**Pediatric Surgery Patients:**
The apparent oral clearance of DMA for pediatric surgery patients (2 to 12 years) was approximately 1.3 times greater compared to adult healthy volunteers and 2.0 times smaller compared to pediatric cancer patients (3 to 11 years). The apparent clearance of DMA for pediatric surgery patients (2 to 11 years) was approximately 1.4 times greater compared to adult healthy volunteers and 1.3 times smaller compared to pediatric cancer patients (3 to 11 years).

Oral Dose: The PK of DMA was studied in 11 children (2 to 12 year old) undergoing elective and uncomplicated surgery under general anesthesia following oral administration of 1.2 mg/kg dose of DM (study AN-PD-0993). The PK parameters of DMA are summarized in the following table.

IV Dose: The PK of DMA was studied in 18 children (2 to 11 year old) undergoing elective and uncomplicated surgery under general anesthesia following IV administration of 1.2 mg/kg dose of DM (study AN-PD-0593). The PK parameters of DMA are summarized in the following table.

| Parameters | Mean (%CV) | | | |
|---|---|---|---|---|
| | Oral | | IV | |
| | Pediatric Surgery Patients (2 to 12 yr, N=11) | Adult Healthy Volunteers (20 to 43 years, N=16) | Pediatric Surgery Patients (2 to 11 yr, N=18) | Adult Healthy Volunteers (19 to 40 years, N=24) |
| Dose | 1.2 mg/kg | 1.3 mg/kg | 1.2 mg/kg | 1.27 mg/kg |
| $AUC_{0-\infty}$ (ng.h/ml) | 933 (61) | 1181 (39) | 1356.0 (42) | 1797 (28) |
| Cmax (ng/ml) | 159 (32) | 225 (24) | 254.6 (22) | 320.0 (25) |
| tmax (h) | 1.39 (70) | 0.70 (30) | 0.63 (57) | 0.62 (64) |
| CLapp,po (ml/min/kg) | 20.77 (49) | 15.5 (35) | - | - |
| CLapp (ml/min/kg) | - | - | 13.13 (47) | 9.39 (28) |
| Vapp (L/kg) | - | - | 5.17 (43) | 5.77 (25) |
| t1/2 (h) | 5.89 (24) | 7.47 (21) | 4.77 (23) | 7.32 (24) |

**Pharmacokinetics in Special Populations:**
· The pharmacokinetics of DMA is similar between male and female healthy volunteers and also similar between young (19 to 40 years) and elderly (≥65 years) healthy volunteers following both oral and intravenous administration of dolasetron mesylate.
Gender and age (19 to 87 years) has no effect on the apparent oral clearance and apparent clearance of DMA in cancer patients receiving chemotherapy.

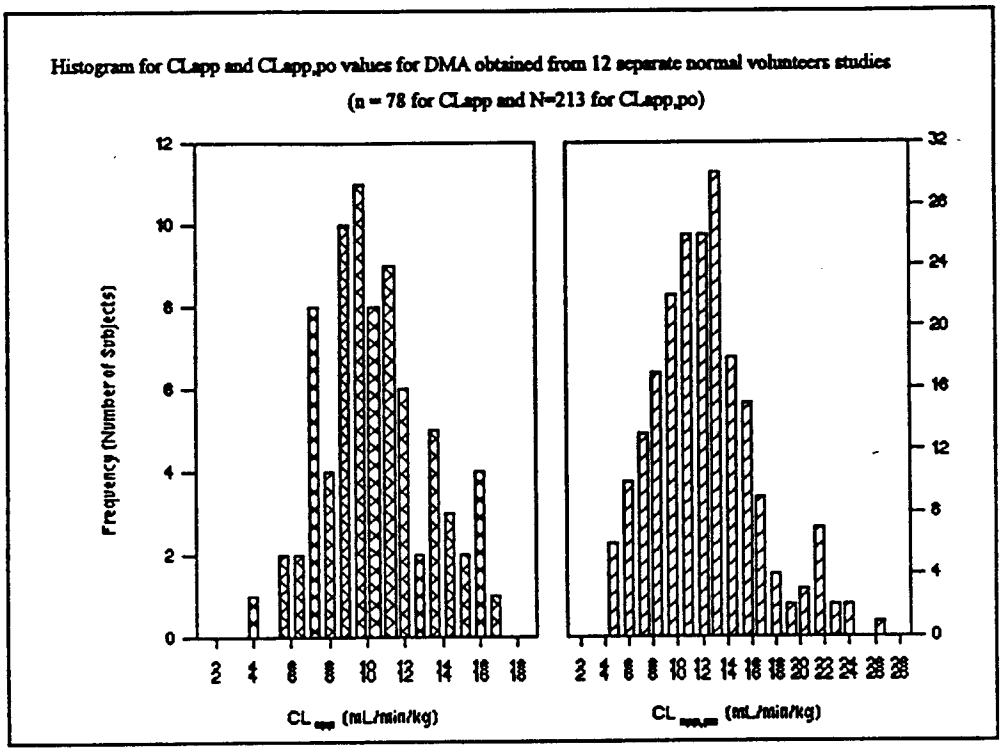
| Mean (%CV) PK Parameters of DMA in Healthy Male, Female and Elderly (>65 yr) Subjects Following IV and Oral Administration of DM | | | | | | |
|---|---|---|---|---|---|---|
| Parameters | IV | | | Oral | | |
| | Male (N=24) | Female (N=24) | Elderly (N=15) | Male (N=24) | Female (N=24) | Elderly (N=15) |
| Dose | 2.54 mg/kg | 2.40 mg/kg | 2.40 mg/kg | 2.54 mg/kg | 2.40 mg/kg | 2.40 mg/kg |
| Cmax ng/ml | 647 (29) | 522 (18) | 646.9 (29) | 601 (35) | 469 (19) | 661.9 (28) |
| $AUC_{0-}$ ng.h/ml | 3638 (33) | 3007 (34) | 4028.1 (39) | 2680 (30) | 2413 (38) | 3593.0 (42) |
| t1/2 h | 7.66 (22) | 8.05 (30) | 6.85 (22) | 8.84 (23) | 9.11 (44) | 7.16 (32) |
| Vapp L/kg | 6.08 (30) | 7.32 (36) | 4.69 (23) | - | - | - |
| CLapp or CLapp,po ml/min/kg | 9.48 (34) | 11.1 (30) | 8.26 (30) | 12.9 (34) | 14.2 (37) | 9.53 (36) |
| CLr ml/min/kg | 2.91 (25) | 3.29 (41) | 2.22 (37) | 2.61 (28) | 3.42 (62) | 1.84 (24) |
| Urinary Exc (% dose) | 32.8 (28) | 33.4 (37) | 27.9 (30) | 21.6 (30) | 27.2 (48) | 21.4 (39) |
| F (%) | - | - | - | 76 (28) | 80 (12) | 89 (16) |

· The apparent oral clearance and apparent clearance of DMA decrease as renal function decreases. With severe renal impairment, the mean apparent oral clearance and apparent clearance of DMA decrease 44% and 48%, respectively, and the mean Cmax of DMA increases 17% (oral) and 34% (iv). Even though, the ranges of individual apparent oral clearance and apparent clearance values of DMA for renally impaired subjects are not considerably different from those observed in healthy normal volunteers, the range of Cmax of DMA for renally impaired subjects for IV administration is greater than those observed for healthy normals. Also, data for cardiac conduction changes showed that frequency of QTc prolongation beyond 440 msec was much higher in severe renal impaired group. The pharmacokinetic and safety results suggest that a dose adjustment may be necessary for renally impaired cancer or surgery patients (reduction of about 30%) .

· The apparent oral clearance of DMA decreases as hepatic function decreases.
Following oral administration of dolasetron mesylate, the mean apparent oral clearance of DMA decreases 42% and the mean AUC of DMA increases 70% with severe hepatic impairment. Also, with severe hepatic impairment, Cmax of DMA increased slightly, 18 % (oral), and was unchanged for IV group. However, the ranges of individual apparent oral clearance, AUC and Cmax of DMA for hepatically impaired subjects are not considerably different from those observed in healthy normal volunteers (note that each group had only 4 to 6 subjects). Following intravenous administration of dolasetron mesylate, the apparent clearance and AUC values of DMA remain relatively unchanged with hepatic impairment. Dose adjustment (reduction) may not be necessary for oral or IV treatment in hepatic impaired patients (safety parameters such as QTc interval prolongations were not evaluated).

