74*	5.48
R_o ($\mu\text{g}/\text{kg}/\text{min}$)						
Mean	2.91	2.91	5.83	6.00	6.00	11.99
C_{ss} (nmol/l)						
Mean	25.5	24.0	49.5	49.7	44.3	93.9
SD	6.2	6.3	12.5	14.4	13.6	27.7
Median	25.0	22.7	47.9	45.1	44.7	89.8
CL_b (l/min/kg)						
Mean	0.121	0.129	0.125	0.130	0.149	0.138
SD	0.030	0.034	0.031	0.037	0.053	0.043
Median	0.116	0.125	0.119	0.134	0.137	0.135

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

Pharmacokinetic parameters of clevidipine and its enantiomers calculated compartmental analysis (one-compartment for 0.18 and 0.91 $\mu\text{g}/\text{kg}/\text{min}$ and two-compartment for 2.72 and 5.48 $\mu\text{g}/\text{kg}/\text{min}$).

Dose rate 0.18 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

Dose rate 0.91 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	0.09*	0.09*	0.18	0.46*	0.46*	0.91
CL_b (l/min/kg)						
Mean	0.096	0.104	0.099	0.107	0.112	0.109
S.D	0.036	0.041	0.038	0.032	0.039	0.035
Median	0.092	0.097	0.094	0.104	0.107	0.109
V_{ss} (l/kg)						
Mean	0.46	0.47	0.44	0.60	0.43	0.48
S.D	0.29	0.35	0.32	0.28	0.31	0.29
Median	0.41	0.41	0.38	0.53	0.32	0.35
$t_{1/2}$ (min)						
Mean	3.3	3.1	3.1	3.8	2.5	2.9
S.D	1.6	1.5	1.6	1.0	1.1	1.0
Median	2.8	2.8	2.5	2.8	2.3	2.6

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

Below:

Pharmacokinetic parameters of clevidipine and its enantiomers calculated by compartmental analysis (one-compartment for 0.18 and 0.91 $\mu\text{g}/\text{kg}/\text{min}$ and two-compartment for 2.72 and 5.48 $\mu\text{g}/\text{kg}/\text{min}$).

Dose rate 2.74 $\mu\text{g}/\text{kg}/\text{min}$ (N=12)

Dose rate 5.48 $\mu\text{g}/\text{kg}/\text{min}$ (N=8)

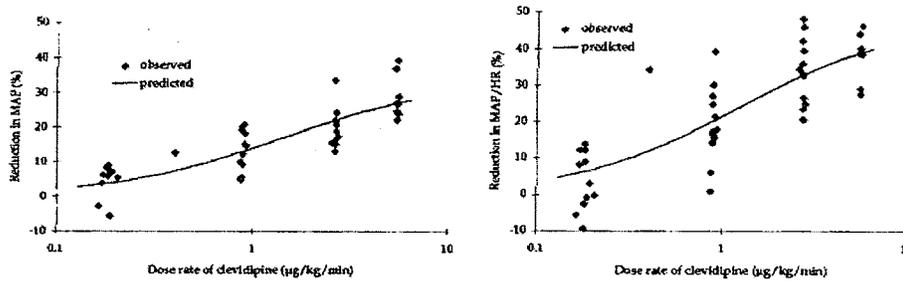
	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate ($\mu\text{g}/\text{kg}/\text{min}$)	1.37*	1.37*	2.74	2.74*	2.74*	5.48
CL_b (l/min/kg)						
Mean	0.112	0.118	0.115	0.121	0.136	0.127
S.D	0.027	0.030	0.027	0.030	0.038	0.033
Median	0.108	0.113	0.111	0.129	0.132	0.127
V_1 (l/kg)						
Mean	0.31	0.30	0.31	0.39	0.38	0.38
S.D	0.14	0.14	0.14	0.15	0.17	0.16
Median	0.25	0.22	0.23	0.38	0.36	0.35
V_{ss} (l/kg)						
Mean	0.58	0.43	0.49	0.74	0.56	0.66
S.D	0.21	0.18	0.19	0.27	0.20	0.25
Median	0.54	0.39	0.46	0.75	0.57	0.64
$t_{1/2\alpha_1}$ (min)						
Mean	1.6	1.6	1.6	1.9	1.7	1.8
S.D	0.4	0.5	0.5	0.4	0.4	0.4
Median	1.5	1.5	1.6	2.0	1.8	1.9
$t_{1/2\beta}$ (min)						
Mean	14.2	11.9	12.5	14.1	13.2	13.6
S.D	2.08	2.92	1.93	3.96	3.61	4.15
Median	14.5	12.4	12.8	16.0	14.5	15.6

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

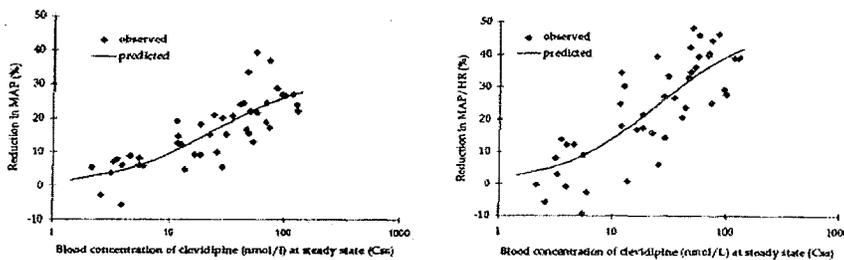
The results seem to indicate that after a bolus administration of clevidipine, 80-90% of the total AUC is associated with the initial phase.

Pharmacodynamics:

According to the derived model, the maximal reduction in MAP (E_{max}) observed with clevidipine was $32 \pm 4\%$ of its control value. Half the maximal reduction in E_{max} was attained at 23 ± 8 nmol/l (EC_{50}). The corresponding values using the dose rates instead of steady state concentrations of clevidipine were $34 \pm 6\%$ and 1.5 ± 0.4 $\mu\text{g}/\text{kg}/\text{min}$ (ED_{50}), respectively. The corresponding values when MAP/HR was used as effect parameter were $49 \pm 6\%$ (E_{max}) and 25 ± 9 nmol/l (EC_{50}), respectively, and 50 ± 6 (E_{max}) and 1.3 ± 0.4 $\mu\text{g}/\text{kg}/\text{min}$ (ED_{50}), respectively.



Above: Individual reductions in MAP and MAP/HR vs dose rates of clevidipine during steady state. the solid line is the model-predicted value.



Above: Individual reductions in MAP and MAP/HR (%) vs venous blood concentrations of clevidipine during steady state (C_{ss}). Solid line is the model-predicted values.

SAFETY:

No serious adverse events were reported throughout the study. Headache and flushing were the most commonly reported adverse events.

In this study, clevidipine was safe and well tolerated at dose rates between 0.18 and 5.48 $\mu\text{g}/\text{kg}/\text{min}$.

In no case was study drug infusion stopped due to AEs. However, within one hour after completion of the clevidipine infusion at the dose rate 2.74 $\mu\text{g}/\text{kg}/\text{min}$ (target infusion rate), patient no. 5 experienced headache, ventricular extrasystoles, nausea and vomiting. It was decided not to expose the patient to another and higher dose rate of clevidipine (ie. a dose rate of 5.48 $\mu\text{g}/\text{kg}/\text{min}$ at the target infusion rate).

CONCLUSIONS:

From the pharmacokinetic evaluation in this study, it can be concluded that clevidipine is a high-clearance compound in moderately hypertensive patients. The different dose rates and the mean blood concentrations of clevidipine at steady state suggest a linear relationship. The differences in the pharmacokinetic parameters of the enantiomers were small and not considered to be of any clinical relevance.

In the absence of values for systemic vascular resistance ($SVR = MAP/HR \times SV$), the extent of vasodilatation induced by clevidipine in this study was evaluated by the reduction in the ratio MAP/HR , rather than using MAP alone. When an E_{max} model was fitted to the reduction in MAP/HR , the E_{max} was 49% and the EC_{50} was 25 nmol/l. These values are similar to those obtained in the study in healthy volunteers

- Clevidipine induces dose-dependent reductions in SBP, DBP and MAP.
- Half the maximal effect of clevidipine on MAP (% reduction from baseline value) is obtained at a blood concentration of 25 nmol/l (EC_{50}). The corresponding value for ED_{50} , i.e. the dose rate producing half the maximal effect, is approximately 1.5 $\mu\text{g}/\text{kg}/\text{min}$.

REVIEWER'S COMMENT:

The reviewer concurs; however assessment of the appropriateness of the pharmacodynamic model used will be available through the pharmacometrics review.

**APPEARS THIS WAY
ON ORIGINAL**

STUDY TMC-CLV-06-01 – A RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-BLIND STUDY IN PATIENTS WITH ESSENTIAL MILD TO MODERATE HYPERTENSION TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS AND SAFETY OF CLEVIDIPINE DURING AND FOLLOWING PROLONGED CONTINUOUS INFUSION.

STUDY INVESTIGATOR AND SITE: Multi-Investigator
Multi-Center

REPORT # TMC-CLV-06-01

MODULE in EDR-5

STUDY DATES: September 21, 2006 – February 20, 2007

Objectives:

1. To determine the extent of any tolerance developed during continuous prolonged clevidipine infusion (72 hours) at four different doses.
2. To evaluate the potential for rebound hypertension following termination of continuous prolonged clevidipine infusion (72 hours) at four different doses.
3. To determine the relationship between blood concentration of clevidipine and magnitude of antihypertensive effect during continuous prolonged clevidipine infusion (72 hours) at four different doses, and for one hour post-treatment.
4. To evaluate the safety and tolerability of a continuous prolonged clevidipine infusion (72 hours) at four different doses.

FORMULATION:

Clevidipine was supplied by _____ and Intralipid® (placebo) was supplied by each study site.

	Clevidipine	Intralipid® (placebo)
Formulation	Lipid emulsion	Lipid emulsion
Strength	0.5 mg/mL	20%
Lot Numbers	KV1438A and KV1429A	1035342, UD12459, 51902, UD12216, 0519, UC11678, UC11572 and UE12534

STUDY DESIGN:

This was a Phase IIb, randomized, single-blind, placebo-controlled, parallel-design study in patients with mild to moderate hypertension. Enrollment of approximately 52 randomized patients was planned at up to four centers within about 3 months from initiation of the study. Informed consent was obtained from patients meeting the inclusion criteria before the initiation of any study-specific procedures.

Patients were allocated to one of four dosing cohorts. Within each cohort, it was planned that 10 patients would be randomized to receive clevidipine and three to receive placebo. Patients were to be treated with study drug continuously for 72 hours and then followed up for 4 days post study drug termination.

A forced titration regimen was used to assess tolerability before the target dose was reached.

Patients with essential hypertension were studied since it was expected that the withdrawal rate due to tachycardia and hypotension would be less than that in healthy subjects.

IV infusions of clevidipine (0.5 mg/mL in 20% lipid emulsion) were administered to patients. Patients were allocated to one of the following four dosing cohorts:

- Cohort 1: Clevidipine 2.0 mg/h or placebo
- Cohort 2: Clevidipine 4.0 mg/h or placebo
- Cohort 3: Clevidipine 8.0 mg/h or placebo
- Cohort 4: Clevidipine 16.0 mg/h or placebo

Within each dosing cohort, it was planned that 10 patients would be randomized to receive clevidipine and three patients to receive placebo. Clevidipine was administered at an initial infusion rate of 2.0 mg/h to patients in each cohort and force titrated in doubling increments every 3 minutes to the target dose in Cohorts 2, 3 and 4.

Due to the lipid load restrictions (maximum of 2.5 g/kg/24 hours), patients weighing less than 64 kg were not enrolled into Cohort 4 (clevidipine 16.0 mg/h or placebo).

The doses administered in this study had previously been administered at shorter durations in healthy volunteers, essential hypertension and cardiac surgery patients.

The range of doses studied represent the doses that are intended to be used in clinical practice.

Primary endpoint:

- Mean percent change in SBP from baseline over the 72 hour treatment period

Secondary endpoints:

- Mean percent change in SBP from baseline over the first 4 hours post study drug infusion.
- Blood concentration of clevidipine over the 72 hour treatment period through 60 minutes post study drug infusion.
- Relationship between the time-matched, placebo-adjusted mean percent change in SBP from baseline and the mean blood concentration of clevidipine over the 72 hour treatment period through 60 minutes post study drug infusion.
- Safety of a prolonged infusion of clevidipine (72 hours) assessed according to clinical laboratory parameters, HR, electrocardiograms (ECGs), and adverse events (AEs).

The following medications were permitted during the screening/run-in, treatment and follow-up periods. The administration of any medication not listed below had to be approved by the Sponsor.

- Non-prescription pain medications could be used for pain per package instructions, and these medications could not contain known stimulants.
- Lorazepam (10 mg oral dose not exceeding once every 24 hours at bedtime) was allowed only during the treatment and follow-up periods.
- Oral contraceptives.

Four study populations were considered in the statistical analysis of this study.

- The intent-to-treat (ITT) population consisted of all patients who were randomized in this study.
- The PK population consisted of all patients who were dosed with clevidipine and had at least one blood concentration measurement.

-
- The safety population consisted of all patients who were dosed with any study drug and was the primary population for all safety analyses.
 - The per-protocol (PP) population consisted of all patients who received 72 hours of continuous treatment at the target dose and had blood samples for PK analysis taken utilizing the correct methodology. The PP population was the primary population for all BP, PK, and PD analyses.

ANALYTICAL METHODS:

Not provided.

PHARMACOKINETICS, PHARMACODYNAMICS, AND STATISTICAL ANALYSIS:

Pharmacokinetics

During the treatment period, blood samples for the determination of blood concentrations of clevidipine and its major metabolite (M1), H152/81, were collected predose and 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours following achievement of the target dose. On Day 4, blood samples for PK analysis were collected at 2, 4, 6, 8, 12, 20, 30, and 60 minutes post end of infusion. All blood samples were collected from the arm that was not receiving study drug infusion.

Pharmacokinetic analysis was performed only on clevidipine and the PK-PD relationship was established only for the parent compound.

The following PK parameters for clevidipine were derived: C_{max} (maximum concentration); C_{ss} (average concentration at steady-state); AUC_{0-t} (area under the concentration-time curve from time zero to the last quantifiable concentration); CL (clearance); and $t_{1/2}$ (elimination half-life).

PK/PD

During the treatment period, BP and HR were obtained at the following timepoints: predose and then every 3 minutes during the titration phase to coincide with dose changes; once target dose was reached, BP and HR were obtained at 5, 10 and 15 minutes and then at 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours following achievement of the target dose.

On Day 4 following study drug termination, BP and HR were obtained at the following timepoints: 2, 4, 6, 8, 12, 20, 30, and 60 minutes and then every 15 minutes for the next 3 hours and then at 6 and 8 hours.

On Day 7, BP and HR were measured to ensure that BP had returned to its prestudy baseline and had stabilized; or the patient was to be referred to their prestudy healthcare physician.

Mean blood concentrations of clevidipine over the 72-hour treatment period through 60 minutes post study drug infusion were plotted against time-matched, placebo-adjusted mean percent change from baseline in SBP, according to dose (PP population).

Statistics

Descriptive statistics, graphs, and patient data listings were used to summarize the CRF and clevidipine blood concentration data. Data from all placebo-treated patients allocated to the four dosing cohorts were pooled. Tabular and graphical summaries were presented according to dose of clevidipine (2.0, 4.0, 8.0, 16.0 mg/h), together with the pooled placebo data. Patient data listings were presented according to dosing cohort for all patients who were enrolled in this study, including all randomized patients and replacements.

The interpretation of the PD and PK results was based on the summary tables and summary figures. No formal PK or statistical analysis was performed.

Unless otherwise specified, baseline was defined as the last observation before study drug initiation.

RESULTS:

Patient 203/005 in Cohort 3 withdrew on the second day of treatment, hence was excluded from all PD and PK analysis. For this patient, SBP was measured and reported in the listings.

Seven patients (Patients 203/001, 203/003, 203/011, 203/019, 203/020, 203/032, and 203/035) in Cohort 3 had their postdose PK blood samples incorrectly collected from the drug infusion arm site. Consequently, PK information from these seven patients was excluded from the present analysis. PD information from these seven patients was excluded from the present analysis since their PK information was excluded. Eight new replacement patients (7 on active and 1 on placebo) were recruited and completed in Cohort 3. PD information from these 7 replacement patients on active treatment was combined with the previous 3 patients on active treatment for Cohort 3 group analysis and interpretation.

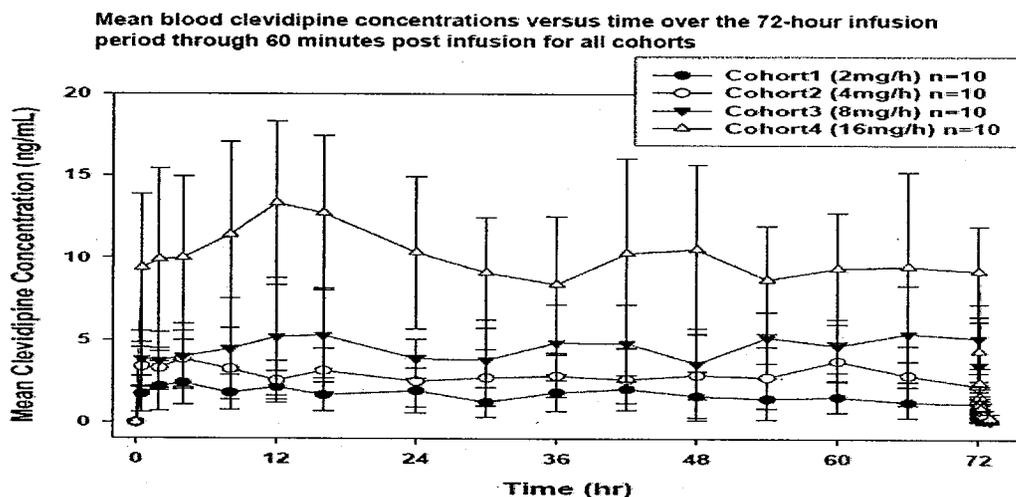
Pharmacokinetics

Following the 72 hour IV infusion of clevidipine, blood concentrations of clevidipine were highly variable throughout the infusion period and decreased in a bi-exponential fashion thereafter following termination of the infusion. The concentration time profile was similar across all dose levels of clevidipine.

Following IV infusion, there was a less than dose proportional increase in C_{max} , C_{35} , and AUC_{0-1} between Cohort 1 (clevidipine 2.0 mg/h) and Cohort 4 (clevidipine 16.0 mg/h).

The mean alpha phase $T_{1/2}$ ranged from 3 to 4 minutes and mean beta phase $T_{1/2}$ ranged from 32 to 37 minutes across dose groups. However, due to the absence of sampling within the first 2 minutes after cessation of clevidipine infusion, the $T_{1/2}$ values reported here are more likely to be the beta and terminal phases, rather than the true alpha and beta phases.