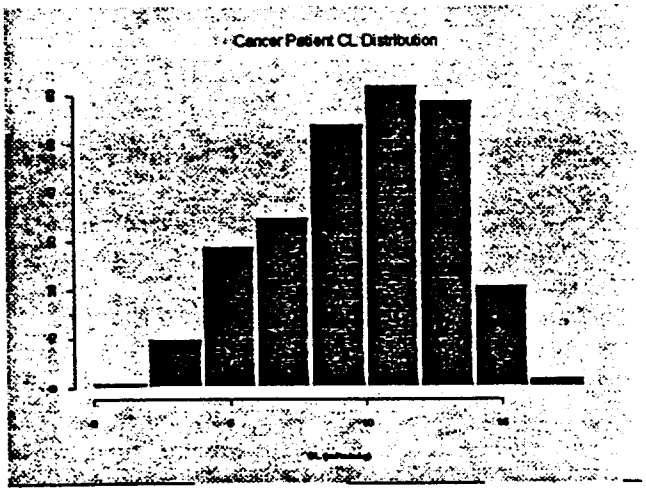
· Following both oral and intravenous administration of dolasetron mesylate, the systemic exposure of DMA increases approximately two-fold in CYPIID6 deficient subjects while Cmax remains unchanged.

The incidence of adverse events observed in CYPIID6 deficient subjects did not differ from that observed in other normal subjects.






In spite of genetic polymorphism in CYPIID6, the apparent oral clearance and apparent clearance values of DMA exhibited a unimodal normal distribution pattern in normal subject as shown above (data pooled from all PK studies in normals) and in Cancer Patients (shown on the right). The safety and pharmacokinetic results suggest that dose adjustment may not be necessary for CYPIID6 deficient cancer or surgery patients.




**Pharmacodynamics on ECG Changes:**
Acute, reversible, and asymptomatic changes in PR interval and QRS duration observed after iv therapeutic doses of dolasetron mesylate, are directly related to plasma concentrations of DMA. The magnitude of these changes with plasma concentrations of DMA are small

;) indicating that small

changes in PR interval and QRS duration are expected with large changes in plasma concentrations of DMA and similar between healthy normal volunteers and cancer patients receiving chemotherapy. Patient demographics such as age, gender, race, body weight, body surface area, height and concomitant drugs such as doxorubicin, cyclophosphamide, verapamil, atenolol, nifedipine, glibenclamide, furosemide, diltiazem, propranolol, and ACE inhibitors had no effect on the PR interval and QRS duration changes.

**Mean Slope and Maximum Observed and Predicted Values for PR Interval and QRS Duration Changes Following Oral and Intravenous Administration of Dolasetron Mesylate**

| Study and Dose | *Slope for Changes (msec/ng/mL)* | | *Maximum PR Interval Changes (msec)* | | *Maximum QRS Duration Changes (msec)* | |
|---|---|---|---|---|---|---|
| | PR interval (SD) | QRS duration (SD) | Observed | Predicted* | Observed** | Predicted* |
| Healthy Subjects | | | | | | |
| MCPR0080<br>50, 100, 200 mg IV and 200 mg oral | 0.0316<br>(0.0210) | 0.0141<br>(0.0132) | 19.8 | 15.8 | 7.9 | 6.5 |
| Cancer Patient | | | | | | |
| MCPR0032<br>0.6, 1.2, 1.8, 2.4, 3.0 mg/kg IV | 0.0353 | 0.0139 | 16.6 | 18.1 | 6.9 | 6.8 |

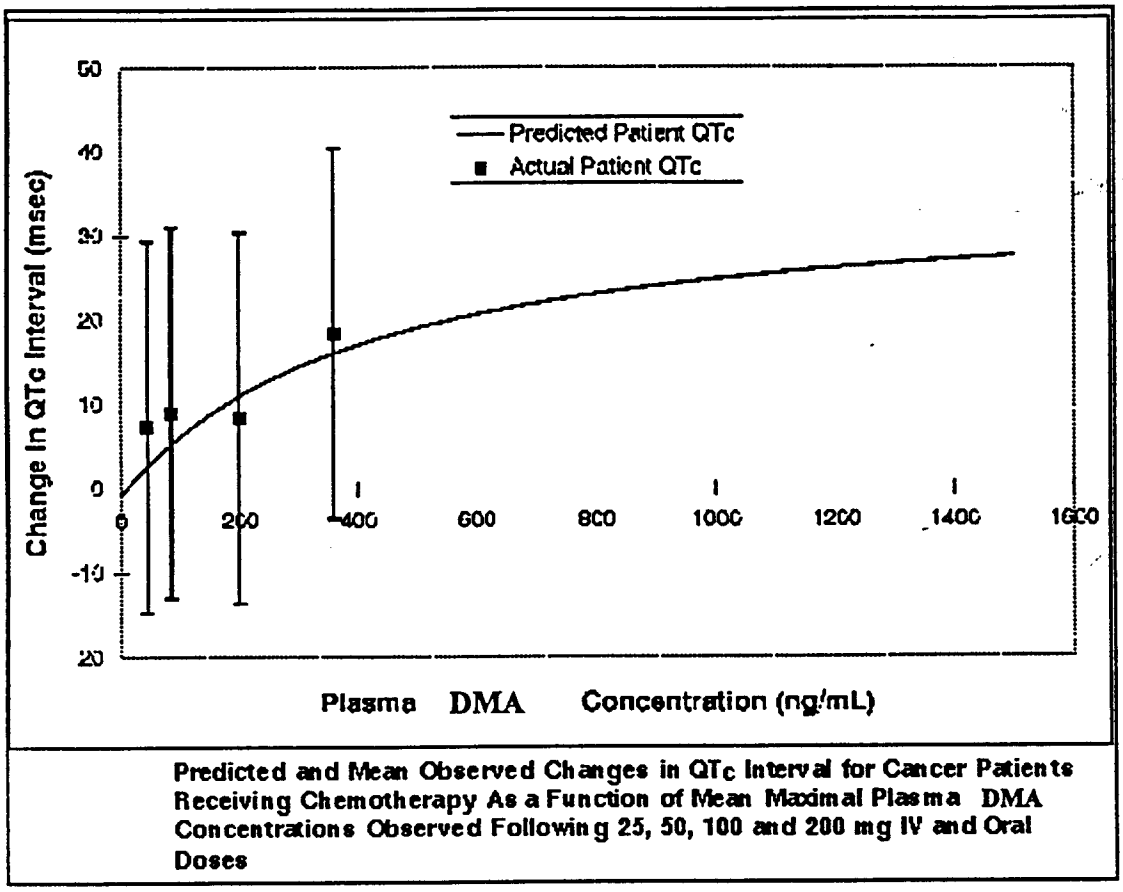
* Predicted values based on the linear model using the mean plasma concentration of DMA at which a maximum PR interval or QRS duration change was observed.

** Mean maximum observed changes after the highest dose in the study

Increases in QTc interval were significantly correlated with plasma concentrations of DMA, the relationship being non-linear with the rate of increases in QTc decreasing with increasing concentration. Cancer chemotherapy, particularly doxorubicin, contributed to the increases observed in patients. The increase was inversely related to baseline QTc. Review of data from outlier patients indicates large variability among acute QTc interval changes, plasma DMA levels and baseline QTc intervals.

Changes in JT interval were, at most, marginally related to plasma concentrations of DMA and confounded by intrasubject variability in the measurements. The same was true for changes in heart rate. The relationship of plasma concentrations of DMA to increases in QTc interval and a significant linear relationship between plasma concentrations of DMA and increases in QRS duration, taken together, support the conclusion that increases in QTc interval after dolasetron mesylate are the result of increases in QRS duration (depolarization) and may not be because of any prolongation of JT interval (repolarization) or heart rate.

The submitted PK-PD analysis were reviewed by the DPE-II with the assumption that QRS, PR and QT intervals were recorded/measured accurately. Also, most ECG recordings were carried out near the peak concentration of DMA (tmax). The paucity of PD data covering the entire corresponding concentration time profile is also a limitation of the submitted PK-PD analysis.