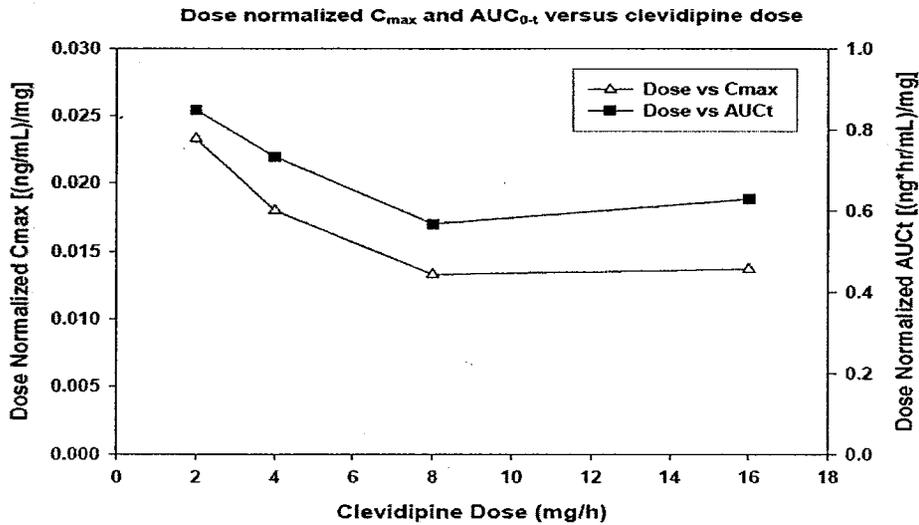
The clearance of clevidipine was similar across all dose groups evaluated.



Following IV infusion, there was a less than dose-proportional increase in C_{max} between Cohort 1 (clevidipine 2.0 mg/h) and Cohort 4 (clevidipine 16.0 mg/h) with an approximately 4.7-fold increase in C_{max} for a 8-fold increase in dose. This trend is also

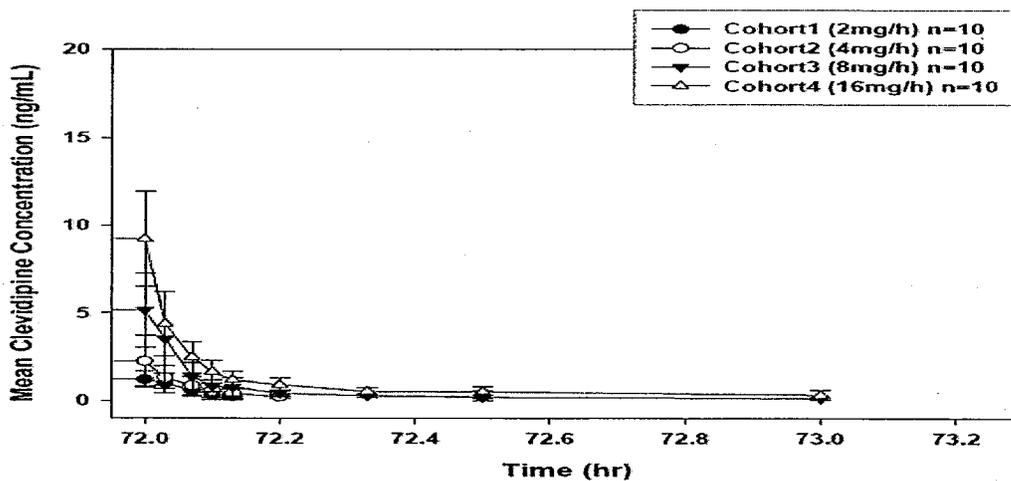
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Reflected above, demonstrating a decrease in the dose normalized C_{max} as dose increases. The disproportional behavior is more pronounced at the lower doses, leveling out for the two highest dose groups. According to the sponsor given the small number of patients in each dose group, this observation should be considered with caution. The same observation was made for AUC with the same caution being given when considering this observation.



Following IV infusion, there was a slightly less than dose-proportional increase in C₅₅ between Cohort 1 (clevidipine 2.0 mg/h) and Cohort 4 (clevidipine 16.0 mg/h) with an approximately 6.7-fold increase in C₅₅ for a 8-fold increase in dose.

Mean blood clevidipine concentration versus time from end of infusion to 1 hour post infusion for all cohorts



Summary of the mean (SD) pharmacokinetic parameters of clevidipine

Cohort	Clevidipine infusion dose (mg/h)	N	C _{max} (ng/mL)	AUC _{0-t} (ng*hr/mL)	C _{ss} (ng/mL)	CL (L/min)	T _{1/2} - alpha (minutes)	T _{1/2} - beta (minutes)
1	2	10	3.363 (1.348)	122 (56)	1.371 (0.696)	33.2 (21.0)	4.18 (2.59) ^a	NC
2	4	10	5.169 (1.666)	211 (92)	2.995 (1.251)	26.1 (10.9)	3.28 (1.06) ^a	37.0 (29.85) ^p
3	8	10	7.677 (2.370)	327 (109)	5.124 (1.623)	28.5 (9.91)	3.16 (1.4)	32.4 (33.61) ^a
4	16	10	15.762 (4.013)	724 (246)	9.203 (3.371)	33.4 (14.7)	3.34 (0.96)	37.33 (21.66) ^c

Source: Appendix 16.5

NC = Not calculated

^a N = 8

^b N = 3

^c N = 9

The mean alpha phase T_{1/2} ranged from 3 to 4 minutes and the mean beta phase T_{1/2} ranged from 32 to 37 minutes across dose groups. Given the PK sampling schedule for the post drug infusion period, it seems likely that the alpha phase was complete before the first postdose sample was drawn at two minutes after stopping the infusion.

Consequently, the T_{1/2} values reported here are representative of the beta and terminal phases, rather than the true alpha and beta phases.

The calculated mean clearance value for clevidipine was approximately 30 L/min, and was similar across all dose groups evaluated.

Pharmacodynamics

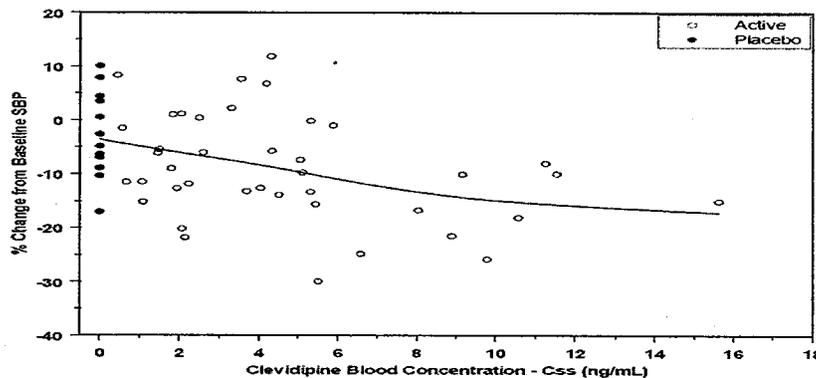
All active treatment cohorts showed a larger percentage decrease from baseline in SBP as compared to placebo, however Cohort 1 (clevidipine 2.0 mg/h) shows a lower percent change in SBP from baseline as compared to placebo than Cohort 2 (clevidipine 4.0 mg/h). For the remaining Cohorts 3 and 4 (clevidipine 8.0 and 16.0 mg/h), the decline in percent change from baseline SBP was dose dependent. The change from baseline SBP was observed to be greater in Cohort 4 as compared to all other cohorts.

A rapid onset of drug effect (decrease in SBP from baseline) was seen for all dose levels of clevidipine. The BP response was maintained at relatively consistent levels throughout the treatment period, with no evidence of a diminishing drug effect.

There was a trend for a greater percent change from baseline SBP with increased steady state blood concentrations of clevidipine, although there was substantial variability. The concentration response curve was fairly shallow in nature. Over the range of C_{ss} values evaluated, there was no apparent maximum response in change from baseline SBP.

(see below)

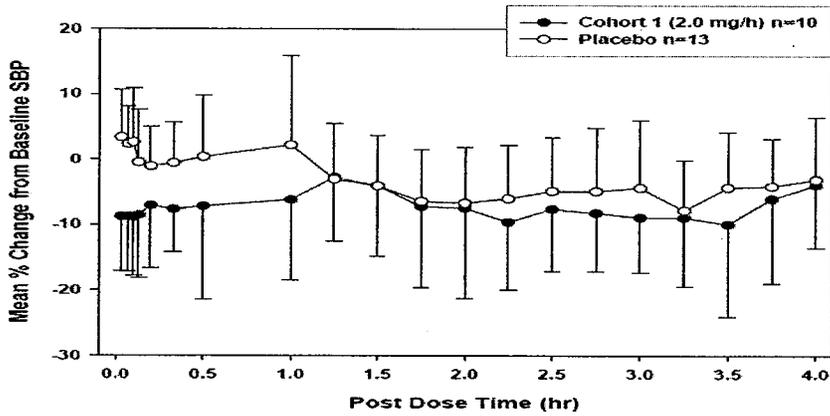
Clevidipine C_{ss} versus mean percent change from baseline in systolic blood pressure at steady state pooled across all cohorts



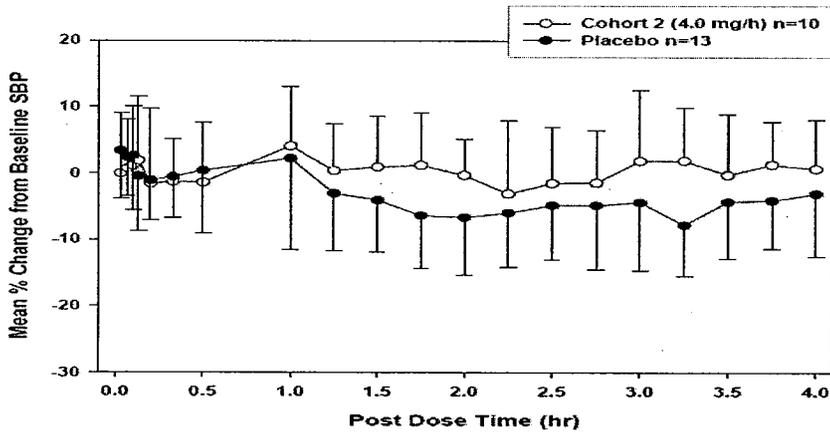
There was no evidence of rebound hypertension following termination of the clevidipine infusion. At all dose levels of clevidipine, there was a rapid return to baseline SBP following cessation of drug treatment.

(see below)

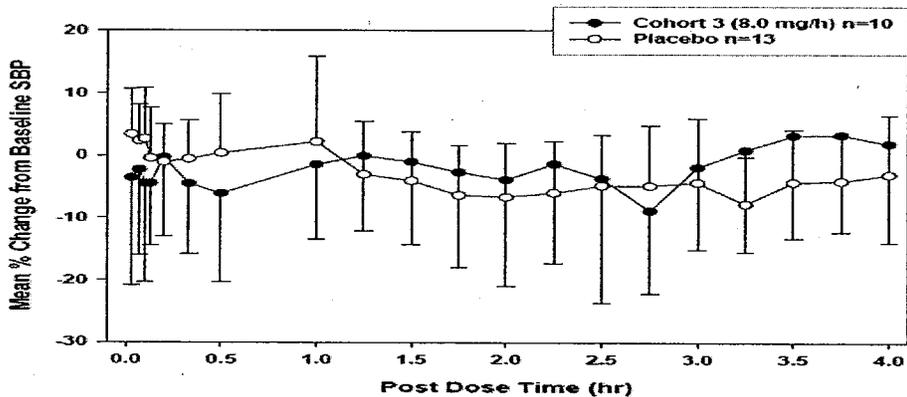
Mean percent change from baseline in systolic blood pressure versus time following the end of study drug infusion: Cohort 1 versus placebo



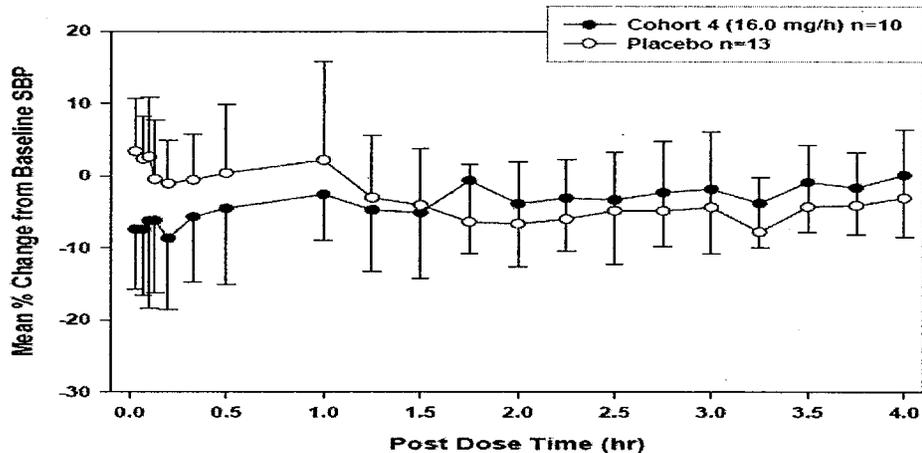
Mean percent change from baseline in systolic blood pressure versus time following the end of study drug infusion: Cohort 2 versus placebo



Mean percent change from baseline in systolic blood pressure versus time following the end of study drug infusion: Cohort 3 versus placebo.



Mean percent change from baseline in systolic blood pressure versus time following the end of study drug infusion: Cohort 4 versus placebo



SAFETY:

One patient experienced AEs which led to discontinuation of study drug and withdrawal from the study. Patient 203/005, a 49-year-old white male with no relevant medical history, experienced a mild, treatment-related AE of sensation of pressure (reported term generalized facial pressure) starting 58 minutes after the start of the IV infusion of clevidipine 8.0 mg/h on Day 1, which lasted for 1 hour. This patient also experienced a mild treatment-related AE of headache (duration 6 hours 58 minutes), starting 1 hour 58 minutes after the initiation of the clevidipine infusion, and a mild treatment-related AE of nausea (duration 2 hours 1 minute) starting 5 hours 58 minutes after the initiation of clevidipine. The IV infusion was stopped after 7 hours 49 minutes, when the patient had received approximately 62.0 mg clevidipine. Concomitant medication was administered for the treatment of headache (paracetamol [1000 mg, oral, as required], and ibuprofen [600 mg, oral, as required]). Ondansetron [4 mg, intramuscular, as required] was administered for the treatment of nausea and headache. All AEs resolved on Day 1 and the patient withdrew from the study on Day 2.

No deaths or SAEs occurred during this study.

Clevidipine was safe and well tolerated when administered as prolonged continuous IV infusions at dose rates of 2.0 to 16.0 mg/h. Forty-three of the 61 patients enrolled experienced one or more adverse events. Overall, 112 AEs were reported: 84 AEs following administration of clevidipine, and 28 AEs following IV administration of placebo. The most common AEs reported across treatments and dose levels were headache, infusion site reaction, infusion site swelling, and infusion site erythema. There were no apparent dose or treatment-related differences in AE incidence, description, severity, or duration between the clevidipine dose cohorts.

CONCLUSIONS:

No tolerance was developed during continuous prolonged clevidipine infusion for 72 hours, with the decrease from baseline in SBP being maintained at relatively constant levels throughout the infusion at all four dose levels.

There was no evidence of rebound hypertension following termination of the clevidipine infusion at all four dose levels, with SBP returning to baseline following cessation of treatment.

There was a general correlation between steady-state clevidipine concentrations and percent change from baseline in SBP across the four dose levels of clevidipine. The relationship was shallow and a maximum effect was not achieved in this study.

When compared with data from studies of short infusions, prolonged continuous administration does not appear to influence the PK or PD characteristics of clevidipine.

Clevidipine was considered to be safe and well tolerated when administered as a prolonged continuous IV infusion over 72 hours across the dose range 2.0 to 16.0 mg/h.

REVIEWER'S COMMENT:

According to the sponsor, the range of doses studied represent the doses that are intended to be used in clinical practice, however

Due to the lipid load restrictions (maximum of 2.5 g/kg/24 hours), patients weighing less than 64 kg were not enrolled into Cohort 4 (clevidipine 16.0 mg/h or placebo).

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STUDY SH-SAD-0006 – DOSE REQUIREMENT AND PHARMACOKINETICS OF CLEVIDIPINE IN PATIENTS DEVELOPING INTRA OPERATIVE HYPERTENSION IN CONNECTION WITH CARDIAC SURGERY.

STUDY INVESTIGATOR AND SITE:

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REPORT # SH-SAD-0006

MODULE in EDR, 5

STUDY DATES: August 1996 – January 1997

OBJECTIVES

The primary objectives of this study were to identify the dose rate of clevidipine required to lower high blood pressure during the pre-bypass phase and the hypothermic period of the bypass phase during cardiac surgery and to investigate safety during these periods.

The secondary objectives were to determine the pharmacokinetics and compare the half-life of clevidipine during the pre-bypass phase and the hypothermic period of the bypass phase.

INVESTIGATIONAL PRODUCT

The clevidipine formulation consists of 0.5 mg/ml of the substance clevidipine in a 20 per cent lipid emulsion for (i.v.) infusion (Batch No. 1246-01-01-01). Twenty per cent Intralipid® was used as carrier (Batch No. H 0662-02-02-04).

Clevidipine, 0.5 mg/ml, was manufactured and bottled by _____ and 20 per cent Intralipid® was manufactured and bottled by _____. All drugs were packed and labelled at Astra Hässle AB, S-431 83 Mölndal, Sweden.

STUDY DESIGN

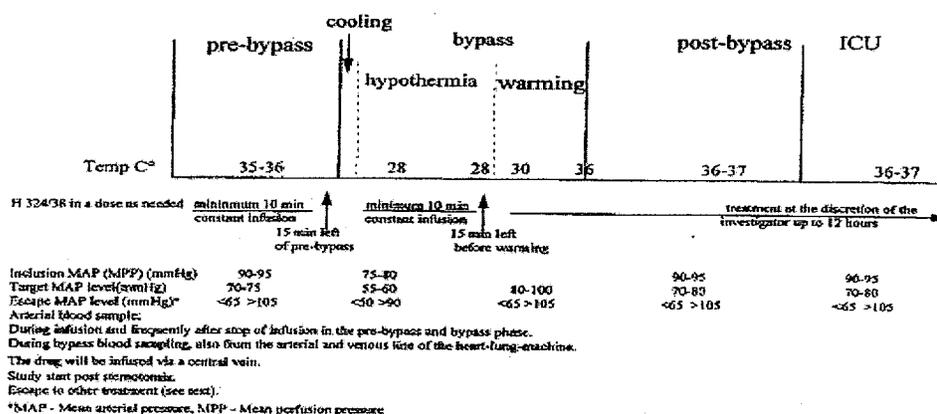
This was an open study. Clevidipine was administered to patients undergoing CABG surgery who developed high blood pressure during the pre-bypass and/or during the hypothermic phase of the bypass period. The infusion of clevidipine was given in a dose sufficient to reduce MAP from 90-95 mm Hg to 70-75 mm Hg during pre-bypass and mean perfusion pressure (MPP) from 75-80 mm Hg to 55-60 mm Hg during bypass hypothermia, aiming at a 20 per cent decrease of MAP and MPP. In an earlier study, the predicted dose rate was up to 3.2 µg/kg/min (7 nmol/kg/min). However, higher dose rates up to a maximum of 22 µg/kg/min (48 nmol/kg/min) could be administered according to the protocol. The infusion began with a quick titration at a starting dose of 0.7 µg/kg/min (1.5 nmol/kg/min) to reach the required MAP/MPP level. Thereafter the infusion rate was kept constant in order to achieve steady state for at least ten minutes. When 15 minutes remained of the pre-bypass period or the hypothermic period of the bypass phase, the infusion was stopped. Blood pressure and haemodynamic parameters were measured, and blood samples were drawn for analysis of clevidipine before the start of infusion, during infusion and after the stop of infusion. The temperature, haemoglobin (Hb) and haematocrite (Hct) were also followed throughout surgery.

Twenty patients were enrolled and 18 patients were randomised into the study. One of the patients discontinued the study due to AE. Seventeen patients were evaluable in the prebypass period (14 males and 3 females) and eight patients in the bypass period (6 males and 2 females).

DURATION OF TREATMENT

The dose rate was adjusted until the desired reduction of MAP/MPP was achieved during the pre-bypass and bypass period, respectively. Then the dose rate was held constant for ten minutes. Infusion of clevidipine was reinstated, at the discretion of the investigator, if MPP increased during rewarming and during weaning off the heart-lung machine. Moreover, administration of clevidipine was continued if needed during the post-bypass period and/or in the intensive care unit (ICU). Clevidipine was given in doses required to achieve adequate blood pressure control. The drug could be given up to 12 hours from the start of study drug infusion.

Study Design



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BIOANALYTICAL ASSAY

The blood samples were analysed for clevidipine by a gas chromatography-mass-spectrometry method (BA-286) at Astra Hässle AB, Mölndal, Sweden. The limit of quantitation (LOQ) was 0.5 nmol/L for clevidipine. Values below LOQ were set to non-determinable (-).

Validation report no.	Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
1312-427 SAD0006	GC-MS	H32438	0.55-36.3	See 1312-427	2.2%-14.6% (low standards) 1.1%-2.9% (high standards)	95.1% (82.1-99.7%)	Linear ^b	0.5 nmol/L ^c

PHARMACOKINETICS, PHARMACODYNAMICS, AND STATISTICAL ANALYSIS

Pharmacokinetics

Peripheral arterial blood samples were taken from an indwelling plastic cannula in the forearm artery for determination of blood concentration of clevidipine during the pre-bypass and bypass phases. The blood samples were drawn during pre-bypass and bypass phases at the following times: after 8, 9 and 10 minutes after the start of infusion and 30 and 45 seconds and 1, 2, 3, 4, 6, 8 and 10 minutes after the stop of infusion. A blood

sample was also drawn before the infusion.

Furthermore, blood samples from pulmonary artery were drawn during the pre-bypass period at the following times: baseline and 8, 9, 10, 12, 16 and 20 minutes after the start of infusion.

Blood samples were also drawn from the arterial (out-flow) and venous line (in-flow) on the heart-lung machine during the bypass phase at baseline, during the constant rate infusion at 5 and 9 minutes after the start of the infusion.

The following pharmacokinetic parameters were estimated for each patient and phase of surgery (pre-bypass/bypass):

R_0 : infusion rate

C_{SS} : steady state concentration estimated as the mean observed blood concentration from the steady state period prior to the stop of the infusion

CL_b : blood clearance calculated by compartmental and non-compartmental analysis as R_0/C_{SS}

$t_{1/2}$: initial half-life

$t_{1/2\alpha}$: terminal half-life

A : zero time intercept for the initial phase following i.v bolus

B : zero time intercept for the terminal phase following i.v bolus

V_1 : initial volume of distribution

V_{dss} : volume of distribution at steady state

An open, two- compartment model was fitted to each individual's blood concentrations obtained during the pre bypass and the bypass surgery. An additional non-compartmental analysis was also performed to determine the blood clearance (CL_b) and the steady state concentration of clevidipine (C_{SS}).

Pharmacodynamics

Dose rates required for adequate blood pressure control during the pre-bypass and bypass periods were evaluated.

NOTE:

Blood concentrations were also planned to be depicted graphically versus SBP, DBP and MAP/MPP. This has not been done as it would not have given more information. Pharmacodynamic - pharmacokinetic modelling was not done since most of the patients received other drugs immediately after stopping the clevidipine infusion (5.3).

Statistics

Descriptive statistics were to be used in the evaluation of pharmacodynamic and pharmacokinetic variables of clevidipine as well as safety variables. A comparison of the half-life ($t_{1/2}$) between the pre-bypass phase and the hypothermic period of the bypass phase was also to be performed.

Hodges-Lehmann estimates of median with 95 % confidence interval was calculated for differences (prebypass vs bypass) in the pharmacokinetic parameters. For dose rate and MAP(MPP) Hodges-Lehmann estimates of median with 95 % confidence interval was calculated during constant infusion in prebypass and bypass.

RESULTS

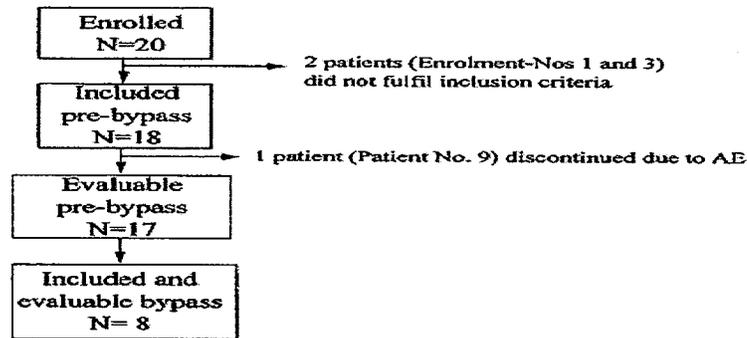


Figure 1. A flow chart of the number of patients enrolled and included in pre-bypass and bypass period, respectively.

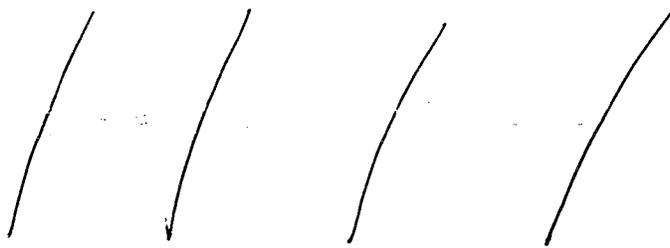
Eighteen patients were included in the pre-bypass phase and eight of these patients were also included in the bypass phase. Due to that many patients did not reach the inclusion pressure in the bypass period, the study was stopped after eight patients in this period (5.3).

Fifteen males and three females were included in the pre-bypass period. Of these six males and two females were also included in the bypass period.

All patients participating in the study were Caucasians.

Pharmacokinetics

Patient No. 3 is not included in the descriptive statistics of the pharmacokinetics due to the fact that only 3 blood samples were drawn after the stop of clevidipine in the pre-bypass period. The reason for this was the start of the bypass period.



Concentrations of clevidipine in peripheral arterial blood and mixed venous blood during pre-bypass and concentration of clevidipine in peripheral arterial blood during bypass, following 10 minutes' constant rate infusion (Pat No 10; the blood concentrations during bypass are normalised to a dose rate of 2.05 $\mu\text{g}/\text{kg}/\text{min}$).

Non-compartmental analysis of blood concentration during pre-bypass. Individual values and descriptive statistics.

Patient	R_0 (nmol/kg/min)*	Arterial blood		Mixed venous blood (pulmonary artery)	
		C_{ss} (nmol/l)	Cl_b (l/min/kg)	C_{ss} (nmol/l)	Cl_b (l/min/kg)
N	17	17	17	16	16
Mean	4.76	87.3	0.061	87.8	0.060
SD	1.87	50.0	0.019	54.1	0.019
Median	4.00	66.4	0.059	72.0	0.056
Min	2.49	26.5	0.032	25.4	0.028
Max	7.31	220.7	0.101	251.5	0.099

* molecular weight 456.3 g

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Difference in pharmacokinetic parameters between prebypass and bypass treatment. Hodges-Lehmann estimates of true median difference and 95% confidence intervals based on data from patients treated during both prebypass and bypass (n=8). Pharmacokinetic parameters calculated by noncompartmental analysis of blood concentration.

Parameter	Estimate	Lower limit	Upper limit
R_0 (nmol/kg/min)	2.36	-0.26	4.86
C_{ss} (nmol/l)	5.8	-55.2	38.2
Cl_b (l/min/kg)	0.027	0.016	0.044

R_0 = infusion rate; Cl_b = Blood clearance

The confidence intervals indicate that Cl_b is higher during bypass compared to pre-bypass.

Difference between pharmacokinetic parameters during the pre-bypass and the bypass. Hodges-Lehmann estimates of true median difference and 95 per cent confidence intervals based on data from patients treated during both pre-bypass and bypass (n=7). Pharmacokinetic parameters calculated by compartmental analysis.

Parameter	Estimate	Lower limit	Upper limit
A	-0,025	-0,040	-0,005
B	0,025	0,005	0,040
Cl_b (l/min/kg)	0.026	0.017	0.041
V_1 (l/kg)	0,01	-0,03	0,03
V_{1ss} (l/kg)	0,01	-0,05	0,03
$t_{1/2\alpha}$ (min)	-0,5	-1,0	-0,2
$t_{1/2\beta}$ (min)	-3,4	-9,8	-1,8

The confidence intervals indicate that model constant B and Cl_b are higher during bypass compared to pre-bypass, while model constant A, $t_{1/2\alpha}$ and $t_{1/2\beta}$ are lower during bypass compared to pre-bypass.

Pharmacodynamics

MAP (mean during steady state) (bpm) vs dose rate mean ($\mu\text{g}/\text{kg}/\text{min}$) during prebypass and bypass. Hodges-Lehmann estimates of true median and 95% confidence intervals.

Parameter	N	Estimate	Lower limit	Upper limit
Individual Mean MAP prebypass	17	72	68	78
Dose rate prebypass	17	2.24	1.60	2.53
Individual Mean MPP bypass	8	55	50	62
Dose rate bypass	8	1.20	0.93	1.60

MPP = mean perfusion pressure

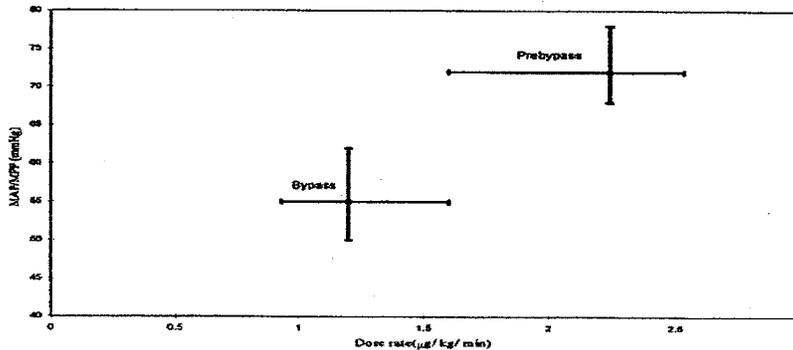


Figure 2. MAP/MPP versus dose rate, median and confidence interval during pre-bypass (n=17) and bypass (n=8).

Safety

Patient No. 09 (male, aged 60) with coronary heart disease and a history of asthma was, owing to intra operative hypertension in connection with cardiac surgery, treated with clevidipine (instituted when MAP had reached 122 mm Hg within a few seconds). After three minutes of titration, during pre-bypass, the infusion with clevidipine was prematurely stopped at a dose rate of 2.7 µg/kg/min, due to hypertension (MAP 109 mm Hg) and bleeding, and treatment with SNP was instituted. Approximately, one hour later, the patient was no longer hypertensive and the bleeding had stopped. Concomitant medication was routine anaesthesia, acetylsalicylic acid, glyceryl trinitrate, propranolol, isosorbid mononitrate, tocopherol and Gaviscon[®] liquid (sodium bicarbonate, calcium carbonate, sodium alginate, aluminium hydroxid).

No serious adverse events were observed.

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CONCLUSIONS

- the mean (\pm SD) dose rate of clevidipine required to control blood pressure during pre-bypass was 2.17 ± 0.85 , with individual values ranged from 1.1 to 3.3 $\mu\text{g}/\text{kg}/\text{min}$.
- the mean (\pm SD) dose rate of clevidipine required to control blood pressure during bypass was 1.26 ± 0.40 , with individual values ranged from 0.9 to 2.05 $\mu\text{g}/\text{kg}/\text{min}$.
- clevidipine is a high clearance drug both during the normothermic and hypothermic phases of the cardiac surgery.
- clevidipine increases the half-lives during hypothermia mainly due to a reduction in the clearance of the drug.
- clevidipine seems to be safe in patients undergoing CABG.

REVIEWER'S COMMENT

The reviewer concurs

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STUDY SH-SAD-0003 – THE EFFICACY OF CLEVIDIPINE IN POSTCARDIAC SURGERY PATIENTS. A DOSE FINDING STUDY.

STUDY INVESTIGATOR AND SITE: Six-investigators
Six-sites

REPORT # SH-SAD-0003

MODULE in EDR, 5

STUDY DATES: June 10, 1996 – March 19, 1997

OBJECTIVES:

To investigate the dose blood pressure response relationship, pharmacokinetics and the tolerability of clevidipine in postcardiac surgical patients.

FORMULATION:

Batch numbers of clevidipine: 0.05 mg/ml in 20% lipid emulsion: KV1171
0.3 mg/ml in 20% lipid emulsion: KV1154 and KV 1169
1 mg/ml in 20% lipid emulsion: KV1155 and KV 1170

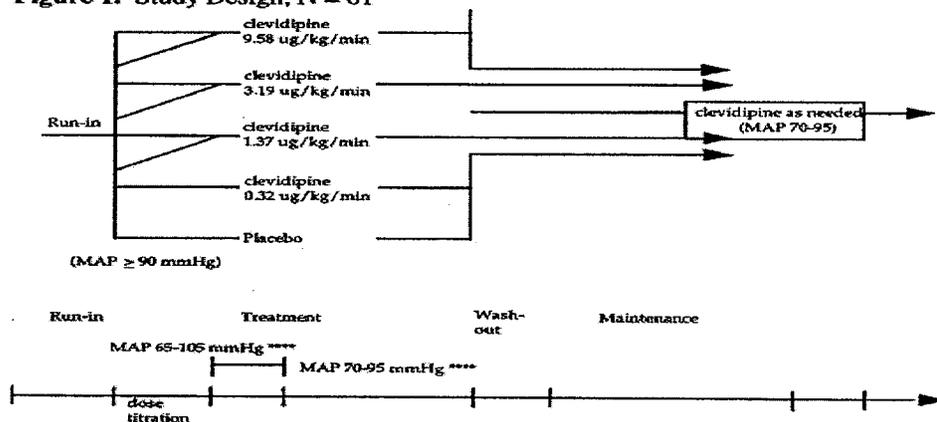
Batch numbers of placebo: Vehicle: KV1153
Vehicle: KV1168

No expiration dates provided in any of the studies.

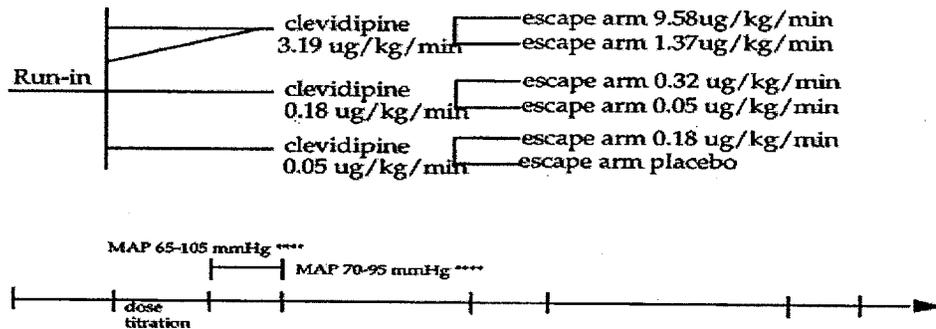
STUDY DESIGN:

This was a multi-centre, open, randomised, placebo-controlled study. Duration of treatment with study drug was 122 minutes with a subsequent optional maintenance phase of treatment with clevidipine up to 12 hours at a dose level that was needed to maintain a mean arterial pressure (MAP) of 70-95 mmHg. There was a run-in period lasting 20 minutes prior to the open treatment randomised phase of 122 minutes duration (including a dose titration phase of 12 minutes duration), and a wash-out period of 20 minutes. Doses of clevidipine administered were 0.05 µg/kg/min, 0.18 µg/kg/min, 0.32 µg/kg/min, 1.37 µg/kg/min, 3.19 µg/kg/min and 9.58 µg/kg/min. Placebo, i.e. 20% lipid emulsion ("Intralipid-like"), was administered at an infusion rate corresponding to the 1.37 µg/kg/min dose arm of clevidipine.

Figure 1. Study Design, N = 61



The extension (N = 30) of the study had three dosing arms (i.e., two new dose arms (0.05 and 0.18 $\mu\text{g}/\text{kg}/\text{min}$), one 3.19 $\mu\text{g}/\text{kg}/\text{min}$ dose arm and additional patients, as shown below:



DURATION OF TREATMENT:

A total of 122 minutes. For patients needing further blood pressure control after the treatment and wash-out periods, an optional maintenance phase was offered for up to 12 hours after the initial infusion of clevidipine at a dose level needed to maintain a mean arterial pressure (MAP) of 70-95 mmHg.

The primary variable was:

- The response rate of each dose level of clevidipine and placebo, where a responder is defined as a patient having at least a 10% reduction from baseline-MAP during the first 22 minute-treatment phase, while still on the randomised dose.

The secondary variables were:

- The mean change from baseline in MAP, SBP, DBP and HR at 22 minutes after the start of initial infusion of clevidipine or placebo, while still on the randomised dose.
- ED₅₀ based upon MAP.
- Safety
- Pharmacokinetics

STATISTICAL METHODS:

The response rate of each dose level of clevidipine was compared with placebo, using Fisher's exact test in a step-down procedure. The lowest dose group significantly different from placebo was considered as the minimum effective dose (MED). The results are stated as the response rates of the six doses of clevidipine and placebo and the corresponding p-values from the comparison to placebo.