**Predicted and Mean Observed Changes in QTc Interval for Cancer Patients Receiving Chemotherapy As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 25, 50, 100 and 200 mg IV and Oral Doses**

Even though probability of prolongation in ventricular repolarization is less with DM and it is acknowledged that there were no instances of Torsades des pointes reported in clinical trials, prolongation of QTc interval raises questions about the 'practicality of use' of this drug. For instance, giving a second or a third dose of DM to treat vomiting (as is possible for DM Injection) will increase the risk for QTc prolongation and possibly the risk of Torsades des pointes. This risk is even greater for patients with reduced clearance of the active metabolite, viz. renal impairment.

Drug-Drug Interactions: The potential for clinically significant drug-drug interactions in the elimination of dolasetron and DMA appears to be minimal since the reduction of dolasetron to DMA is complete and stable due to the ubiquitous nature of the mediating enzyme (carbonyl reductase) and DMA is eliminated by multiple routes (renal excretion and metabolism by hydroxylation and glucuronide conjugation). The potential of DMA to affect elimination of other drugs has not been studied. However, the potential for DMA to inhibit in vivo metabolism of CYPIID6 and CYPIIIA substrates appears to be minimal since the in vitro inhibition constants (Ki) of DMA for CYPIID6 and CYPIIIA mediated metabolism (30 μM

and 674 μM, respectively) are much greater than plasma concentrations of DMA observed after therapeutic doses of dolasetron mesylate.

The drug-drug interaction potential for dolasetron mesylate was evaluated as follows:

**1. Cimetidine and Rifampin:** Formal drug-drug interaction studies in normal volunteers were conducted using a nonspecific P450 inhibitor, cimetidine, and a classic P450 enzyme inducer, rifampin, to describe the magnitude of an interaction involving oxidative metabolism of DMA.

Mean (%CV) Steady-State PK Parameters of DMA Obtained Following Once Daily Oral Administration of DM (200 mg/day) Alone, with Cimetidine (1200 mg/day), and with Rifampin (600 mg/day) for 7 Days

| PK Parameters | Mean (%CV) | | |
|---|---|---|---|
| | DM alone (N=18) | DM with Cimetidine (N=18) | DM with Rifampin (N=17) |
| AUCss (ng.h/ml) | 3654 (31) | 4551 (33) | 2682 (31) |
| Cmaxss (ng/ml) | 732.7 (24) | 842.2 (31) | 614.3 (23) |
| tmax (h) | 0.67 (29) | 0.78 (10) | 0.82 (18) |
| t1/2 (h) | 8.8 (19) | 8.4 (18) | 7.4 (20) |
| CLapp,po (ml/min/kg) | 10.5 (29) | 8.4 (28) | 14.4 (30) |
| Urinary Exc. (% dose) | 21.7 (47) | 25.2 (37) | 19.8 (52) |

**2. Concomitant Medications in Cancer Patients:** Population pharmacokinetics, when practical, were examined to determine whether concomitant medications in clinical databases are significant covariates that affect pharmacokinetics of DMA in the target population. When investigated in 273 cisplatin- treated cancer patients participating in a multicenter safety and efficacy trial by a covariate analysis of population PK modeling, of the concomitant medications tested, atenolol was found to be a significant covariate affecting the apparent clearance of DMA. The mean apparent clearance for DMA for patients on atenolol decreased by 27 % compared to patients not on atenolol. A possible mechanism for this interaction could be the inhibition in the active secretion of DMA by the kidney since atenolol also appears to be actively secreted by the kidney[1]. However, apparent clearance values of DMA for patients on atenolol were well within the values observed in patients not on atenolol ) therefore this interaction may not be of much clinical importance. Other concomitant medications such as furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glibenclamide and propranolol had no effect on the apparent clearance of DMA.

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[1] Boyd, R A ; Chin, S K; Dn-Pedro O; Williams, R L; Giacomin, K M; Clin. Pharmacol. Ther. 1989 48: 403-410

## Comparison of Human PK to Animals:

The overall biotransformation pathways of DM are identical in animals (rat, dog and monkey) and man. Qualitatively, the PK of DM and the metabolite, DMA, in animals and man appear to be similar. The mass balance breakdown of $^{14}$C-DM in different species was similar (Urine, Feces and Total).

| Mean PK Parameters for DM and DMA after IV Administration of DM | | | | |
|---|---|---|---|---|
| DM | | | | |
| Parameters | Rat | Dog | Monkey | Healthy Subjects (N=5) |
| WT (kg) | 0.269 | 12.1 | 6.20 | 74.3 |
| Dose (mg/kg) | 15.0 | 6.0 | 5.0 | 5.0 |
| CL (ml/min/kg) | 189 | 187 | 402.9 | 95.8 |
| Vd (L/kg) | 1.1 | 1.2 | 5.56 | 5.39 |
| t1/2 (min) | 6.6 | 6 | 9 | 151 |
| AUC (ng.h/ml) | 978 | 401 | 173 | 660 |
| DMA | | | | |
| Cmax (ng/ml) | 668 | 677 | 756 | 1926 |
| tmax (h) | 0.25 | 0.31 | 0.08 | 0.56 |
| CLapp (ml/min/kg) | 180 | 19.6 | 57.4 | 7.76 |
| Vdapp (L/kg) | 10.06 | 104.74 | 139.66 | 529.15 |
| t1/2 (h) | 2.4 | 5.1 | 4.23 | 10.88 |
| AUC (ng.h/ml) | 1035 | 3883 | 1098 | 7993 |

In following table, the two-hour plasma DM and DMA concentrations measured in animals during toxicity studies are compared to those observed in healthy subjects and cancer patients after administration of the highest dose of dolasetron mesylate.

| Comparison of 2 Hour Plasma Concentration (Mean ± SD) after Administration of DM | | | | |
|---|---|---|---|---|
| Species | Route | Dose (mg/kg/day) | 2-Hour Plasma Concentration (ng/ml) | |
| | | | DM | DMA |
| Rat | IV<br>po | 60.0<br>100.0 | 3302<br>91 ± 51 | 2860<br>1437 ± 432 |
| Dog | IV | 6.0 | < 10 | 524 |
| Monkey | IV<br>po | 5.0<br>50.0 | < 10 | 122 ± 30<br>351 ± 120 |

| | | | | |
|---|---|---|---|---|
| Healthy Subjects | IV<br>po | 5.0<br>5.0 | 25 ± 5.6 | 1085 ± 240<br>643 ± 123 |
| Cancer Patients | IV<br>po | 3.0<br>2.8 | _<br>_ | 412 ± 200<br>494 ± 356 |

In rats, after iv administration of 60 mg/kg/day dose of dolasetron mesylate, some rats died due to convulsions, while at 100 mg/kg/day oral dose was free of significant toxic effects. In dogs, at 6.0 mg/kg/day iv dose of dolasetron mesylate, emesis was noted in male dogs, while in monkeys, after oral and iv administration of 50 mg/kg and 5 mg/kg dose of dolasetron mesylate, respectively, no treatment-related clinical signs were observed. The two-hour plasma dolasetron concentration was much lower in dog, monkey, and man compared to rat due to the rapid disappearance of dolasetron from plasma. The two-hour plasma DMA concentration in healthy subjects and cancer patients was either similar or lower than those observed rats and dogs.

**In-vitro Dissolution:** The following table summarizes the in vitro dissolution performance of formulation used in pivotal phase III trial and formulation proposed for marketing (200 mg). The sponsor is proposing to market 50 mg and 200 mg tablet strengths which are compositionally proportional. The lots sizes were adequately representative of production lot sizes. The dissolution was carried out using USP paddle apparatus at 50 rpm and in 0.1 N HCL (900 ml) at 37.0 ± 0.5 °C.

| Lot # | Times | N | Mean | Low | High | % CV |
|---|---|---|---|---|---|---|
| C-51610 Phase III Formulation | 15 min<br>30 min<br>45 min | 12<br>12<br>12 | 97 %<br>99 %<br>99 % | 89 %<br>98 %<br>98 % | 99 %<br>100 %<br>100 % | 3 %<br>1 %<br>1 % |
| R-54062 Proposed Market Formulation | 10 min<br>20 min<br>30 min | 12<br>12<br>12 | 53 %<br>99 %<br>100 % | 37 %<br>95 %<br>100 % | 84 %<br>100 %<br>100 % | 30 %<br>2 %<br>0.7 % |

# Comments:

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B. **(to be sent to Sponsor)**

1. The Division of Pharmaceutical Evaluation II, OCPB would recommend a dissolution specification

2. In the bioequivalence study MCPR0089, the batch size of to-be-marketed 200 mg tablet was

C. **(Labelling Comments)**

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DRAFT LABELING

1. The proposed table under "Pharmacokinetics in Humans (po)" should include variability on CLapp/F and $t_{1/2}$ parameters (e.g. % CV).