Postcardiac surgical patients (CABG, valve replacement, or both) aged 18-80 years with an ejection fraction (EF) of ≥ 0.3 and two consecutive readings of MAP ≥ 90 mmHg, separated by 5 minutes at the end of the run-in period, were eligible for study participation.

Following the operation in the ICU, patients initially entered a 20 minute run in period followed by a randomised, open label treatment phase of 122 minutes duration (including a dose titration phase of 12 minutes duration). Patients received one of the following treatments:

- Placebo (20 % lipid emulsion administered at an infusion rate corresponding to the 1.37 µg/kg/min dose arm of clevidipine)
- clevidipine 0.32 µg/kg/min,
- clevidipine 1.37 µg/kg/min,
- clevidipine 3.19 µg/kg/min
- clevidipine 9.58 µg/kg/min.

An extension of the study involving a further 30 randomised patients was provided (Amendment 4) utilising three dosing arms (i.e., two new dose arms (0.05 and 0.18 µg/kg/min) and additional patients to the 3.19 µg/kg/min dose arm. In the extension, patients received one of the following treatments:

- clevidipine 0.05 µg/kg/min,
- clevidipine 0.18 µg/kg/min,
- clevidipine 3.19 µg/kg/min

Patients subsequently entered a wash-out period of 20 minutes and a maintenance phase with optional treatment with Clevidipine for up to 12 hours after the initial infusion, at a dose level that was needed to maintain a mean arterial pressure (MAP) of 70-95 mmHg.

The clevidipine formulation consists of 1 mg/ml and 0.3 mg/ml of the substance clevidipine in 20% lipid emulsion ("Intralipid-like"). This was later amended (Amendment 2) to read the clevidipine formulation consists of 1 mg/ml and 0.3 mg/ml of the substance clevidipine in 20% lipid emulsion. The 0.3 mg/ml was used for delivering the 0.32 and 1.37 µg/kg/min doses and 1 mg/ml was used for delivering the 3.19 and 9.58 µg/kg/min doses. To ensure correct dosing, the investigators were provided with a list of infusion rates.

In the extension phase of the trial (Amendment 4), the clevidipine formulation consisted of 1 mg/ml, 0.3 mg/ml and 0.05 mg/ml of the substance clevidipine in 20% lipid emulsion. In the extension, 0.05 mg/ml was used for delivering the 0.05 and 0.18 µg/kg/min doses, 0.3 mg/ml was used for delivering the 0.32 and 1.37 µg/kg/min doses and 1 mg/ml was used for delivering the 3.19 and 9.58 µg/kg/min doses.

BIOANALYTICAL ASSAY

The samples were analysed for clevidipine by a gas chromatography-mass-spectrometry method (BA-286) at Astra Hässle AB, Mölndal, Sweden. The limit of quantitation (LOQ) was 0.5 nmol/l for clevidipine. Values below LOQ were set to non-determinable (-).

Method desc.	Compound	Conc. nmol/L	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
GC-MS	H 32438	0.5-950	See 1312-426	2.4%-15.6% (low standards) 1.0%-5.9% (high standards)	97.7% (91.9-105.1%)	Linear ^b	0.5 nmol/L ^c

PHARMACOKINETICS, PHARMACODYNAMICS, AND STATISTICAL ANALYSIS

Pharmacokinetics

Peripheral arterial blood samples for determination of clevidipine were collected at the following times:

Run-in period: at the end of the run-in period.

Treatment and Maintenance phases: blood samples were to be taken at 10, 18, 33, 48, 68 and 88 minutes after the start of constant rate infusion, amended to read after the start of the fixed dose infusion. If no change of the dose had been performed, the first sample was to be taken at 22 minutes after the start of the initial infusion and at 122 minutes after start of initial infusion and after stop of infusion at times: 30 seconds, 1, 1.5, 2, 3, 6, 12, 18 and 20 minutes (i.e. during wash-out). If restarting the infusion with clevidipine was required during the wash-out phase (between 122-142 minutes after the start of the initial infusion with clevidipine or placebo), a blood sample was to be taken immediately prior to restarting the infusion with clevidipine. If infusion with clevidipine continued past 142 minutes after the start of the initial infusion with clevidipine or placebo, then blood sampling was to be performed every 60 minutes. A stable infusion had to be maintained for 20 minutes prior to the blood sampling. If not, no blood sampling was to be performed for that timepoint.

Pharmacokinetics of clevidipine were determined by the population approach. The clevidipine concentrations vs. time were fitted by non-linear mixed effect modeling by the computer program, NONMEM. The clevidipine concentrations vs. time data were analysed using 1, 2, and 3 compartment models. The analyses was performed with the weight-adjusted dose rate ($\mu\text{g}/\text{min}/\text{kg}$) and the absolute dose rate ($\mu\text{g}/\text{min}$).

The potential relationship of the covariates age, body surface area, and gender of the pharmacokinetic parameters was evaluated by modeling each parameter P (volume or clearance) as a linear function of covariates, i.e., $P = \theta_1 + \theta_2 * C$, where P denotes the pharmacokinetic parameter, C denotes the covariate, and $\theta_1 + \theta_2$ were estimated by NONMEM. For further details about the NONMEM program, subroutines used, and model discrimination.

Pharmacodynamics

MAP, HR, SBP and DBP were recorded in conjunction with blood sampling for determination of blood concentrations of clevidipine (except during wash-out phase). In addition, these assessments and ECG

were recorded prior to (approximately 20 minutes before the start of the initial infusion of clevidipine or placebo) and at the end of the run-in period (immediately before the start of the initial infusion of clevidipine or placebo), at each dosage step during the titration period, at 22 minutes after start of infusion (or 10 minutes after change of dose arm), at the end of the treatment and maintenance phases and upon discharge from the Intensive Care Unit (ICU) (i.e. within 24 hours after the start of initial infusion of clevidipine or placebo). MAP, SBP, DBP and HR were also measured at each second minute during the wash-out period, and during each change of infusion during the maintenance phase.

Statistics

Pharmacokinetics of clevidipine were determined by the population approach. The clevidipine concentrations vs. time were fitted by non-linear mixed effect modeling by the computer program, NONMEM. The clevidipine concentrations vs. time data were analysed using 1,2, and 3 compartment models. The analyses was performed with the weight-adjusted dose rate ($\mu\text{g}/\text{min}/\text{kg}$) and the absolute dose rate ($\mu\text{g}/\text{min}$).

RESULTS:

Approximately 140 patients were to be randomised into the study at six centres in order to obtain 90 evaluable patients, with at least 12 patients per treatment group. A total of 129 patients were enrolled and 91 were randomised to treatment and were included in the pharmacodynamic and safety analyses, while 67 of the 91 patients randomised were included in the pharmacokinetic analysis.

All patients participating in the study were Caucasians.

During the study, (including the extension phase of the trial) the following dosages of clevidipine were given:

- 0.05 $\mu\text{g}/\text{kg}/\text{min}$
- 0.18 $\mu\text{g}/\text{kg}/\text{min}$
- 0.32 $\mu\text{g}/\text{kg}/\text{min}$
- 1.37 $\mu\text{g}/\text{kg}/\text{min}$
- 3.19 $\mu\text{g}/\text{kg}/\text{min}$
- 9.58 $\mu\text{g}/\text{kg}/\text{min}$

Beta-blockers were allowed the morning of surgery.

Pharmacokinetics

It was stated in the protocol that calculations of the pharmacokinetics of clevidipine should be determined with model or model independent analysis for each patient. Nonlinear least square regression analysis with the computer program WinNonlin (version 1.0 or later) were to be used in the model dependent analysis. The C_{ss} were to be estimated as the mean observed concentration from the three last samples prior to the stop of the constant infusion and clearance were to be calculated as R_0 (infusion rate) / C_{ss} and/or from parameter estimates. However, to obtain maximal information about the pharmacokinetics of clevidipine in the present study, it was decided to determine the pharmacokinetics with compartment modeling by the population approach. The clevidipine concentrations vs. time data were fitted by non linear mixed effect modeling by NONMEM.

The pharmacokinetic parameters for clevidipine.

Parameters	Estimated Value
V1	2.79L
V2	13.8L
CL1	4.25 L/min
CL2	0.75 L/min
k10	1.52 min ⁻¹
k12	0.2703 min ⁻¹
k21	0.0546 min ⁻¹
t _{1/2α}	0.38 min
t _{1/2β}	15.0 min

The results show that clevidipine is a high clearance drug with a relatively small volume of distribution. The high clearance value and the small volume of distribution result in extremely short half-lives of clevidipine, 0.4 min and 15 min, respectively. Converting the obtained data to a unit disposition function shows that the initial half-life accounts for more than 99 % of the initial concentration or approximately 85 % of the total area under the curve (AUC) following an i.v. bolus administration.

Pharmacodynamics

On-going analysis of the pharmacodynamic results during the trial revealed the following:

- the lowest infusion rate of 0.32 µg/kg/min (anticipated no effect dose level) decreased MAP from baseline by approximately 20%, which was more than anticipated for a no effect dose level (of clevidipine).
- additional data were required to determine if the 3.19 µg/kg/min infusion rate represented the maximally tolerated dose.

Therefore, it was decided that an additional 30 patients would be randomised to three dose arms in the extension trial and two additional clinical sites would be added. Two of the dose arms were two lower infusion rates of clevidipine, 0.05 and 0.18 µg/kg/min. The third dose arm was allocating additional patients to the already existing 3.19 µg/kg/min infusion arm.

The pharmacodynamic analysis was restricted to the data obtained during the first 22 minutes of the study according to the protocol.

Response

Below: Response rates of the six doses and placebo, and the corresponding p-values from the comparison to placebo

Randomised dose	Non-responders n (%)	Responders n (%)	p-value, comparison with placebo
Placebo	11 (100)	0 (0)	
0.05 µg/kg/min	10 (91)	1 (9)	0.500
0.18 µg/kg/min	9 (69)	4 (31)	0.067
0.32 µg/kg/min	4 (40)	6 (60)	0.004
1.37 µg/kg/min	3 (25)	9 (75)	<0.001
3.19 µg/kg/min	1 (5)	19 (95)	<0.001
9.58 µg/kg/min	0 (0)	14 (100)	<0.001

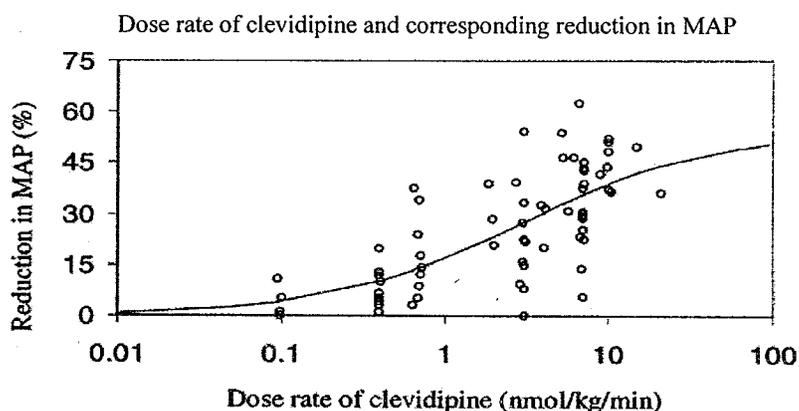
The lowest dose rate of clevidipine in which the response rate was significantly different from placebo is 0.32 µg/kg/min. With regard to the responder analysis, 0.32 µg/kg/min is considered as the minimum effective dose (MED).

BP and HR

There was a statistically significant difference in MAP, SBP and DBP between all doses of clevidipine and placebo ($p < 0.05$), except for clevidipine 0.05 µg/kg/min ($p > 0.05$).

Below: MAP (mmHg), change from baseline to 10 min, estimates, 95% confidence intervals and p-values for the comparison between placebo and the different dose arms

Comparison	Estimated difference	95% Confidence intervals		p-value
		lower	upper	
0.05 vs placebo	-1.6	-12.0	8.8	0.759
0.18 vs placebo	-10.7	-20.5	-0.9	0.033
0.32 vs placebo	-17.8	-28.2	-7.4	0.001
1.37 vs placebo	-26.6	-36.3	-16.9	<0.001
3.19 vs placebo	-36.5	-45.4	-27.6	<0.001
9.58 vs placebo	-47.5	-57.7	-37.4	<0.001



Below: SBP, change from baseline to 10 min, estimates, 95% CI and p-values for the comparison between placebo and the different dose arms

Comparison	Estimated difference	95% Confidence intervals		p-value
		lower	upper	
0.05 vs placebo	-4.0	-17.7	9.6	0.558
0.18 vs placebo	-15.4	-28.4	-2.5	0.020
0.32 vs placebo	-26.7	-40.7	-12.6	<0.001
1.37 vs placebo	-39.2	-52.1	-26.2	<0.001
3.19 vs placebo	-53.3	-65.2	-41.4	<0.001
9.58 vs placebo	-68.9	-82.4	-55.4	<0.001

Below: DBP, change from baseline to 10 min, estimates, 95% CI and p-values for the comparison between placebo and the different dose arms

Comparison	Estimated difference	95% Confidence intervals		p-value
		lower	upper	
0.05 vs placebo	-1.5	-9.8	6.9	0.724
0.18 vs placebo	-8.7	-16.7	-0.7	0.033
0.32 vs placebo	-12.3	-20.6	-4.0	0.004
1.37 vs placebo	-21.0	-28.8	-13.1	<0.001
3.19 vs placebo	-26.9	-34.0	-19.8	<0.001
9.58 vs placebo	-38.2	-46.0	-30.5	<0.001

There was no statistically significant difference between placebo and clevidipine with regard to HR (p<0.05).

Below: HR (beats/min), change from baseline to 10 min, estimates, 95% CI and p-values for the comparison between placebo and the different dose arms

Comparison	Estimated difference	95% Confidence intervals		p-value
		lower	upper	
0.05 vs placebo	0.2	-3.8	4.3	0.918
0.18 vs placebo	-0.8	-4.7	3.1	0.678
0.32 vs placebo	-0.6	-4.7	3.4	0.760
1.37 vs placebo	-0.6	-4.4	3.3	0.772
3.19 vs placebo	-3.1	-6.7	0.4	0.079
9.58 vs placebo	-1.7	-5.4	2.0	0.369

Safety

Clevidipine was safe and well tolerated up to a dose rate of 9.58 µg/kg/min. However, at this highest dose rate, hypotension resulting in discontinuation of study therapy occurred in 28 per cent of the patients. The highest recommended dose rate in further studies will thus be 3.19 µg/kg/min. No fatal SAEs occurred in the study.

CONCLUSIONS

- EFFICACY RESULTS

The results show that the lowest dose group of clevidipine in which the response rate was significantly different from placebo is 0.32 µg/kg/min. This is considered the minimum effective dose (MED) of clevidipine.

There was a statistically significant difference (p< 0.05) in MAP, SBP and DBP between placebo and all doses of clevidipine, except for 0.05 µg/kg/min (p>0.05). No statistically significant difference in HR was found between placebo and the six doses of clevidipine.

- PHARMACOKINETIC RESULTS

The pharmacokinetic results from the study demonstrate that clevidipine is a high clearance drug with relatively small volume of distribution with an initial half-life of 0.4 minutes and a terminal half-life of 15 minutes. These results corroborate previous findings. The initial half-life of clevidipine is an important feature, as it accounts for more than 99% of the initial concentration or 85% of the total AUC, following an unit i.v. bolus dose. The terminal tail is less than 1% of the initial concentration. The short half life of clevidipine predicts a rapid achievement of steady state blood concentration and a fast onset of effect after start of infusion.

REVIEWER'S COMMENT

The appropriateness of the analysis will be assessed by the pharmacometrician. However, results in this study are consistent with previous findings when a population pharmacokinetics analysis was not performed.

**APPENDIX IV
QT STUDY REVIEW**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22,156
Brand Name	Cleviprex
Generic Name	Clevidipine
Sponsor	The Medicines Company
Indication	
Dosage Form	IV emulsion
Drug Class	Calcium Channel Antagonist
Therapeutic Dose	2-32 mg/hr (titration)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	105 mg/h
Application Submission Date	July 2, 2007
Review Classification	Standard
Date Consult Received	August 23, 2007
Clinical Division	CDRP / HFD 110
PDUFA Date	May 2, 2008

Summary of Findings

6.1 Overall Summary of Findings

The sponsor conducted a two-part study. Part I was an open-label, nonrandomized pilot study in 8 subjects to assess the effect of Intralipid® (20% IV fat emulsion) on ECG parameters; the effect of two fenoldopam infusion rates to attain prespecified heart rates; and the ability to detect the effect of moxifloxacin on uncorrected QT during heart rate control. The QT-IRT did not analyze these data.

The QT-IRT primarily focused on the data obtained in the main study phase. This phase was a randomized, single-blind, vehicle (Intralipid®) and heart rate (fenoldapam) controlled 2-treatment crossover study in healthy volunteers, with an additional nonrandomized, open-label moxifloxacin treatment with heart rate control.

Compared to the vehicle- and heart rate-control group, administration of clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner.

- The maximum decrease (and corresponding two-sided 90% CI) in the mean change in $\Delta\Delta\text{QTcF}$ for the 3.2 mcg/kg/min and 12 mcg/kg/min dose groups were -9.4 ms (-16, -3 ms) and -16 ms (-21, -11 ms).
- A log-linear model described the relationship between clevidipine concentrations and changes in $\Delta\Delta\text{QTcF}$. Based on this relationship the expected $\Delta\Delta\text{QTcF}$ for a mean C_{max} of 9 ng/ml was -11 ms (-15, -7 ms) and 25 ng/ml was -15 ms (-20, -10 ms) following 3.2 and 12 mcg/kg/min, respectively.
- The mean $\Delta\Delta\text{QTcF}$ for moxifloxacin was approximately 10 ms at T_{max} with lower 90% confidence interval greater than 5 ms at several timepoints (Table 13). Since ten QT measurements were obtained over a short time, multiplicity adjustment may not be appropriate to compute confidence intervals.

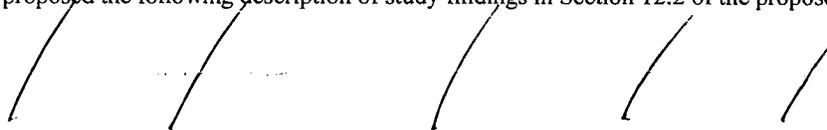
The study had multiple deficiencies in the design (see comments below). As a result, the QT-IRT is not persuaded by the sponsor's data that quantification of the effect of administering clevidipine on the QT interval can be adequately assessed.

Limitations of the Study

1. A precise estimate of the effect of administering clevidipine on the QT interval cannot be determined since the main study lacked a true placebo control group.
 - In the main study, the negative-control group contained two treatments that were not given to the clevidipine group: Intralipid® and fenoldapam. Intralipid® (20% fat emulsion) was administered by IV infusion for the same duration (23 hour 20 minutes) as clevidipine treatment. Fenoldapam was administered for 45 minutes during the up-titration period and discontinued 20 minutes prior to collecting ECGs for the suprathereapeutic dose.
 - The sponsor attempted to assess the effect of administering Intralipid® on the QT interval in stage I of the study (Table 6). The sponsor concluded that there did not appear to be any effect of administering Intralipid® on the QTcF interval. However, this evaluation was descriptive only and definitive conclusions cannot be made.
 - The effect of administering fenoldapam on the QT interval is not known.
2. The assessment of assay sensitivity has the following limitations:
 - Administration of moxifloxacin was not blinded. Lack of blinding may result in changes in the conduct of the trial in the moxifloxacin arm (e.g. changes of the behavior of the investigators and/or the subjects), which may introduce bias and affect the QT interval.
 - The study design is a 2-period crossover part plus moxifloxacin arm at the 3rd period. Therefore, the effect of moxifloxacin is confounded with the period effect.
 - The timing of ECGs to determine assay sensitivity is inadequate. After moxifloxacin administration, ten ECGs were collected for 2.5 hours which coincide with T_{max}. We typically recommend that a full moxifloxacin profile since we also consider the time-course of QTc during our assessment of assay sensitivity.
 - Moxifloxacin was co-administered with fenoldapam for 45 minutes. Fenoldapam was administered starting from 1 hour 15 minutes to 2 hours after dosing moxifloxacin. The effect of administering fenoldapam on the QT interval is not known.
 - Moxifloxacin treatments were compared with vehicle- and HR-control at analogous periods rather than actual time from administration as shown in Table 8.
3. The mean plasma concentrations achieved with the suprathereapeutic dose are approximately 30% lower than the mean concentrations when the highest clinical dose is administered.
 - At the suprathereapeutic dose (12 mcg/kg/min or 60 mg/hr for 83 kg patient), clevidipine plasma concentrations were 3-fold higher than concentrations following the therapeutic dose (3.2 mcg/kg/min or 16 mg/hr for 83 kg patient).
 - In the proposed label, subjects can be titrated to a maximum of 32 mg/hr with an expected mean C_{max} of 32 ng/mL (assuming linear PK and with a mean observed C_{max} was 16 ng/mL for 16 mg/hr in study TMC-CLV-06-01) which is not covered by the observed mean C_{max} of 25.4 ng/mL obtained in this study with 12 mcg/kg/min.

Proposed Label

The sponsor proposed the following description of study findings in Section 12.2 of the proposed label:



Reviewer's Comments: The mean plasma concentrations achieved with the suprathereapeutic dose are approximately 30% lower than the mean concentrations when the highest clinical dose (32 mg/h) is administered.

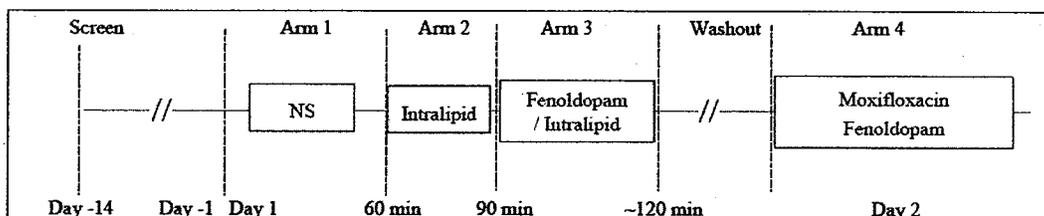
6.6.4. Study Description

6.6.4.1. Design

The study was conducted in 2 phases: a pilot study (Stage I) and the Main Study.

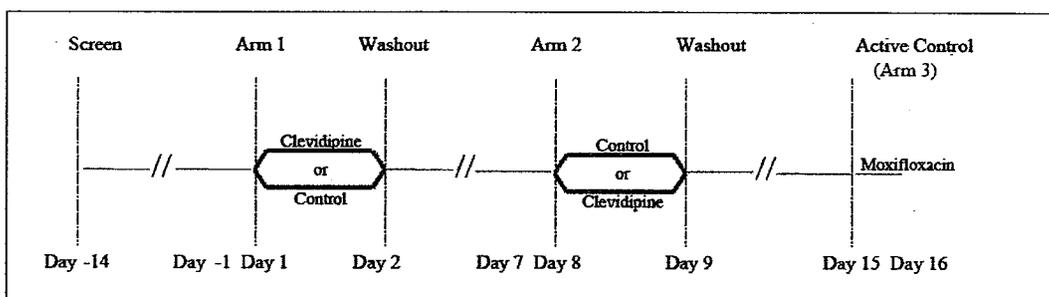
Stage I: An open-label, nonrandomized pilot study to assess: the effect of Intralipid® (20% intravenous [IV] fat emulsion) on ECG parameters.

Figure 3: Study Schematic of Stage I Treatment Arms



Main Study: A randomized, single-blind, vehicle (Intralipid®)- and heart rate-controlled, 2-treatment crossover trial in healthy volunteers, with an additional nonrandomized, open-label positive control treatment (moxifloxacin) with heart rate control, designed to determine the ECG effects and pharmacokinetics associated with IV administration of clevidipine.

Figure 4: Study Schematic of Main Study Treatment Arms



6.6.4.2. Controls

Rather than a standard placebo, a control arm was used. It consisted of Intralipid® infusion to coincide in time and approximate quantity to that given with clevidipine during therapeutic, up-titration, and suprathreshold infusions and with fenoldopam for heart rate control during the equivalent time of the up-titration period.

Oral moxifloxacin was administered with fenoldopam infusion.

6.6.4.3. Blinding

The positive (moxifloxacin) control was not blinded.

6.6.5. Treatment Regimen

6.6.5.1. Treatment Arms

Clevidipine (0.5 mg/mL in 20% lipid emulsion), administered IV over a total infusion time of 23 hours 20 minutes, as follows:

- Therapeutic infusion period (22 hours 15 minutes) – starting at a dose of 0.4 µg/kg/min, with an up-titration to a continuous infusion of 3.2 µg/kg/min
- Up-titration period (45 minutes) – starting at 22 hours 15 minutes, infusion dose increased in increments of 1.1 µg/kg, every 5 minutes, until 12 µg/kg/min or a dose not tolerated by the

subject was reached. If a dose was not tolerated the immediate previous lower dose was resumed.

- Supratherapeutic infusion period (20 minutes) – start at 12 µg/kg/min or highest tolerated dose.

Negative Control: Vehicle- and Heart Rate Control

1. Intralipid® was administered via a peripheral IV cannula in a volume equal to the volume of the dose of clevidipine, in the same manner as that described for clevidipine, for the total infusion period of 23 hours 20 minutes.
2. Corlopam® (Fenoldopam) was provided as a 40.0 µg/mL solution in NS. (1 mL of 10.0 mg/mL in a solution of 250 mL NS). Fenoldopam infusion rates were 0.1 µg/kg/min, 0.3 µg/kg/min and 0.5 µg/kg/min.
 - At 20 hours 45 minutes, NS began at 4 mL/min via a separate peripheral IV cannula.
 - At 22 hours 15 minutes, into the NS cannula, fenoldopam was administered as follows:
 - Fenoldopam infusion Level 1: 0.1 µg/kg/min 15 min duration
 - Fenoldopam infusion Level 2: 0.3 µg/kg/min 15 min duration
 - Fenoldopam infusion Level 3: 0.5 µg/kg/min 15 min duration
 - This infusion was discontinued at 23 hours

Positive-Control: Moxifloxacin 400 mg

— tablets were available as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin). Subjects received a single oral dose of 400 mg moxifloxacin to swallow with water. Fenoldopam was administered as described in the Stage I treatment.

- On the treatment day at time 3 hours, in relation to the time of day, prior to start of dose in the infusion arms, subjects received a single oral dose of 400 mg moxifloxacin to swallow with water.
- Normal saline was administered at 4 mL/min starting 15 minutes prior to the time of moxifloxacin dosing until 1 hour 15 minutes.
- At 1 hour 15 minutes fenoldopam was administered as described above in this section under Vehicle- and Heart rate-control.
- Fenoldopam (or NS at 4 mL/min if fenoldopam was not tolerated) was administered until 2 hours after oral moxifloxacin then IV infusion was discontinued.

6.6.5.2. Sponsor's Justification for Doses

“The therapeutic dose, continuous infusion of 3.2 µg/kg/min for 22 hours 15 minutes, was intended to represent the dose at which a majority of patients demonstrate therapeutic response clinically. The supratherapeutic dose, upward titration to a maximally tolerated dose up to 12 µg/kg/min which was then continued for at least 20 minutes, was intended to achieve serum concentrations of clevidipine and its primary metabolite, H152/81, which are higher than those likely to be encountered clinically.

The presence of a metabolite with a longer half-life than the parent compound requires a long initial period of infusion to allow serum levels of the metabolite to approximate steady state. After the maintenance infusion, a period of up-titration to a maximally tolerated or maximal dose followed by continued administration of that dose for at least 20 minutes was used to increase levels of the parent compound and its metabolite to levels in excess of those likely to be encountered in clinical practice.”

Reviewer's comment: The 12 mcg/kg/min dose (supra-therapeutic) corresponding to 60 mg/hr for a 83 kg patient is double the highest proposed clinical dose of 32 mg/hr. However, in the proposed label, subjects can be titrated to a maximum of 32 mg/hr with an expected mean C_{max} of 32 ng/mL (assuming linear PK and with a mean observed C_{max} was 16 ng/mL for 16 mg/hr in study TMC-CLV-06-01) which is not covered by the observed mean C_{max} of 25 ng/mL obtained in this study with 12 mcg/kg/min.

6.6.5.3. Instructions with Regard to Meals

Subjects should have been given their morning meal at the usual time on Days 1 and 8 and after the discontinuation of the infusions on Days 2, 9, and 15.

6.6.5.4. ECG and PK Assessments

Table 4: Sampling Schedule for Main Stage — Clevidipine and Vehicle- and Heart Rate-Controlled Infusion Arms (Double Blind Phase)

Study Assessment	Screening Period	Pre-Treatment (Night before)	Baseline (Saline infusion, -1.5 to 0 hours)				Therapeutic Infusion (0 to 22 h 15 min)						Up-Titration Infusion	Supra-therapeutic Infusion ³ (23 to 23.3 hours)				Post-Infusion ³ (23.3 to 36 hours)								
	-14 Days to -3 Days	Day 0 and Day 7	-1.5 h	-1.0 h	-30 min	-15 min	2 h	4 h	8 h	12 h	20 h	22 h	21 h	21.5 h	22 h	(22 h 15 min to 23 hours)	23 h	23h 5 min	23h 10 min	23h 15 min	23h 20 min	23.5 h	24 h	27 h	28 h	36 h
Informed consent	X																									
Medical history	X																									
Chemistry and hematology ¹	X																									
Urine pregnancy ²	X	X																								
Blood alcohol and urine drug screen	X	X																								
Normal Saline Infusion (4 mL/min) ⁷												X	X	X												
12-lead ECG	X	X	X	X			X							X												X
Vital Signs	X	X		X	X																					
Physical exam	X																									
Height and weight	X	X																								
Interim history		X																								
Holter ⁶						X																				
Extracted 12-lead ECG			X	X	X	X	X					X	X	X	X ⁵		X	X		X	X	X	X	X	X	
Concomitant medications	X	X																								
Pharmacokinetic samples ⁴				X	X	X	X					X	X	X		X		X				X	X			
AE and SAE reporting																										

- As described in Section 9.7.3
- Women of childbearing potential only
- See Table 14 for the exact times for Therapeutic Infusion, Supra-therapeutic Infusion, and Post-infusion Periods BP and HR times.
- The sampling timepoints were: -10 min, 2 h 20 min, 8 h 20 min, 20 h 50 min, 21 h 20 min, 21 h 50 min, 23 h 5 min, 23 h 18 min, 24 h 20 min, and 27 h 20 min. Sample should have been drawn to accommodate extraction of ECGs from Holter.
- See Table 18 below for times of extracted ECGs.
- Holter electrodes were to be applied and recording no later than 90 minutes prior to infusion start.
- NS was administered at 4 mL/min starting 20 h 45 min until 22h 15 min when fenoldopam infusion was initiated.

(Sponsor's Table 3, page 44 of Clinical Study Report TMC-CLV-05-01)

Table 5: Sampling Schedule for Main Stage — Moxifloxacin Arm (Open Label Phase)

Study Assessment	Pre-Treatment	Baseline				Moxifloxacin Treatment							
	Day 14	-90 h	-30 min	-15 min	0	HR titration			2 h	3 h	4 h	6 h	8 h
						1 h 15 min	1 h 30 min	1 h 45 min					
Moxifloxacin drug administration					X								
NS (4 mL/min) ⁵				X	X								
HR titration with fenoldopam/NS								X					
Informed consent													
Medical history													
Chemistry and hematology ¹	X												
Urine pregnancy ²	X												
Blood alcohol and urine drug screen	X												
12-lead ECG	X		X									X	
Vital Signs	X		X	X				X ⁴				X	
Physical exam													
Height and weight	X												
Interim history	X												
Holter					X								
Extracted 12-lead ECG from Holter								X ³					
Concomitant medications	X												
Pharmacokinetic samples													
AE reporting								X					
SAE reporting								X					

- Note – Dose time is 3 hours earlier, in relation to time of day, than start of clevidipine and control arm therapy
- As described in Section 9.7.3
 - Women of childbearing potential only
 - See Table 19 below for times of extracted ECGs.
 - Continuous HR monitoring and BP was as necessary during fenoldopam infusion (See Table 14).
 - NS was to be administered at 4 mL/min starting 15 minutes prior to dosing with moxifloxacin until 1h 15 min when fenoldopam was administered

(Sponsor's Table 4, page 45 of Clinical Study Report TMC-CLV-05-01)

6.6.5.5. Baseline

The baseline ECGs were designated as all ECGs extracted during the time -1:30 to 0:00 in each of the clevidipine or control arms and all ECGs extracted during the time -0:30 to 0:00 for the moxifloxacin arm.

6.6.6. ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Electrocardiogram data was recorded onto the flash memory cards, which were delivered to a core laboratory at the end of each treatment period. All definitive ECG measurements were derived from these continuous recordings. Subjects were supine and quiet from 5 minutes prior to the end of each recording period. Blood drawing, vital sign measurements, and other procedures followed the period of ECG acquisition.

The core ECG laboratory scanned all Holter recordings and identified arrhythmia, artifact, or signal loss preventing adequate interpretation of the recording. Each ECG was interpreted using digital, on-screen software allowing the placement of electronic markers at the beginning and end of each ECG interval. Three ECG complexes were marked on each ECG in the lead with the longest apparent QT interval. Three individual ECGs were extracted from each critical observation period and the results of these 3 averaged to comprise a single observation for statistical purposes.

A single cardiologist reader was assigned to each subject and was blinded to the treatment arms. The order of visits was randomly shuffled to minimize the possibility that the blinded reviewers would be aware of sequencing of treatment in relation to effect on heart rate. In addition, reviewers were blinded to date and time of visits.

6.6.7. Sponsor's Results

6.6.7.1. Study Subjects

46 healthy male and female subjects 18 -60 years of age with normal baseline ECGs and blood pressure were enrolled. 14 subjects were terminated early. The reasons for withdrawal were:

- The protocol stipulated subjects with the following had to be withdrawn or dose of clevidipine or fenoldopam reduced if the blood pressure fell to less than 90 mmHg systolic or less than 45 mmHg diastolic on 2 vital sign readings repeated within 2 minutes; six subjects were discontinued for this reason.
- Two were discontinued due to AEs; both subjects had headaches.
- Three "withdrew consent."
- Two withdrew due to lack of transportation
- One withdrew due to work schedule conflicts

6.6.7.2. Statistical Analyses

Stage I Analysis

There is no effect seen during stable infusion of normal saline (NS), Intralipid infusion as seen in Table 6 were none of the comparison pairs are statistically significant.

Table 6 Paired Average Values by Subject

Pair	Int	Diff	Lower 95% two-sided CI	Upper 95% two-sided CI	N	p	significant
NS vs BL	HR	1.38	-2.87	5.62	8	0.469	
	QT	0.31	-5.53	6.16	8	0.903	
	QTcB	4.63	-5.48	14.73	8	0.315	
	QTcF	3.19	-2.78	9.14	8	0.246	
IL vs BL	HR	0.06	-1.72	1.84	8	0.936	
	QT	2.19	-3.03	7.40	8	0.354	
	QTcB	2.88	-0.92	6.67	8	0.117	
	QTcF	2.69	-0.98	6.36	8	0.127	
IL vs NS	HR	-1.31	-5.74	3.11	8	0.506	
	QT	1.88	-4.79	8.54	8	0.527	
	QTcB	-1.75	-13.30	9.80	8	0.731	
	QTcF	-0.50	-7.80	6.80	8	0.876	
IL vs NS and BL	HR	-0.63	-3.24	1.99	8	0.590	
	QT	2.03	-3.19	7.26	8	0.389	
	QTcB	0.56	-6.39	7.52	8	0.854	
	QTcF	1.09	-3.86	6.05	8	0.618	

NS=Normal saline, BL=Baseline,IL=Intralipid
 (Sponsor's Table, page 753 of Clinical Study Report TMC-CLV-05-01)

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The ability to detect the repolarization effect of moxifloxacin was assessed in 8 subjects. The estimated mean change in QTcF at 2 hours post moxifloxacin dosing was 10.4 ms (95% CI 1.9-18.9 ms) (see Table 7).

Table 7 Paired Analysis of All ECGs and Direct Comparison of Uncorrected QT

Interval	Time	Diff	Lower 95% two-sided CI	Upper 95% two-sided CI	N	p	significant
HR	1:20	3.25	0.00	6.50	8	0.050	
HR	1:35	1.13	-2.08	4.33	8	0.434	
HR	1:40	5.25	0.59	9.91	8	0.032	*
HR	1:45	4.63	2.06	7.19	8	0.004	**
HR	1:50	-0.25	-3.65	3.15	8	0.867	
HR	1:55	-0.13	-5.38	5.13	8	0.957	
HR	2:00	1.25	-3.90	6.40	8	0.584	
QT	1:20	-2.75	-15.23	9.73	8	0.618	
QT	1:35	-0.38	-6.90	6.15	8	0.896	
QT	1:40	-7.88	-16.12	0.37	8	0.059	
QT	1:45	-7.13	-18.20	3.95	8	0.172	
QT	1:50	0.38	-6.93	7.68	8	0.907	
QT	1:55	2.88	-11.36	17.11	8	0.648	
QT	2:00	6.68	-5.70	19.45	8	0.237	
QTcB	1:20	7.38	-4.66	19.41	8	0.191	
QTcB	1:35	4.63	-4.79	14.04	8	0.284	
QTcB	1:40	10.63	-1.71	22.96	8	0.081	
QTcB	1:45	6.63	-4.48	17.73	8	0.201	
QTcB	1:50	0.25	-14.90	15.40	8	0.970	
QTcB	1:55	4.38	-8.28	17.03	8	0.441	
QTcB	2:00	12.13	1.56	22.69	8	0.030	*
QTcF	1:20	3.88	-7.29	15.04	8	0.439	
QTcF	1:35	3.13	-3.70	9.95	8	0.315	
QTcF	1:40	4.25	-4.30	12.80	8	0.278	
QTcF	1:45	2.00	-8.34	12.34	8	0.661	
QTcF	1:50	0.13	-11.75	12.00	8	0.981	
QTcF	1:55	4.13	-6.59	14.84	8	0.393	
QTcF	2:00	10.38	1.86	18.89	8	0.024	*

(Sponsor's Table, page 755 of Clinical Study Report TMC-CLV-05-01)

Reviewer's comment: Stage I of the study does not demonstrate assay sensitivity. With only 8 subjects in phase 1, the data collected are descriptive only and any conclusions made by the sponsor should be viewed with caution.