2. The proposed table under "Pharmacokinetics in Humans (iv)" should include variability on CLapp/F and $t_{1/2}$ parameters (e.g. % CV).

3. Under "Pharmacokinetics in Humans" the sponsor should include a variability (e.g. %CV) on volume of distribution.

4. Under "Clinical Studies (po)" section, the sponsor should state the following for PONV indication: "Men have not been clinically studied to establish efficacy".

5. The sponsor states in (iv) labelling: "the distribution of MDL 74,156 to blood cells is not extensive". However, partitioning of $^{14}C$-radioactivity in plasma versus blood was studied. Sponsor is requested to clarify whether including MDL 74,156 in place of $^{14}C$-radioactivity in this statement is appropriate.

# Appendix I

## Tablet Formulation

The following table describes the formulations for dolasetron tablet. These are the strengths tested in different clinical pharmacology trials in phase III. There is no difference in formulation between phase III-tablet and to-be-marketed tablet It should be noted that only 50 mg and 200 mg strengths are proposed by the sponsor for marketing and they are compositionally proportional.

| Composition of Dolasetron Mesylate Tablet (mg) | Tablets Theoretical Quantity per | | | |
|---|---|---|---|---|
| Component | 25 mg Tablet | 50 mg Tablet | 100 mg Tablet | 200 mg Tablet |
| Dolasetron Mesylate Monohydrate | | | | |
| Croscarmellose Sodium | | | | |
| Lactose | | | | |
| Magnesium Stearate | | | | |
| Pregelatinized Starch | | | | |
| Total Tablet Weight | | | | |

All tablet sizes and shapes are the same for phase III and commercial tablets. The 25 and 50 mg are standard round concave tablets. The 100 and 200 mg are capsule shaped tablets for ease of swallowing. All tablet strengths for Phase III clinical studies were

There is no difference between phase III and commercial formulations for the 25 mg tablets. The commercial formulations for the other three strengths contain different amounts of red iron oxide in the . The 50 mg tablets are light pink, the 100 mg tablets are pink and the 200 mg tablets are dark rose (dark pink, mauve).

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**In vitro metabolism/DMA Inhibition of dextrorphan and 1'hydroxymidazolam Formation**

**Objective:** The study was designed to evaluate the potential for DM to interact with CYP2D6 and CYP3A substrates (dextromethorphan and midazolam respectively) using in vitro human liver microsome studies

**Summary:** DMA is a potent 5-HT3 receptor antagonist and has been shown to be metabolised by CYP2D6, CYP3A and FMO. The effect of DMA on dextrorphan formation and 1'hydroxymidazolam formation was assessed in three human livers. The CYP2D6 mediated O-demethylation of dextromethorphan was competitively inhibited by DMA with Ki ranging from The in vivo inhibition of CYP2D mediated biotransformation should be unlikely as the therapeutic concentration of DMA is much below 17 μM. Likewise, DMA was found to non-competively inhibit the 1'-hyroxylation of midazolam with a Ki ranging from μM. Thus, the potential for DMA to inhibit the in vivo metabolism of CYP3A substrates appears to be minimal.

Figure 1A. *Dextrorphan Formation in the Presence of MDL 74,156 In a Human Liver Microsomal Sample (IUL-3)*

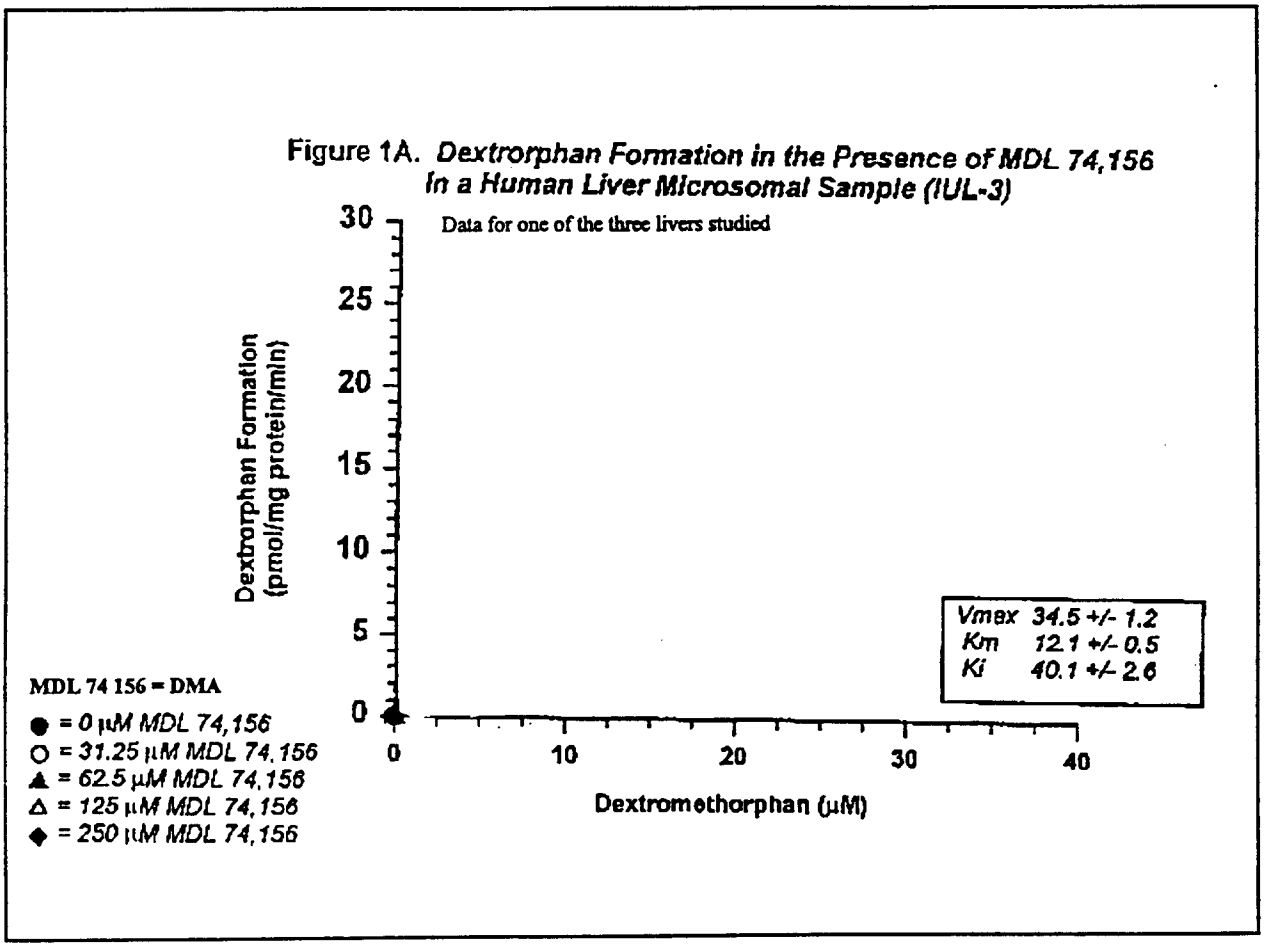
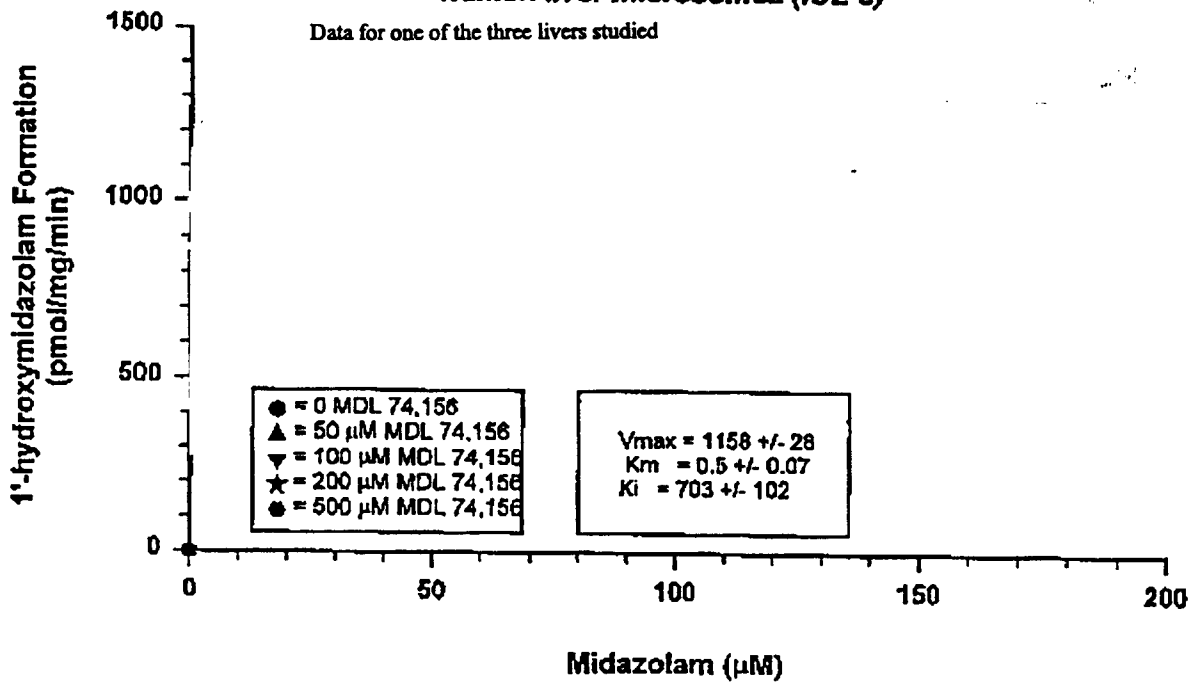


Figure 2A. *Inhibition of 1-hydroxymidazolam formation by MDL 74,156 in human liver microsomes (IUL-3)*

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**Pharmacokinetics and Metabolism of Dolasetron (DM) Following Oral Administration of $^{14}$C-DM**

Protocol Number: 73147-1-C-029

**Objectives:**

To investigate the disposition of DM and its reduced metabolite, DMA
To determine total recovery of the administered dose
To identify and profile urinary metabolites of DM following a single IV dose of $^{14}$C-DM to normal volunteers.

**Formulation:** The following table presents a 10 mg/ml oral $^{14}$C-DM solution used in the study.

| | |
|---|---|
| Batch No | C-49128 |
| Site of Manufacturing | |
| Date of Manufacturing | 11-29-90 |
| Dosage Form | Injectable Solution |
| Strength | 10 mg/ml |
| Specific Activity | 5 µCi/ml |
| Batch Size | |
| | 10 ml solution in ampule |

Study Design and Sampling:

This was an open-label, single dose fashion with six healthy non-smoking male volunteers between ) years of age. Each subject received a single oral dose of 300 mg $^{14}$C-DM (100 µCi). Serial blood, urine and fecal samples were collected until the radioactivity of the last two samples was less than two times background radioactivity.

**Data Analysis:**

Pharmacokinetic parameters were calculated from plasma and urine concentration-time data by model independent methods and total mass recovery was determined from urinary and fecal elimination of $^{14}$C-radioactivity.

**Results:**

The recovery of $^{14}$C-radioactivity, DM and DMA is shown in the following table. The mean plasma concentration-time plots and pharmacokinetic parameters for $^{14}$C-radioactivity, DM and DMA are presented in Figure 1 and Table 2.

Table 1 Excretion of $^{14}$C-radioactivity, DM and DMA following oral administration of 300 mg $^{14}$C-DM (N = 6)

| | Percent of Dose (%)* | | |
|---|---|---|---|
| | Urine | Feces | Total |
| $^{14}$C-radioactivity | 58.6 ± 10.4 | 25.3 ± 9.2 | 83.9 ± 7.6 |
| DM | ND | | |
| DMA | 30.1 ± 14.5 | | |

ND Not detected
* Mean ± SD

Figure 1 Mean plasma concentration versus time plots for $^{14}$C-radioactivity, DM and DMA following single oral administration of 300 mg $^{14}$C-DM (N = 6)

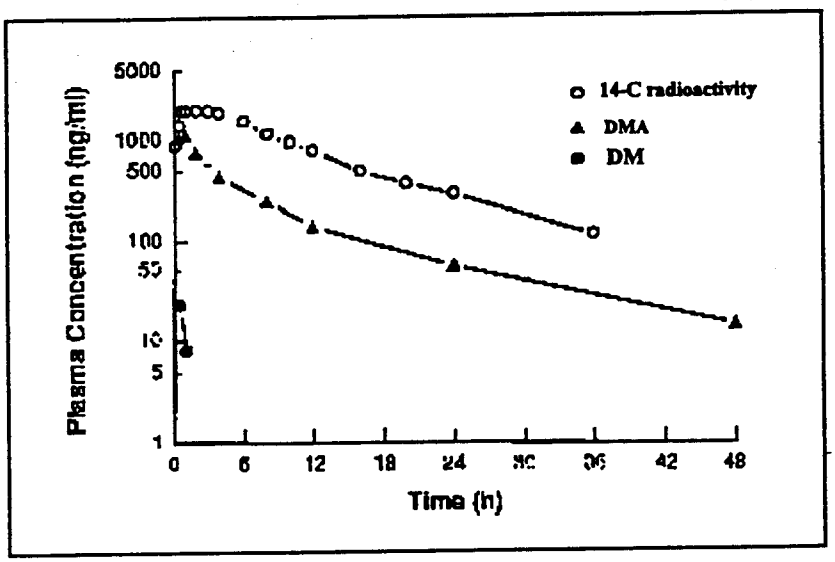



Table 2 Mean (%CV) pharmacokinetic parameters for $^{14}$C-radioactivity, DM and DMA

| | 14-C radioactivity (%cv) | DMA (%cv) |
|---|---|---|
| $AUC_{0-}$ (ngeq or ng.h/ml) | 26027 (15) | 6854 (46) |
| Cmax (ngeg/ml or ng/ml) | 2119 (13) | 1197 (28) |
| tmax (h) | 1.52 (76) | 0.77 (34) |
| CLapp,po (ml/min/kg) | 2.76 (12) | 9.10 (42) |
| K* | 0.86 (8) | NA |
| CLr (ml/min/kg) | 1.60 (13) | 2.31 (11) |
| $AUC_{0-}$ ratio (%)** | NA | 34.8 (40) |

NA: Not applicable
* : Blood to plasma concentration ratio of 14-C radioactivity
** : $AUC_{0-}$ ratio of DMA to 14-C radioactivity calculated based on molar equivalent concentrations

Approximately 84 % of the intravenously administered $^{14}$C-radioactivity was recovered in urine (58.6 %) and feces (25.3 %) in 4 days after dosing. No quantifiable amount of DM was excreted in urine, suggesting that DM is extensively metabolised. About 30 % of the dose was excreted in urine as DMA.

More than 98 % of urinary $^{14}$C-radioactivity was identified. These included DMA (60.9 %), 5' OH-DMA (3.4 %), 6' OH-DMA (6.7 %) and the conjugates of DMA, 5'OH-DMA and 6'OH-DMA (28.1 %). The existence of the N-oxide of DMA was also evident (1.0 %), although it represents a very minor part of the overall metabolism of DM. The conjugates consisted of DM glucuronide (17.2 %), 5' OH-DMA glucuronide (5.6 %), 6' OH-DMA glucuronide (2.0 %), 6' OH-DMA sulfate (1.3 %) and unidentified conjugates (2.0 %). The majority (> 85 %) of urinary DMA was excreted as a R(+)-enetiomer. The profiling results of urinary metabolites were similar to those observed after an iv dose.