Primary Analysis

The primary endpoint is the maximal mean difference in uncorrected QT between clevidipine and vehicle- and heart rate-control after baseline correction at each time point.

Reviewer's Comment: This pre-specified primary endpoint was not used. Instead, the sponsor relied on QTcF and exponential individual-correction (QTcEi). QTcB was presented for completeness.

Moxifloxacin treatments were compared with vehicle- and HR-control at analogous periods rather than actual time from administration as shown in Table 8.

Table 8. Pairing of Moxifloxacin Observations with Control Observations

Control Arm	Designation	Moxi Arm	Designation
-1 h	Baseline 1	- 30 min	MoxiBaseline 1
-30 min	Baseline 2	- 15 min	MoxiBaseline 2
21.5 h	Therapeutic concentration 2	40 min	Moxi 1
22 h	Therapeutic concentration 3	1 h 0 min	Moxi 2
22 h 20 min	Up-titration HR 1	1 h 20 min	MoxiFeno 1
22 h 28 min	Up-titration HR 2	1 h 28 min	MoxiFeno 2
22 h 36 min	Up-titration HR 3	1 h 36 min	MoxiFeno 3
22 h 42 min	Up-titration HR 4	1 h 42 min	Moxi/Feno 4
22 h 50 min	Up-titration HR 5	1 h 50 min	Moxi Feno 5
22 h 58 min	Up-titration HR 6	1 h 58 min	Moxi Feno 6
23 h 10 min	Supratherapeutic 1	2 h 15 min	Moxi Late 1
23 h 15 min	Supratherapeutic 2	2 h 30 min	Moxi Late 2

Source: Thorough QT Study Analysis Report for the Main Study, Appendix 16.1.12.2

(Sponsor's Table 29, page 99 of Clinical Study Report TMC-CLV-05-01)

Time-matched raw mean differences and upper bound of 95% one-sided CI between clevidipine and vehicle- and heart rate-control were estimated and listed in Table 9. Time-matched raw mean differences and lower bound of 95% one-sided CI between moxifloxacin and vehicle- and heart rate-control were estimated and listed in Table 10. Figure 5 details the complete results of paired t-testing for the control-subtracted changes from baseline for QTcF ($\Delta\Delta\text{QTcF}$).

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Table 9. $\Delta\Delta$ QTcF Intervals – Clevidipine vs. Control

Time	dQTcF Clev	dQTcF Ctrl	Diff(ddQTcF)	StdErr	N	UB 95% one-sided CI	>10 msec
EI1	-8.1	-1.7	-6.4	3.24	32	-0.9	
EI2	-14	-9.1	-4.9	2.1	32	-1.3	
TC1	-9.2	-3.4	-5.8	3.256	33	-0.3	
TC2	-11.5	-2.1	-9.4	3.831	33	-2.9	
TC3	-10.6	-2.6	-8.1	3.785	33	-1.7	
UT1	-11.4	-1.2	-10.2	3.428	33	-4.4	
UT2	-13.2	-2.3	-10.9	3.07	33	-5.7	
UT3	-15	-1.5	-13.5	2.697	33	-8.9	
UT4	-18.4	-2	-16.4	3.126	32	-11.1	
UT5	-19.1	0.3	-19.4	3.173	31	-14.0	
UT6	-21.9	-3.4	-18.6	3.001	33	-13.5	
ST1	-20.4	-4.4	-15.9	2.967	33	-10.9	
ST2	-19	-4.7	-14.3	3.154	33	-9.0	
PI1	-9.8	-7.9	-1.9	3.347	33	3.8	
PI2	-11	-10.8	-0.3	3.226	31	5.2	
PI3	-15	-16.2	1.2	2.746	33	5.8	

UB = upper boundary.

(Sponsor's Table 10.3, page 812 of Clinical Study Report TMC-CLV-05-01)

Table 10. $\Delta\Delta$ QTcF Intervals – Moxifloxacin vs. Control

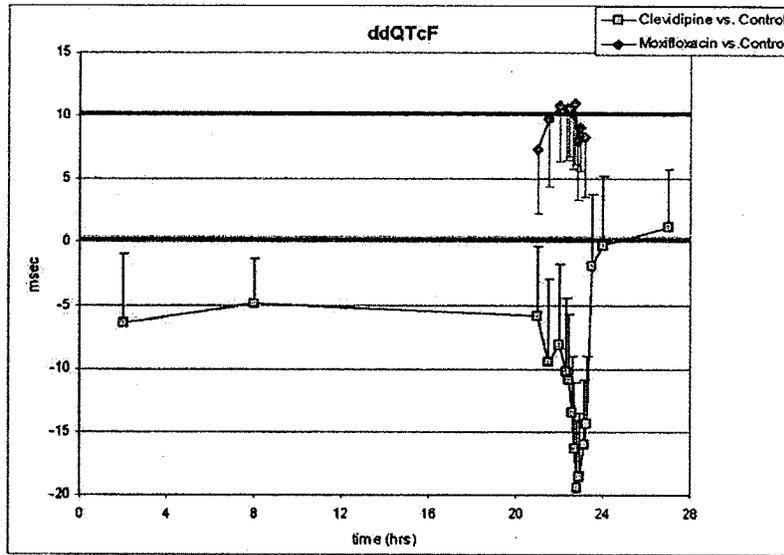
Time	dQTcF Mox	dQTcF Ctrl	Diff(ddQTcF)	StdErr	N	LB 95% one-sided CI	>0 msec
M1	5.1	-2.2	7.3	2.970	32	2.3	***
M2	7.0	-2.8	9.8	3.193	32	4.4	***
MF1	9.6	-1.2	10.8	2.635	32	6.4	***
MF2	8.2	-2.4	10.6	2.437	31	6.5	***
MF3	9.0	-1.6	10.6	2.257	32	6.8	***
MF4	8.6	0.6	8.0	2.709	32	3.4	***
MF5	6.0	-3.3	9.3	1.967	31	6.0	***
MF6	6.4	-4.5	10.9	2.864	32	6.1	***
ML1	3.7	-4.6	8.3	2.781	32	3.6	***
ML2	8.1	-2.0	10.1	2.585	32	5.8	***

LB = lower boundary.

(Sponsor's Table 10.4, page 812 of Clinical Study Report TMC-CLV-05-01)

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Figure 5. $\Delta\Delta$ QTcF for Clevidipine and Moxifloxacin with 1-sided 95% CI



(Sponsor's Figure 17, page 114 of Clinical Study Report TMC-CLV-05-01)

For the primary analyses, no values of mean for clevidipine exceeding 0 and all upper bounds considerably below 10 ms. The maximum of the means is at the last observation at 27 hours with a mean of 1.2 ms and the upper bound of the 95% CI one-sided of 5.8 ms.

For moxifloxacin, each value of the $\Delta\Delta$ QTcF lower bounds exceeds 0. All $\Delta\Delta$ QTcF moxifloxacin values exceed the E14 threshold for adequate assay sensitivity. The maximal mean effect is 10.9 ms at the fifth up-titration time, 1 hour 50 minutes with a lower bound of the 95% CI one-sided of 6.1 ms. The minimum of the lower bounds is at the first observation at 40 minutes and is 2.3 ms.

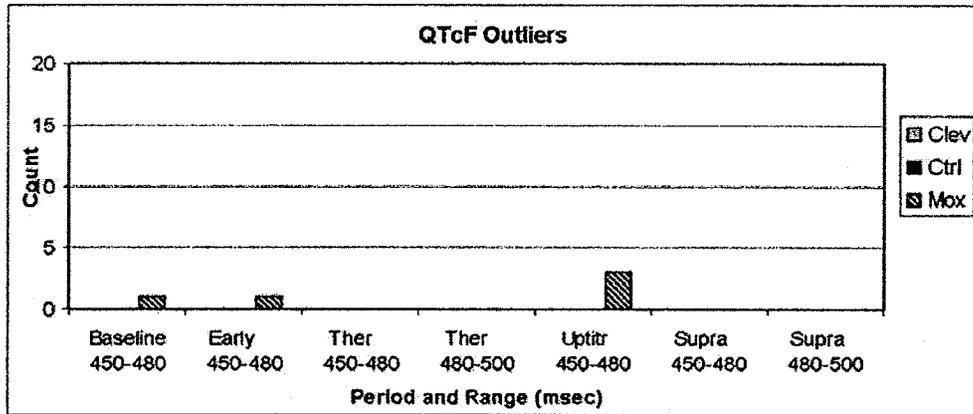
Reviewer's comments: To establish assay sensitivity, at least one lower bound of 90% confidence interval with multiplicity justification should be greater than 5 ms. In this study moxifloxacin was measured 10 times over 2.5 hours, therefore, multiplicity adjustment may not be appropriate.

Categorical Analysis

Outliers for absolute values of QTcF were tabulated in Figure 6 according to the following ranges: ≥ 450 to < 480 , ≥ 480 to < 500 , and ≥ 500 . The majority of outlier values are for moxifloxacin treatment. No trends are evident for QTcF for clevidipine outliers to be more prevalent than control at similar time points.

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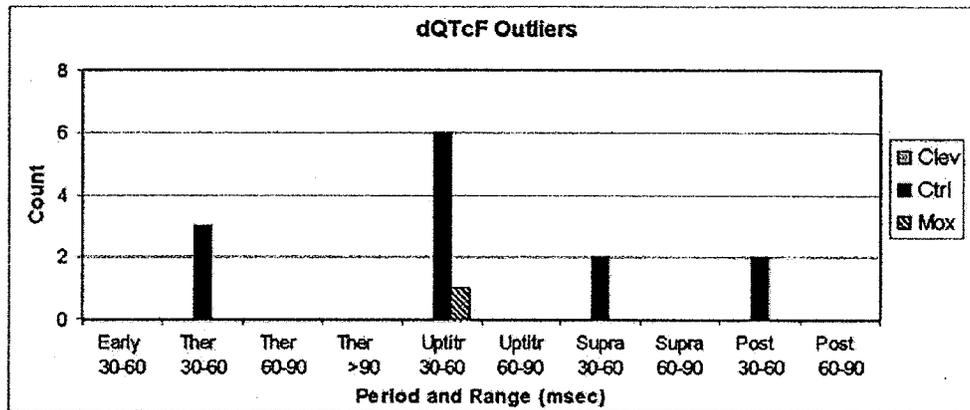
Figure 6. Intervals Outliers



(Sponsor's Figure 12.1, page 822 of Clinical Study Report TMC-CLV-05-01)

Outliers for delta values of QTcF were tabulated according to the following ranges: ≥ 30 to < 60 , ≥ 60 to < 90 , and ≥ 90 .

Figure 7. Delta Interval Outliers



(Sponsor's Figure 12.2, page 824 of Clinical Study Report TMC-CLV-05-01)

Additional Analyses

The sponsor also performed similar analysis for QTcB and individual (QTcEi) corrected QT using exponential equation. The results from QTcEi are similar to the results of QTcF. However, the results from QTcB were essentially uninterrupted. The maximal mean, control-subtracted change of QTcB, while in excess of the E14 criteria, was influenced by the heart rate changes associated with clevidipine. There were wide swings in the $\Delta\Delta\text{QTcB}$ response.

6.6.7.3. Safety Analysis

No deaths or SAEs were observed. Two AEs of headache led to subject discontinuation and six other subjects were discontinued for hypotension. No subjects were observed to have syncope, seizure, or a ventricular arrhythmia. The sponsor concludes: "Overall, the changes in the clinical safety assessments were unremarkable."

6.6.7.4. Clinical Pharmacology

Pharmacokinetic Analysis

The time course of clevidipine and its major metabolite, H152/81, followed the predicted pattern with maximal values at the end of the suprathreshold infusion. Clevidipine levels dropped rapidly after discontinuation (see Table 11 and Figure 8).

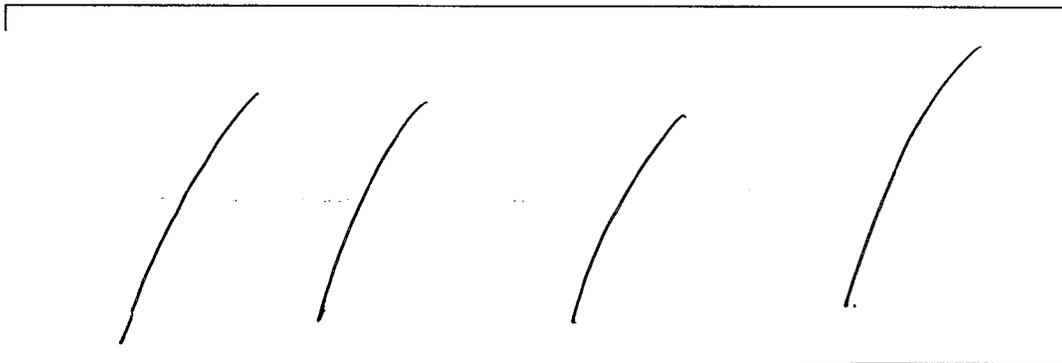
There was a rapid change in QTc findings immediately after discontinuation of clevidipine despite the persistence of levels of H152/81. The metabolite did not appear to have QT activity.

Table 11. Mean Maximum Concentration.

T_{max}	C_{max} Clevidipine (ng/mL)	C_{max} H152/81 (mcg/mL)
23h 15min from start of the 23h infusion	20.56	6.11

(Sponsor's Table 37, page 117 of Clinical Study Report TMC-CLV-05-01)

Figure 8. Concentration Time Course



(Sponsor's Figure 17, page 117 of Clinical Study Report TMC-CLV-05-01)

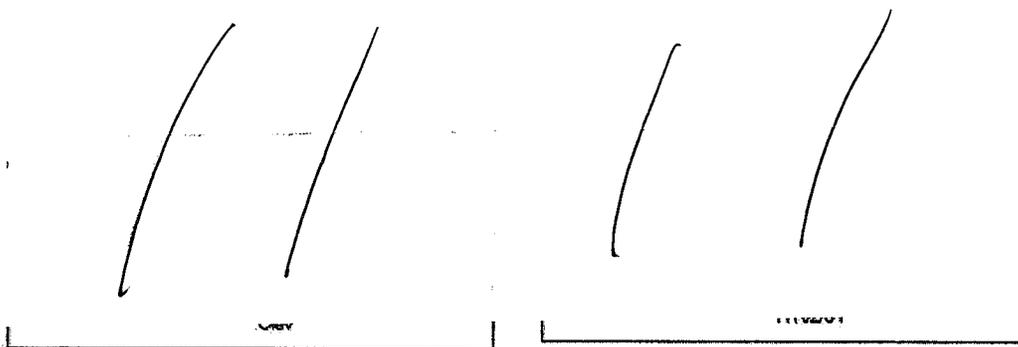
Exposure-Response Analysis

The relationships for $\Delta\Delta QTcF$ and $\Delta\Delta QTcEi$ values for clevidipine and concentration showed a negative relationship and were statistically significant. All slope values were negative for H152/81 (see Figure 9).

Figure 9. $\Delta\Delta QTcF$ vs. Clevidipine (left) and H152/81 (right) concentrations.

Combined Subjects $\Delta\Delta QTcF$ By Clev

Combined Subjects $\Delta\Delta QTcF$ By H152/81



(Sponsor's Figures 25, page 882 of Clinical Study Report TMC-CLV-05-01)

REVIEWERS' ASSESSMENT

6.7 Statistical Assessments

Our evaluation is based on the sponsor's data and in accordance with ICH E14 guidelines on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. We used the following data set submitted in the NDA to carry out some of the independent analyses for statistical evaluation of the results:

http://erom.fda.gov/eRoom/CDER1/CDERnterdisciplinaryReviewTeamQTGroup/0_b33f

This data set includes individual values of the 3 replicates ECG measurements. Forty six patients were enrolled in the main study. 32 patients completed the main study; 14 patients had early termination (1 patient completed the first 2 periods of the study). Therefore, the main analysis was based on the data from 33 patients (32 completers and the early withdrawn patient who completed the first 2 periods of the study). The assay sensitivity analysis was based on the data from the 32 completers. Categorical analysis was based on all the data from the 46 enrolled patients.

6.7.1. Inferential Analysis

We calculated the raw mean differences as well as the corresponding 90% CI between clevidipine/moxifloxacin and control at each time point. The QTcF of moxifloxacin treatment were measured at different time frame. We compared moxifloxacin treatments with the control using the time matching table provided by the sponsor (Table 8). QTcF change from baseline (for each subject the baseline is calculated as the average of all baseline values for that treatment) and the difference of QTcF change from baseline between control and clevidipine with the corresponding 90% CI at each time point are summarized in Table 12. Similar results for moxifloxacin and control are listed in Table 13. The results are similar to the sponsor's reported results. Figure 10 provides a time-matched mean Δ QTcF change from control values.