**Conclusions:**

Renal excretion was the major route for the intravenously administered $^{14}$C-radioactivity. DM is rapidly and extensively metabolized. DMA was eliminated by multiple routes (i.e. excretion, hydroxylation, glucuronide conjugation and N-oxidation) with t1/2 of about 7 hours. The N-oxidation of DMA was a very minor elimination pathway compared to other routes. DMA was the major metabolite, representing 35 % and 61 % of $^{14}$C-radioactivity in plasma and urine, respectively.

**Pharmacokinetics and Metabolism of Dolasetron (DM) Following Intravenous Administration of $^{14}$C-DM**

Protocol Number: 73147-1-C-011

**Objectives:**

To investigate the disposition of DM and its reduced metabolite, DMA
To determine total recovery of the administered dose
To identify and profile urinary metabolites of DM following a single IV dose of $^{14}$C-DM to normal volunteers.

**Formulation:** The following table presents a 10 mg/ml injection $^{14}$C-DM solution used in the study.

| | |
|---|---|
| Batch No | IC-4435 |
| Site of Manufacturing | |
| Date of Manufacturing | 11-29-90 |
| Dosage Form | Injectable Solution |
| Strength | 10 mg/ml |
| Specific Activity | 5 μCi/ml |
| Batch Size | |
| | 10 ml solution in ampule |

**Study Design and Sampling:**

This was an open-label, single dose fashion with six healthy non-smoking male volunteers between years of age. Each subject received a single dose of 100 mg $^{14}$C-DM (51 μCi) by intravenous infusion over 6 to 7 minutes. Serial blood, urine and fecal samples were collected until the radioactivity of the last two samples was less than two times background radioactivity.

**Data Analysis:**

Pharmacokinetic parameters were calculated from plasma and urine concentration-time data by model independent methods and total mass recovery was determined from urinary and fecal elimination of $^{14}$C-radioactivity.

**Results:**

The recovery of $^{14}$C-radioactivity, DM and DMA is shown in the following table. The mean plasma concentration-time plots and pharmacokinetic parameters for $^{14}$C-radioactivity, DM and DMA are presented in Figure 1 and Table 2.

Table 1 Excretion of $^{14}$C-radioactivity, DM and DMA following intravenous administration of 100 mg $^{14}$C-DM (N = 6)

| | Percent of Dose (%)* | | |
|---|---|---|---|
| | Urine | Feces | Total |
| $^{14}$C-radioactivity | 65.3 ± 6.6 | 16.2 ± 5.5 | 81.5 ± 11.1 |
| DM | ND | | |
| DMA | 19.7 ± 2.6 | | |

ND Not detected * Mean ± SD

Figure 1 Mean plasma concentration versus time plots for $^{14}$C-radioactivity, DM (MDL 73, 147) and DMA (MDL 74,156) following single intravenous administration of 100 mg $^{14}$C-DM (N = 6)

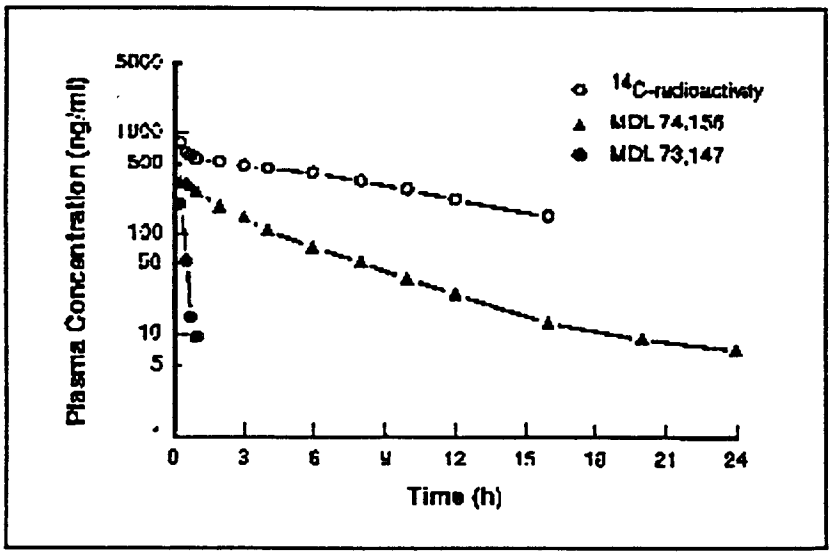



Table 2 Mean (%CV) pharmacokinetic parameters for $^{14}$C-radioactivity, DM and DMA

| | 14-C radioactivity (%cv) | DM (%cv) | DMA (%cv) |
|---|---|---|---|
| $AUC_{0-}$ (ngeq or ng.h/ml) | 7668.7 (8) | 124.9 (21) | 1447.5 (10) |
| Cmax (ngeg/ml or ng/ml) | NA | NA | 367.2 (29) |
| tmax (h) | NA | NA | 0.46 (54) |
| CL (ml/min/kg) | 2.96 (13) | 136.3 (11) | NA |
| V (L/kg) | 2.40 (22) | 1.47 (26) | NA |
| K* | 1.07 (10) | NA | NA |
| CLr (ml/min/kg) | NA | ND | 2.20 (14) |
| $AUC_{0-}$ ratio (%)** | NA | 2.21 (22) | 25.6 (12) |

NA: Not applicable
* : Blood to plasma concentration ratio of 14-C radioactivity
** : $AUC_{0-}$ ratio of DMA to 14-C radioactivity calculated based on molar equivalent concentrations

Approximately 82 % of the intravenously administered $^{14}$C-radioactivity was recovered in urine (65.3 %) and feces (16.2 %) in 4 days after dosing. No quantifiable amount of DM was excreted in urine, suggesting that DM is extensively metabolised. About 20 % of the dose was excreted in urine as DMA. The mean blood to plasma concentration ratio of $^{14}$C-radioactivity was 1.07,

**Pharmacokinetic and Safety Evaluation of Single IV Dose (1.2 mg/kg) of DM in Children Undergoing Elective and Uncomplicated Surgery Under General Anesthesia**

Study: AN-PD-0593

**Objectives:** To evaluate the pharmacokinetic profile of a single IV dose (1.2 mg/kg) of DM administered preoperatively to pediatric patients undergoing elective and uncomplicated surgery under general anesthesia.

**Formulation:** The manufacturing history of the 20 mg/ml injectable solution used in this study is presented in the following table.

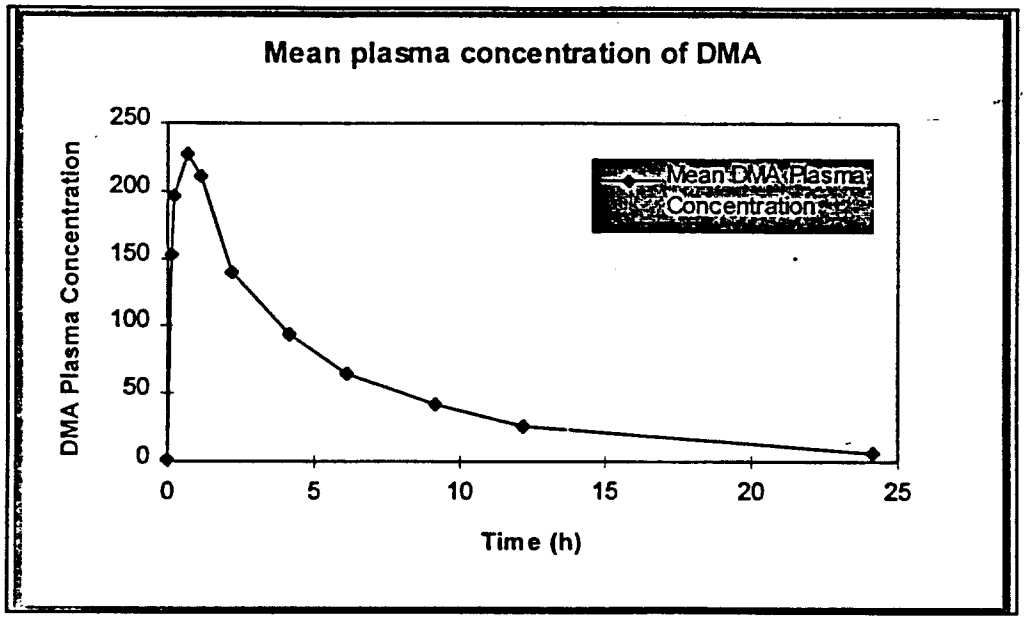
| | |
|---|---|
| Batch Number | 92A014 |
| Site of Manufacturing | |
| Date of Manufacturing | march 1992 |
| Dosage Form | Injectable Solution |
| Strength | 20 mg/ml |
| Batch Size | |

**Study Design and Sampling:** The study was an open-label, single center, pharmacokinetic study in pediatric patients between the ages of . years old. Eighteen children undergoing elective and uncomplicated surgery were administered single doses of 1.2 mg/kg of DM using an syringe pump by infusion over a 10 minute period. DM was administered immediately preoperatively.

Serial blood samples (2 ml) were taken prior to infusion of dolasetron, at the end of infusion (time 0), and at 0.08 (5 minutes), 0.5, 1, 2, 4, 6, 9, 12 and 24 hour after the completion of the DM infusion.

**Results:** Figure 1 and the following table presents mean plasma profile and mean plasma pharmacokinetic parameters for DMA in pediatric surgery patients.






| Parameters | Mean (%CV) |
|---|---|
| Cmax (ng/ml) | 254.6 (22) |
| tmax (h) | 0.63 (57) |
| $AUC_{0-}$ (ng.h/ml) | 1356.0 (42) |
| t1/2 (h) | 4.77 (23) |
| CLapp (ml/min/kg) | 13.13 (47) |
| Vapp (L/kg) | 5.17 (43) |

**Conclusion:** Children under general anesthesia when given DM as a single IV dose (1.2 mg/kg) showed greater mean apparent clearance (40%) and shorter terminal half-life (36%) for DMA compared to healthy adults.

**Pharmacokinetics of Single IV and Oral Doses of DM in Women**
Study: AK-KW-0993

**Objectives:**

1. To characterize the plasma pharmacokinetics of DM and its active metabolite DMA
2. To determine the urine pharmacokinetics of DM and its metabolites, total, R(+) and S(-) DMA, 5'OH and 6'OH DMA in women,
3. compare the pharmacokinetics of DM for healthy women and men

**Formulation:** A 20 mg/ml injectable solution was used in the study.

| | |
|---|---|
| Batch Nos. | 92A014 |
| Site of Manufacturing | |
| Date of Manufacturing | March 1992 |
| Dosage Form | Injectable Solution |
| Strength | 20 mg/ml |
| Batch Size | |

**Study Design and Sampling:** The study was conducted in an open-label, randomized, two-way balanced cross-over design with 24 healthy, female subjects between the ages of [redacted] years. Each fasted subject received one of the following treatments in each period:

Treatment A: 2.4 mg/kg DM given by a 12 minute iv infusion
Treatment B: 2.4 mg/kg DM given as a single oral solution dose.

A 7 day drug-free interval (wash-out period) was included between treatments. Serial blood and urine samples were collected for 48 hours after dosing.

Conclusions:



Almost no DM was detected after oral administration in women.
No DM was detected in urine after both routes of administration. Amount of total DMA excreted in urine accounted for % of total dose administered. The R(+) DMA enantiomer accounted for the majority of DMA present in urine (>87 %).
Absolute apparent bioavailability as measured by DMA of oral DM solution was 80 % in women.
Pharmacokinetics of DM and its major active metabolite, DMA, were similar in both men and women.

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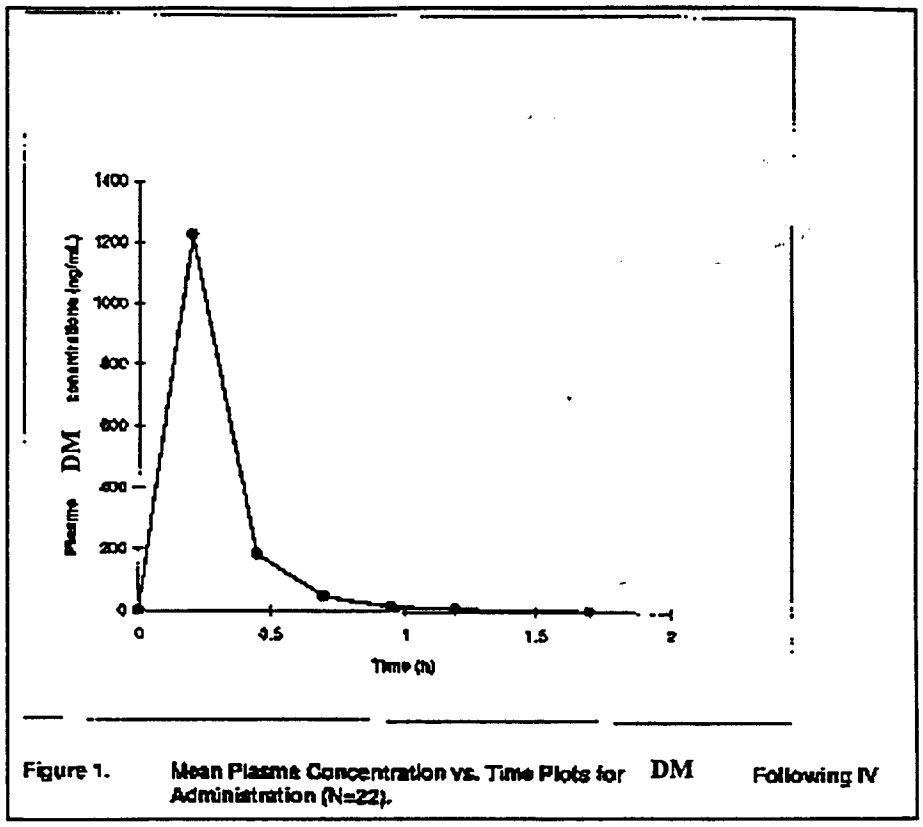


Figure 1. Mean Plasma Concentration vs. Time Plots for DM Following IV Administration (N=22).

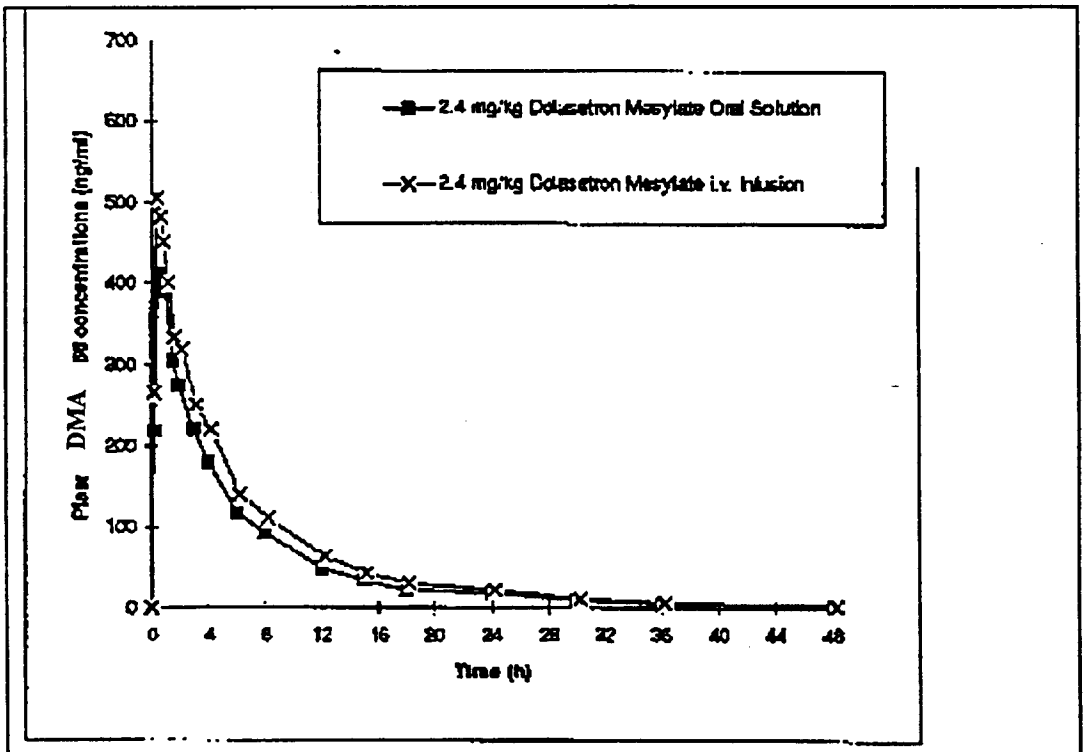


Figure 2. Mean Plasma Concentration vs. Time Plots for MDL 74.156 Following IV and Oral Administration (N=24) DMA