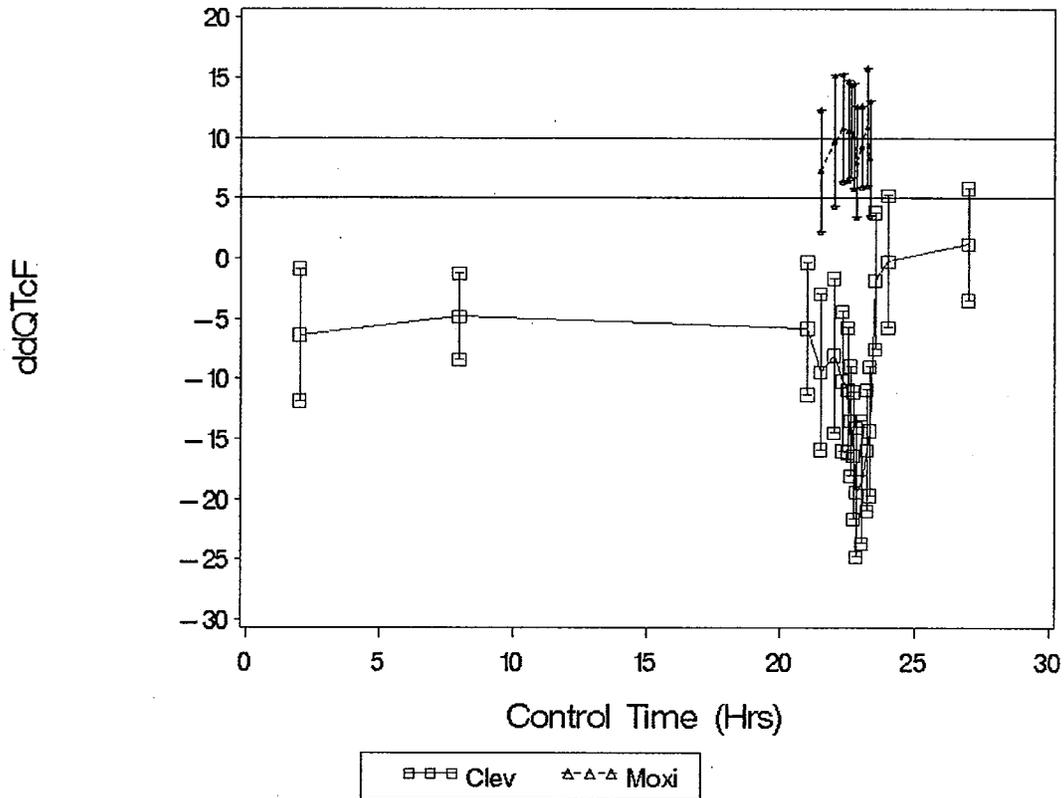
Table 12. Summary of Comparison of Clevidipine with Control

Time	Δ QTcF			90% CI
	Clev	Ctrl	$\Delta\Delta$ QTcF	
2 h	-8.06	-1.70	-6.36	(-11.85, -0.87)
8 h	-14.02	-9.27	-4.84	(-8.40, -1.28)
21 h	-9.25	-3.45	-5.79	(-11.30, -0.29)
21.5 h	-11.52	-2.11	-9.41	(-15.89, -2.92)
22 h	-10.62	-2.59	-8.04	(-14.44, -1.63)
22 h 20 min	-11.39	-1.21	-10.18	(-15.97, -4.38)
22 h 28 min	-13.23	-2.31	-10.91	(-16.10, -5.72)
22 h 36 min	-14.98	-1.51	-13.48	(-18.04, -8.92)
22 h 42 min	-18.35	-1.99	-16.36	(-21.65, -11.07)
22 h 50 min	-19.09	0.69	-19.37	(-24.75, -13.99)
22 h 58 min	-21.99	-3.20	-18.54	(-23.63, -13.44)
23 h 10 min	-20.36	-4.44	-15.91	(-20.94, -10.88)
23 h 15 min	-19.04	-4.73	-14.31	(-19.65, -8.97)
23.5 h	-9.75	-7.93	-1.82	(-7.50, 3.85)
24 h	-11.05	-10.81	-0.24	(-5.71, 5.23)
27 h	-14.83	-15.99	1.21	(-3.44, 5.86)

Table 13. Summary of Comparison of Moxifloxacin with Control

Ctrl Time	Moxi Time	Δ QTcF			90% CI
		Moxi	Ctrl	$\Delta\Delta$ QTcF	
21.5 h	40 min	5.08	-2.11	7.32	(2.29, 12.35)
22 h	1 h 0 min	6.95	-2.59	9.79	(4.38, 15.21)
22 h 20 min	1 h 20 min	9.61	-1.21	10.85	(6.39, 15.31)
22 h 28 min	1 h 28 min	8.23	-2.31	10.63	(6.50, 14.76)
22 h 36 min	1 h 36 min	8.95	-1.51	10.60	(6.77, 14.43)
22 h 42 min	1 h 42 min	8.14	-1.99	10.17	(5.79, 14.55)
22 h 50 min	1 h 50 min	8.55	0.69	8.04	(3.44, 12.63)
22 h 58 min	1 h 58 min	6.23	-3.20	9.32	(5.98, 12.66)
23 h 10 min	2 h 15 min	6.45	-4.44	10.96	(6.10, 15.82)
23 h 15 min	2 h 30 min	3.71	-4.73	8.35	(3.63, 13.07)

Figure 10. Time-Matched Mean Δ QTcF Change from Control Values



Based on the above analysis, the statistical reviewer makes the following conclusions:

- All the upper bounds of the two-sided 90% confidence intervals on the mean difference in change from baseline between the clevidipine treatment group and control were less than 10 ms at all time points.
- The unadjusted largest 90% lower bound for moxifloxacin is 6.77 ms, which is above 5 ms.

6.7.2. Categorical Analysis

The statistical reviewer performed the categorical analysis on the individual triplicate readings. Since the collected data show some signals of QT shortening, the statistical reviewer also calculated the percentage of the observations less than -60 ms and between -60 ms to -30 ms after baseline correction (Table 18 and Table 19).

No observations have QTcF larger than 500 ms.

Table 14. Frequency for QTcF > 450 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	3	7.32%	242	5	2.07%
Baseline - Moxifloxacin	32	1	3.13%	192	3	1.56%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	2	5.26%	1588	2	0.13%

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Moxifloxacin	32	5	15.63%	956	17	1.78%
Control	40	2	5.00%	1905	4	0.21%

Table 15. Frequency for QTcF > 480 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	1	3.13%	192	1	0.52%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	0	0.00%	1588	0	0.00%
Moxifloxacin	32	1	3.13%	956	1	0.10%
Control	40	0	0.00%	1905	0	0.00%

Table 16. Frequency for Δ QTcF between 30 ~ 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	3	7.89%	1588	5	0.31%
Moxifloxacin	32	14	43.75%	956	25	2.62%
Control	39	4	10.26%	1857	36	1.94%

Table 17. Frequency for Δ QTcF > 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	0	0.00%	1588	0	0.00%
Moxifloxacin	32	0	0.00%	956	0	0.00%
Control	39	1	2.56%	1857	5	0.27%

Table 18. Frequency for Δ QTcF between -60 ~ -30 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	1	2.44%	242	1	0.41%
Baseline - Moxifloxacin	32	1	3.13%	192	1	0.52%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	19	50.00%	1588	231	14.55%
Moxifloxacin	32	3	9.38%	956	5	0.52%
Control	39	16	41.03%	1857	55	2.96%

Table 19. Frequency for Δ QTcF <-60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	6	15.79%	1588	15	0.94%
Moxifloxacin	32	1	3.13%	956	1	0.10%
Control	39	4	10.26%	1857	6	0.32%

6.8 Clinical Pharmacology Assessments

6.8.1. Exposure-Response Modeling

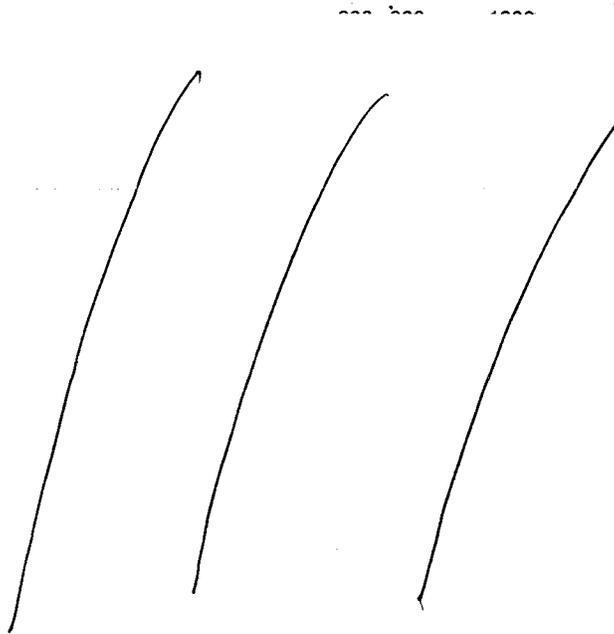
Only the subset of the ECG with corresponding clevidipine concentrations were used for the concentration-QT analysis (i.e. 9 out of 17 time points).

6.8.1.1. QTc Corrections

The observed QT-RR interval relationship is presented in Figure 11 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI) methods.

The QTcF appears to be the most reasonable QT correction method removing the heart rate effect in QT illustrated by a horizontal trend in the QTcF vs. RR relationship. The QTcF correction method was therefore used for the reviewer's concentration-QTcF analysis.

Figure 11. Baseline day QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).



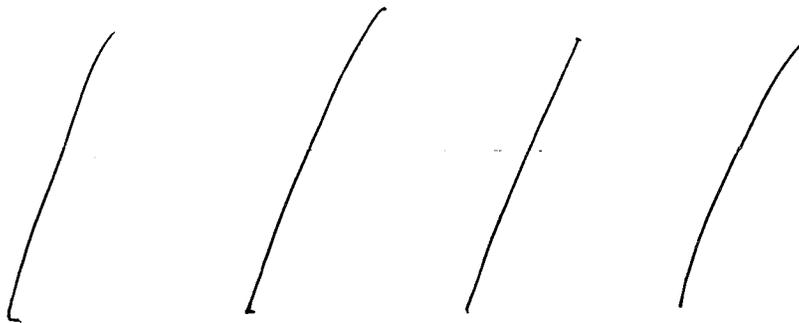
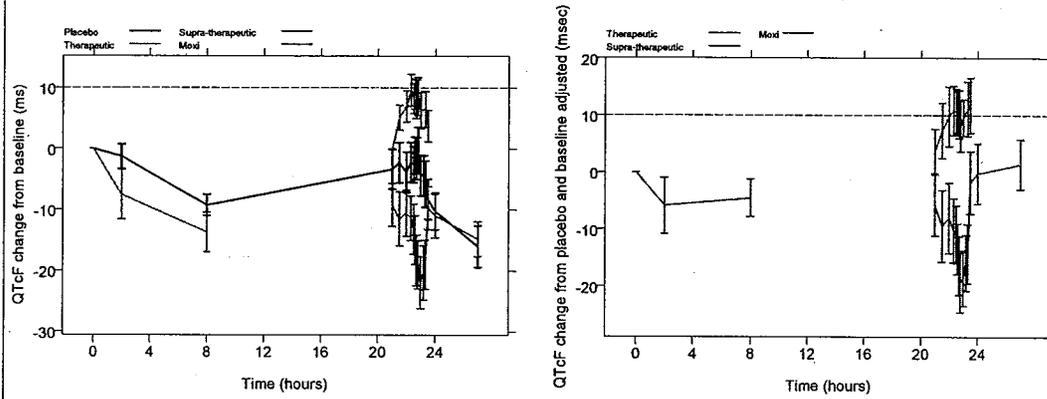
6.8.1.2. $\Delta\Delta\text{QTcF}$ and Concentration Time Profiles

The mean ΔQTcF (change from baseline), $\Delta\Delta\text{QTcF}$ (change from baseline and vehicle- and heart rate-control corrected), clevidipine and its main metabolite H152/82 concentration profiles are shown in Figure 12.

The minimum $\Delta\Delta\text{QTcF}$ of -20 ms occurs around 23 hours postdose which coincide with the peak clevidipine concentration.

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Figure 12. Mean (90% CI) Δ QTcF Change from Baseline (top left), $\Delta\Delta$ QTcF (top right), and Clevidipine concentration (bottom left), and H152/82 concentration (bottom right) profiles for control (black line), therapeutic dose of 3.2 mcg/kg/min (blue line), supra-therapeutic dose of 12 mcg/kg/min (red line), and moxifloxacin (green line) arm.

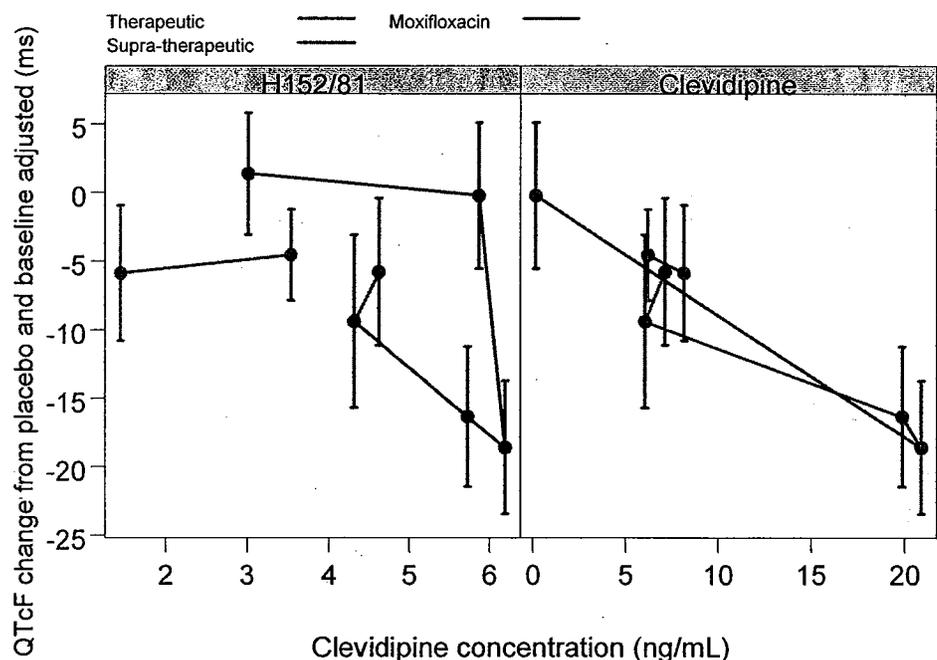


*Moxifloxacin was assessed 0- 2.5 hrs from baseline measurement but visualized around 21-23.5 hrs in order to subtract mean control Δ QTcF for moxifloxacin $\Delta\Delta$ QTcF calculations.

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There was no delay observed between $\Delta\Delta\text{QTcF}$ and clevidipine concentrations while there was a delay between the metabolite H152/81 and $\Delta\Delta\text{QTcF}$. The drug effect on the QT interval therefore appears to be caused by clevidipine and not the metabolite H152/81.

Figure 13. Mean (90% CI) $\Delta\Delta\text{QTcF}$ vs. H152/81 (Left) and Clevidipine (Right) concentrations



6.8.1.3. Concentration-QTcF Analysis

The relationship between $\Delta\Delta\text{QTcF}$ and clevidipine concentrations was investigated by linear mixed-effects modeling. Data collected from the 3.2 mcg/kg/min and 12 mcg/kg/min clevidipine dose groups was used for the clevidipine concentration-QTcF analysis.

Linear and log-linear models were initially tested with the log-linear models describing the data best.

The following three log-linear models were considered:

- Model 1 is a log-linear model with an intercept;
- Model 2 is a log-linear model with mean intercept fixed to 0 (with variability);
- Model 3 is a log linear model with no intercept.

Table 20 summarizes the results of the clevidipine-QTcF analyses. The intercept was not found to be statistical significant. However, model 1 was applied for further analysis due to better description of the observed data.

Table 20. Exposure-Response Analysis of Clevidipine associated $\Delta\Delta\text{QTcF}$ Prolongation

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} \cdot \log(\text{Clevidipine Concentration})$		
Intercept, ms	-2.63 (-7.65, 2.39) 0.38	14.4
Slope, ms per log ng/mL	-3.76 (-4.99, -2.53) <0.0001	0.0

Residual Variability, ms	12.2	--
Model 2: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \log(\text{Clevipidine Concentration})$ (Fixed Intercept)		
Intercept, ms	0 (fixed)	14.7
Slope, ms per log ng/mL	-4.07 (-5.18, -2.96) <0.0001	0.0
Residual Variability, ms	12.2	--
Model 3: $\Delta\Delta\text{QTcF} = \text{slope} * \log(\text{Clevipidine Concentration})$ (No Intercept)		
Slope, ms per log ng/mL	-4.96 (-6.78, -3.13) <0.0001	5.38
Residual Variability, ms	15.4	--

Based on model 1, the predicted $\Delta\Delta\text{QTcF}$ interval at the mean peak clevipidine concentration after steady-state dosing of the therapeutic dose of 3.2 mcg/kg/min and single dose of 12 mcg/kg/min is presented in Table 21. The lower 90% CI of the mean $\Delta\Delta\text{QTcF}$ is -15.4 ms and -19.5 for the therapeutic and supra-therapeutic doses.

Table 21: Predicted Change of $\Delta\Delta\text{QTcF}$ Interval at Peak Clevipidine Concentration using a Log-Linear Model with Intercept.

Dose Group	Predicted change in $\Delta\Delta\text{QTcF}$ interval (ms)	
	Mean	90% Confidence Interval
3.2 mcg/kg/min (steady-state)		
Mean C_{max} (9.33 ng/ml)	-11.0	(-15.4, -6.62)
12 mcg/kg/min (single dose)		
Mean C_{max} (25.4 ng/ml)	-14.8	(-19.5, -10.1)

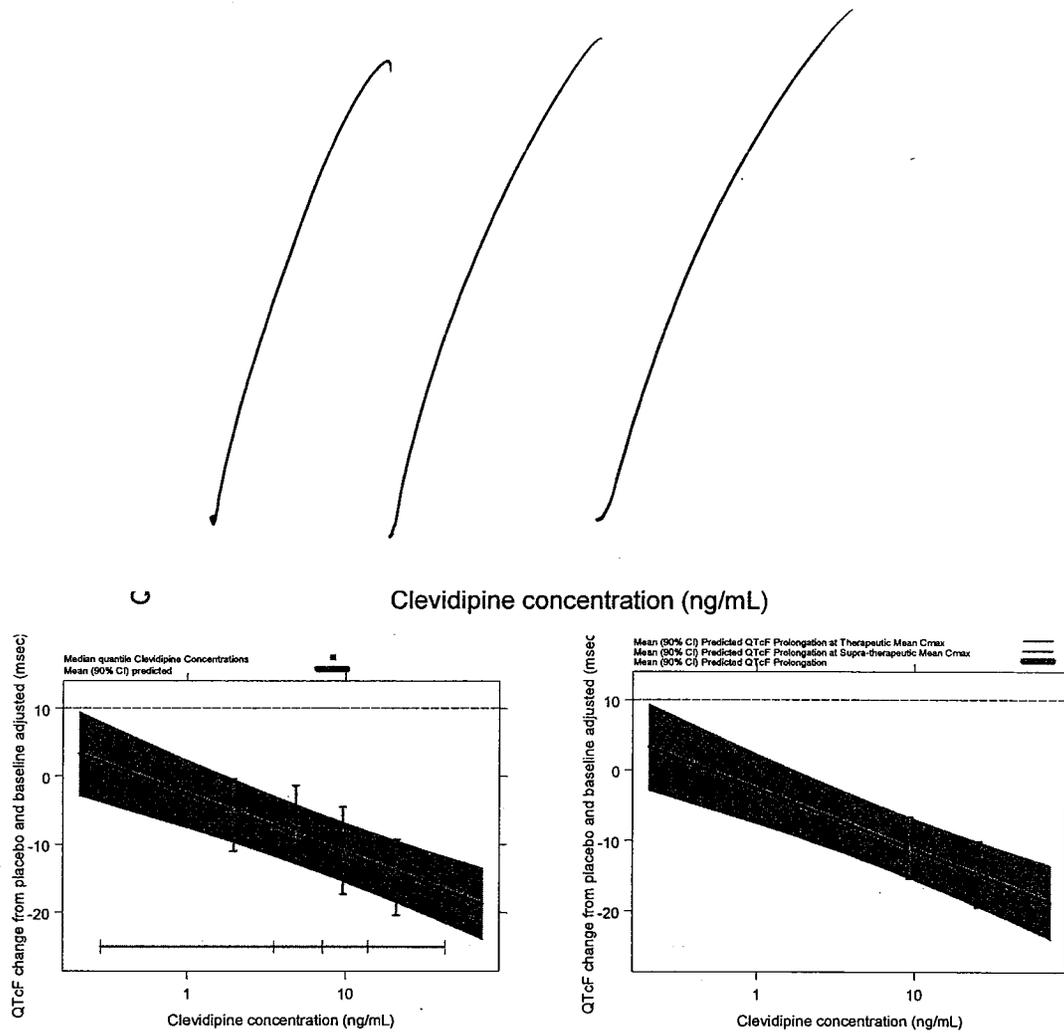
The relationship between clevipidine concentrations and $\Delta\Delta\text{QTcF}$ is visualized in Figure 14 where the raw data is shown on top with the concentrations on the log-normal scale.

The goodness-of-fit is illustrated in the bottom left graph of Figure 14 showing the observed median-quartile concentrations and associated mean $\Delta\Delta\text{QTcF}$ (90% CI) within the mean (90% CI) predicted $\Delta\Delta\text{QTcF}$ (black line with shaded grey area).

The mean (90% CI) predicted $\Delta\Delta\text{QTcF}$ at mean C_{max} after steady-state dosing of 3.2 mcg/kg/min and single dose of 12 mcg/kg/min is shown in the bottom right graph of Figure 14.

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Figure 14 (Top) $\Delta\Delta\text{QTcF}$ vs. Clevidipine concentration. (Bottom left) Mean (90% CI) predicted $\Delta\Delta\text{QTcF}$ (black line with shaded grey area) vs. Clevidipine concentration with observed median-quartile concentrations and associated mean $\Delta\Delta\text{QTcF}$ (90% CI) overlaid (blue). (Bottom right) Predicted $\Delta\Delta\text{QTcF}$ at mean C_{max} after steady-state dosing of therapeutic dose (3.2 mcg/kg/min, blue line) and supra-therapeutic dose (12 mcg/kg/min, red line).



6.9 Clinical Assessments

None of the events identified as significant in ICH E14 (i.e., death, SAE, seizure, syncope, and ventricular arrhythmia) are reported to have occurred in this study.

APPENDIX

6.10 Highlights of Clinical Pharmacology

Clinical Pharmacology Information Request	Clinical Pharmacology Information
Therapeutic Dose	2 to 32 mg/hour for up to 72 hours.
Maximum Tolerated Dose	Clevidipine IV emulsion was safe and well tolerated up to a dose rate of 105.1 mg/h for 20 minutes in healthy volunteers.
Principal Adverse Events	Common adverse reactions: hypotension, tachycardia, dizziness, flushing, nausea, vomiting, headache, polyuria. Dose-limiting adverse reactions: hypotension, tachycardia, headache, nausea, vomiting (these were the common reasons for discontinuations in phase I/II).
Maximum Dose Level Tested	32 mg/h in patients with severe hypertension. 105.6 mg/h in patients with perioperative hypertension.
Maximum Exposure Achieved	Continuous infusion of 16 mg/h for 72 hours, C _{max} = 15.8 ng/mL (SD = 4.0, % CV = 25.5); AUC _{0-t} = 723.8 ng*h/mL (SD = 246.3, % CV = 34.0).
Range of Linear PK	In healthy volunteers, there is a linear relationship between dose rate and clevidipine blood concentrations following a 20 min infusion over a dose range of 3.2 to 105.1 mg/h. In patients with essential hypertension, there is a linear relationship between dose rate and blood concentration following a 2 hour infusion at doses of 0.86 to 26.3 mg/h. In patients with essential hypertension at doses of 2 to 16 mg/h administered for 72 hours, there is a linear and slightly less than dose proportional increase in mean C _{max} , mean AUC _{0-t} and mean C _{ss} .
Accumulation at Steady State	Clevidipine is administered by Intravenous infusion. C _{ss} occurs rapidly due to the short half-life.

Metabolites	Clevidipine is rapidly metabolized by hydrolysis in blood and in extravascular tissues by nonspecific carboxyl esterases to pharmacologically inactive carboxylic acid metabolite (M1).
Absorption	Not applicable because clevidipine is administered by intravenous infusion.
Distribution	Mean $V_{ss} = 0.504$ L/kg (SD = 0.129). In a population pharmacokinetic evaluation of patients with essential hypertension, V_1 was found to be 63.1 L (% CV = 16.5) and V_2 was found to be 144 L (% CV = 30) for a 70 kg patient. Clevidipine is greater than 99.5% plasma protein bound.
Elimination Route	Clevidipine is rapidly metabolized to pharmacologically inactive metabolites. No intact drug is excreted in urine or feces. Mean cumulative dose (radioactivity) is excreted 68% in urine and 15% in feces over 7 days. The majority of radioactivity is excreted in 72 hours.
Elimination Half-life	The initial half-life is approximately 1 minute (SD=0.3) and accounts for approximately 85 – 90% of clevidipine elimination. The terminal half-life is about 12 minutes (SD=2.9). In essential hypertensive patients receiving continuous infusion of 16 mg/h for 72 hours, the mean terminal half-life is 37 minutes (SD=21.7). The initial half-life of the major blood carboxylic acid metabolite (M1) is about 1 h (SD=0.02) and the terminal half-life is about 9.2 h (SD=0.8).

Elimination Clearance Mean clearance values for venous samples for patients after cardiac surgery were 0.09 L/min/kg and for healthy volunteers 0.1-0.2 L/min/kg.

In a population pharmacokinetic evaluation of patients with hypertension, the typical value of clearance for a 70 kg patient was 1220 L/h (% CV = 8).

<p>Intrinsic Factors</p>	<p>In a population pharmacokinetic evaluation of patients with hypertension, the covariates of age, body weight, sex and race were examined.</p> <p>Given the rapid clearance exhibited by clevidipine together with the direct effect pharmacodynamic behavior, dose adjustments based on covariates are not warranted.</p> <p>As a result, and in agreement with the FDA, these factors were not examined in special population studies.</p>
<p>Extrinsic Factors</p>	<p>Pharmacokinetic drug interactions are unlikely since clevidipine is metabolized by plasma esterases. Clevidipine and its primary blood metabolite do not induce or inhibit cytochrome P450 isoenzymes at clinically relevant concentrations. As a result, and in agreement with the FDA, no drug interaction studies were performed.</p> <p>In clinical trials clevidipine has been administered with many concomitant medications before, during and after cardiac surgical procedures and in patients with severe hypertension without any observed drug interactions.</p> <p>Food effects were not studied because clevidipine is administered by intravenous infusion.</p>
<p>Expected High Clinical Exposure Scenario</p>	<p>Study TMC-CLV-05-01 (QTc evaluation) provides cardiac safety data on healthy volunteers exposed to the expected upper end of the recommended dosing regimen (16 mg/h) for most patients, although some patients may require dosing up to 32 mg/h. In this study, a 16 mg/h dose was maintained continuously for approximately 23 hours and then rapidly increased to supratherapeutic levels (58 mg/h) for 20 minutes to mimic an unintended overdose situation.</p> <p>At 16 mg/h the mean C_{ss} was approximately 6.5 ng/mL, while at the supratherapeutic dose of 58 mg/h the mean C_{ss} ranged from 18 – 21 ng/mL.</p> <p>Clevidipine will be administered in a highly monitored clinical setting. Unintended overdose is unlikely, but will be recognized immediately if it occurs, due to the hemodynamic effects of the drug. Due to its rapid clearance, high exposures can be rapidly titrated to lower levels.</p>

6.11 Table of Study Assessments

Stage I

Study Assessment	Screening Period	Pre-Treatment (Night before infusion)	Pre-dose (-30 min)	Baseline Saline infusion (0-30 min)	Saline infusion (30-60 min)	Intralipid ⁶ infusion (60-90 min)	Intralipid ^{6/7} Fenoldopam (90-120 min)	Moxifloxacin / Fenoldopam (Day 2) ⁷
Informed consent	X							
Medical history	X							
Chemistry and hematology ¹	X							
Urine pregnancy ²	X	X						
Blood alcohol and urine drug screen	X	X						
12-lead ECG	X	X	X					X ³
Vital signs	X	X			X ⁵	X ⁵	X ⁵	X ⁵
Physical exam	X	X						
Height and weight	X	X						
Interim history		X						
Study drug administration				X	X	X	X	X
Continuous 12-lead ECG (Holter)				← X ⁶ →				X
Extracted 12-lead ECG from Holter ⁴				X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X
AE and SAE reporting				← X →				

¹ As described in Section 9.7.3

² Women of childbearing potential only

³ 4 hours post-administration of moxifloxacin

⁴ See Table 17 below for times of extracted ECGs.

⁵ See Table 13 for assessment schedule.

⁶ Continuous 12 lead ECG (Holter) starts at -80 minutes

⁷ NS administration prior to fenoldopam for 90 minutes to mimic day 1 NS infusion. HR and BP monitoring were to have mimicked Day 1 procedures during fenoldopam infusion.

Main Stage

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APPENDIX V
PHARMACOMETRICS REVIEW

NOTE: Table of Contents page numbers are different than specified due to incorporation of the review into Appendix V of the overall review.

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This review appears separately in the clinical pharmacology
section of this approval package

APPENDIX VI COMPOSITION

Formulations constant during product development

Clinical supplies were prepared throughout the clinical development of clevidipine in exactly the same manner and contained the same composition and concentration of excipients as the proposed commercial product. Dosage strength varied through development from 0.05 to 3.0 mg/mL for practical reasons. Phase III clinical trials used the to-be-marketed concentration of 0.5 mg/mL, filled in 100 mL or 50 mL glass bottles with stoppers and an aluminum overseal, manufactured according to the proposed commercial methods at the commercial manufacturing facilities and stored under recommended conditions (see Section 2.3.P.2 in Module 2 of original NDA).

Clevidipine emulsion:

See section above in original NDA under Module 2.

Table 1

Composition of clevidipine emulsion 0.5 mg/mL

Component	Reference to quality standard	Function	Quantity ^a		
			mg/mL	Per 50 mL/ bottle	Per 100 mL/ bottle
Clevidipine	In-house standard	Active ingredient	0.5	25 mg	50 mg
Soybean oil	USP/Ph Eur	—	200	10 g	20 g
Glycerin	USP/Ph Eur	—	22.5	1.13 g	2.25 g
Purified egg yolk phospholipids	In-house standard	—	12	0.6 g	1.2 g
Sodium hydroxide	NF/Ph Eur	For pH adjustment		pH 6.0 to	

^a Clevidipine Emulsion when filled in 100 mL bottles has an overfill volume of approximately — when filled in 50 mL bottles has an overfill volume of approximately — See Section 3.2.P.2.2.2 Overages, for more information.
USP = United States Pharmacopeia; NF = National Formulary; Ph Eur = European Pharmacopoeia; q.s. = quantity sufficient

Appendix VII
COVER SHEET AND OCPB FILING/REVIEW FORM

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Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-156	Brand Name	Cleviprex
OCPB Division (I, II, III)	DPE 1	Generic Name	Clevidipine IV Emulsion
Medical Division	HFD-110	Drug Class	<u>Dihydropyridine Calcium Channel Blocker</u>
OCPB Reviewer	Lydia Velazquez	Indication(s)	when the use of oral therapy is not feasible or desirable
OCPB Team Leader	Patrick Marroum	Dosage Form	Injectable emulsion 0.5 mg/mL Single-use vial 50 or 100 mL
		Dosing Regimen	Titrated to desired BP response 16 to 32 mg/hour
Date of Submission	2 July, 2007	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	March 2, 2008	Sponsor	The Medicines Company
PDUFA Due Date	May 2, 2008	Priority Classification	XXS
Division Due Date	March 30, 2008		

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	2		Annotated label and proposed label
Reference Bioanalytical and Analytical Methods	X			In Summary format, studies do not have individual analytical methods report.
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	2		
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	4		Dose proportionality, QT study, Mass balance, Conc-response
multiple dose:				
<i>Patients-</i>				
single dose:	X	3		1 HTN during the by-pass phase and/or hypothermic part of the bypass phase in CABG, 1 Essential HTN, 1 Elevated BP post CABG
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Not known if fed or fasted, healthy volunteers
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
<i>In-vitro</i> effects on primary drug:	X	1		Na thiopental, Fentanyl, Morphine, Isoflurane, Diltiazem, Propofol, Pancuronium bromide, Vecuronium bromide
<i>In-vitro</i> :	X	5		CYP 450 studies - 2 induction studies (1 parent, 1 metabolite), 2 inhibition of parent drug, 1 inhibition of metabolite
Subpopulation studies -				
Effect of Temperature on half-life	X	1		In-vitro determination of clevidipine half-life in human blood at different temperatures and dilutions

Pseudocholinesterase Deficiency	X	1		In-vitro evaluation of genetic influence on the elimination rate of clevidipine
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	13		1 Short (20 min) and long-term (24 hr) infusion. Conc response relationships in healthy volunteers, 12 Healthy volunteers and HTN used for PM analysis
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Permeability				
Efflux				
QT Study	X	1		
Total Number of Studies		24		Includes 4 for PM analysis that should be assessed

Filability and QBR comments

	"X" IF YES	COMMENTS
Application filable ?	X	Analytical study reports are in summary format, studies do not have individual analytical methods report.
Comments sent to firm?		Please send all individual study analytical methods study reports. Currently the analytical study reports are in a summery format. Studies do not have individual analytical assay methods reports. If in NDA, please direct to where they are located.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22-156, HFD-110 (FrommE), HFD-860 (MehtaM, MarroumP, VelazquezL), CDR Central Document Room

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lydia Velazquez
3/20/2008 03:50:55 PM
BIOPHARMACEUTICS

Patrick Marroum
3/21/2008 09:54:41 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860) Tracking/Action Sheet for Formal/Informal Consults	
From: Patrick J. Marroum Ph.D.		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 9/2/03	IND No.: 65114 Serial No.: 005	NDA No.	DATE OF DOCUMENT 6/17/03
NAME OF DRUG Clevidipine	PRIORITY CONSIDERATION	Date of informal/Formal Consult:	
NAME OF THE SPONSOR: The Medicines Company			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<input type="checkbox"/> PRE-IND meeting <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL AMENDMENT <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED			
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input checked="" type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)			
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (SPECIFY BELOW): []			
REVIEW ACTION			
<input checked="" type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)			
<input type="checkbox"/> Oral communication <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []			
<input type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW): []			
REVIEW COMMENT(S)			
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input checked="" type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
COMMENTS: The following clinical Pharmacology and Biopharmaceutics issues were discussed during the teleconference: 1-The proposed in vitro CYP inhibition and induction studies are acceptable. Based on the results, a decision whether in vivo drug interaction studies would be needed will be made. 2-The proposal not to perform a renal impairment study is acceptable since the drug has a very short half-life and very little is excreted unchanged in the urine and will only be administered <u> </u> for up to <u> </u> hours only. 3-The sponsor was advised that they need to provide justification for not measuring the formaldehyde levels. Alternatively, they can get a small number of healthy volunteers where they measure the levels of formaldehyde and formic acid after clevidipine administration to show that the levels of these metabolites are not toxic.			
SIGNATURE OF Team Leader: Patrick J Marroum Ph.D. _____ SIGNATURE OF Director: Mehul Mehta Ph.D. _____		Date <u> 9/2/03 </u> Date <u> 9/2/03 </u>	
C.: HFD # 110; TL: []; DD: []		Project Manager: _____ Date _____	

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this page is the manifestation of the electronic signature.**

/s/

Patrick Marroum
9/3/03 10:34:48 AM
BIOPHARMACEUTICS

Mehul Mehta
9/3/03 10:43:33 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults	
From: LYDIA VELAZQUEZ, Pharm.D.		To: DOCUMENT ROOM HFD-110	
DATE: 7/28/04	IND No. 65-114 Serial No. 022	NDA No. --	DATE OF DOCUMENT: 6/22/04
NAME OF DRUG Clevidipine		PRIORITY CONSIDERATION Standard	Date of informal/Formal Consult:
NAME OF THE SPONSOR: The Medicines Company			
TYPE OF SUBMISSION			
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED			
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input checked="" type="checkbox"/> MEETING PACKAGE (TYPE B MTG.)			
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (SPECIFY BELOW): []			
REVIEW ACTION			
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)			
<input type="checkbox"/> Oral communication with Name: [] <input checked="" type="checkbox"/> Comments communicated in the meeting.			
<input type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW):			
REVIEW COMMENT(S)			
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input checked="" type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
COMMENTS: The Medicines Company has requested a meeting to discuss pre-clinical toxicology and clinical pharmacology issues regarding clevidipine. The proposed indication for this short-acting L-selective calcium channel blocker is for the _____ Specific issues were discussed that might constitute deficiencies in an NDA submission. The following Clinical Pharmacology and Biopharmaceutics questions were discussed: <ul style="list-style-type: none"> • The Division concurs that further drug interaction studies specific to cytochrome P450 are not required. • The proposed pharmacokinetic formaldehyde study will not provide information as to where the conversion of clevidipine to formaldehyde takes place and whether the formation of formaldehyde is distributed and centralized in a specific organ. As a result, an animal study with radiolabeled clevidipine would best answer this question. 			
SIGNATURE OF REVIEWER: <u>Lydia Velazquez Pharm.D.</u>		Date: <u>7/28/04</u>	
SIGNATURE OF TEAM LEADER: <u>Patrick Marroum, Ph.D.</u>		Date: <u>7/28/04</u>	
CC.: IND 65-114, HFD-110, HFD-860 (Velazquez, Marroum, Mehta, Rahman)			

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this page is the manifestation of the electronic signature.**

/s/

Lydia Velazquez
7/28/04 04:50:35 PM
BIOPHARMACEUTICS

Type B Meeting

Patrick Marroum
7/28/04 04:56:33 PM
BIOPHARMACEUTICS