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**Pharmacokinetics of Single IV and Oral Doses of DM in Healthy Elderly Volunteers**

Study: AN-EP-0992

**Objectives:**

1. To characterize the PK of DM including its metabolite (DMA) in healthy elderly volunteers
2. To assess the absolute bioavailability in elderly
3. To estimate the renal clearance
4. To measure the urinary excretion of its metabolites

**Formulation:**

A 20 mg/ml injectable solution was used for in this study for both IV infusion and oral solution treatment.

| | |
|---|---|
| Batch No. | 92A014 |
| Site of Manufacturing | |
| Date of Manufacturing | March 92 |
| Dosage Form | Injectable Solution |
| Batch size | |

**Study Design and Sampling:**

This study was a randomized, open-label, two-way balanced cross-over trial conducted in one clinical site with 18 healthy elderly volunteers (male and female) over 65 years of age. Each participant received in a random sequence a single dose of DM (2.4 mg/kg) IV or orally. Blood samples were collected prior to and at 10, 20, 30, 45, 60 minutes and 1.5, 2, 3, 4, 6, 8, 12, 15, 18, 24, 30, 36, 48 and 60 hours post-dose. Urine was collected at intervals (0-8, 8-16, 16-24, 24-36 and 36-60 hours). The washout period was 14 days.

**Results:** Figure 1 and 2 present plasma concentration time plots for DM and DMA obtained following IV and oral administration of 2.4 mg/kg of DM. Mean PK parameters are summarized in Table 1 and 2. The mean percent of the dose excreted in urine for DM, (+) DMA, (-) DMA, 5'OH-DMA, and 6'OH-DMA are presented in Table 3.

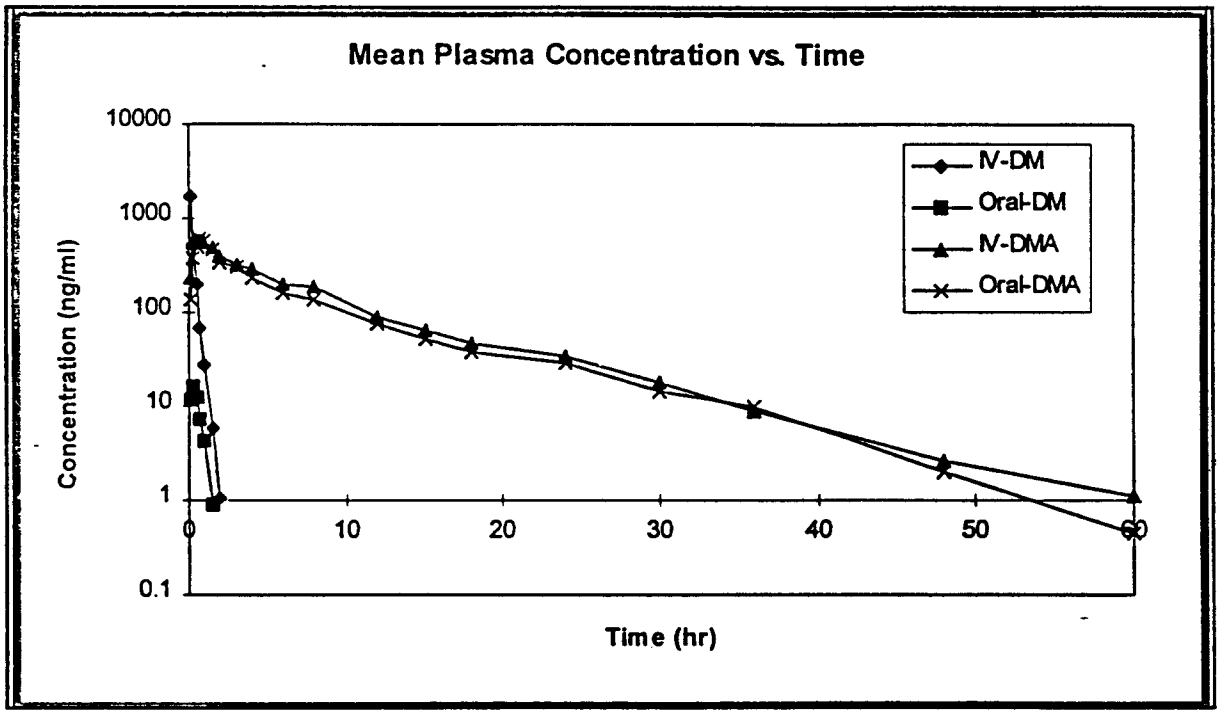



Table 1. Mean PK parameters of DM following single IV and P.O. doses of 2.4 mg/kg of DM

| Parameters | IV | Oral |
|---|---|---|
| $AUC_{0\text{-last}}$ (ng.h/ml) | 395.27 ± 177.33 | 11.17 ± 5.81 |
| $AUC_{0-\infty}$ (ng.h/ml) | 398.19 ± 177.54 | 18.00 ± 5.73 |
| Kel (h-1) | 3.25 ± 0.97 | 1.76 ± 0.74 |
| t1/2 (h) | 0.24 ± 0.11 | 0.50 ± 0.27 |

| | | |
|---|---|---|
| Cmax (ng/ml) | 1465.06 ± 769.89 | 18.05 ± 8.79 |
| Tmax (h) | - | 0.32 ± 0.10 |
| Absolute Bioavailability | - | 0.05 ± 0.02 |

Table 2. Mean PK parameters of DMA following single IV and P.O. doses of 2.4 mg/kg of DM

| Parameters | IV | Oral |
|---|---|---|
| $AUC_{0\text{-last}}$ (ng.h/ml) | 3945.66 ± 1567.98 | 3467.19 ± 1403.98 |
| $AUC_{0-\infty}$ (ng.h/ml) | 4028.08 ± 1583.71 | 3592.95 ± 1503.30 |
| Kel (h-1) | 0.105 ± 0.020 | 0.133 ± 0.142 |
| t1/2 (h) | 6.85 ± 1.54 | 7.16 ± 2.30 |
| CLapp (ml/min.kg) | 8.26 ± 2.46 | 9.53 ± 3.39 |
| Vd/F (L/kg) | 4.69 ± 1.07 | 5.63 ± 2.22 |
| Cmax (ng/ml) | 619.66 ± 190.6 | 661.85 ± 182.83 |
| Tmax (h) | - | 0.87 ± 0.60 |
| Absolute Bioavailability | - | 0.89 ± 0.14 |

Table 3. Mean percentage (± SD) of the Dose excreted in Urine for 0-60 hours

| | IV | Oral |
|---|---|---|
| DM | Not detected | Not detected |
| DMA | 27.85 (8.42) | 21.42 (8.43) |
| (+) DMA | 25.35 (7.79) | 18.88 (7.65) |
| (-) DMA | 2.5 (0.72) | 2.54 (0.85) |
| 5'OH-DMA | 1.99 (0.74) | 1.79 (0.68) |
| 6'OH-DMA | 5.45 (2.25) | 5.15 (2.06) |

The urinary excretion ratios of R(+) and S(-) to total DMA following oral and intravenous administration of dolasetron mesylate were similar between healthy male volunteers and elderly.

**Conclusions:**

In healthy elderly subjects, apparent clearance of DMA tended to be lower than the young healthy subjects. This difference however, may not be clinically significant ( in light of variation observed in CLapp in patients). When apparent clearance of DMA was compared between elderly males and females, no difference was noted.

**Pharmacokinetics of Orally and Intravenously Administered Dolasetron in Subjects with Renal Impairment**

**Study:** MCPR0033

**Objectives:** To evaluate the impact of renal impairment on the absorption and disposition of DM and DMA following single IV and oral dose administration of DM.

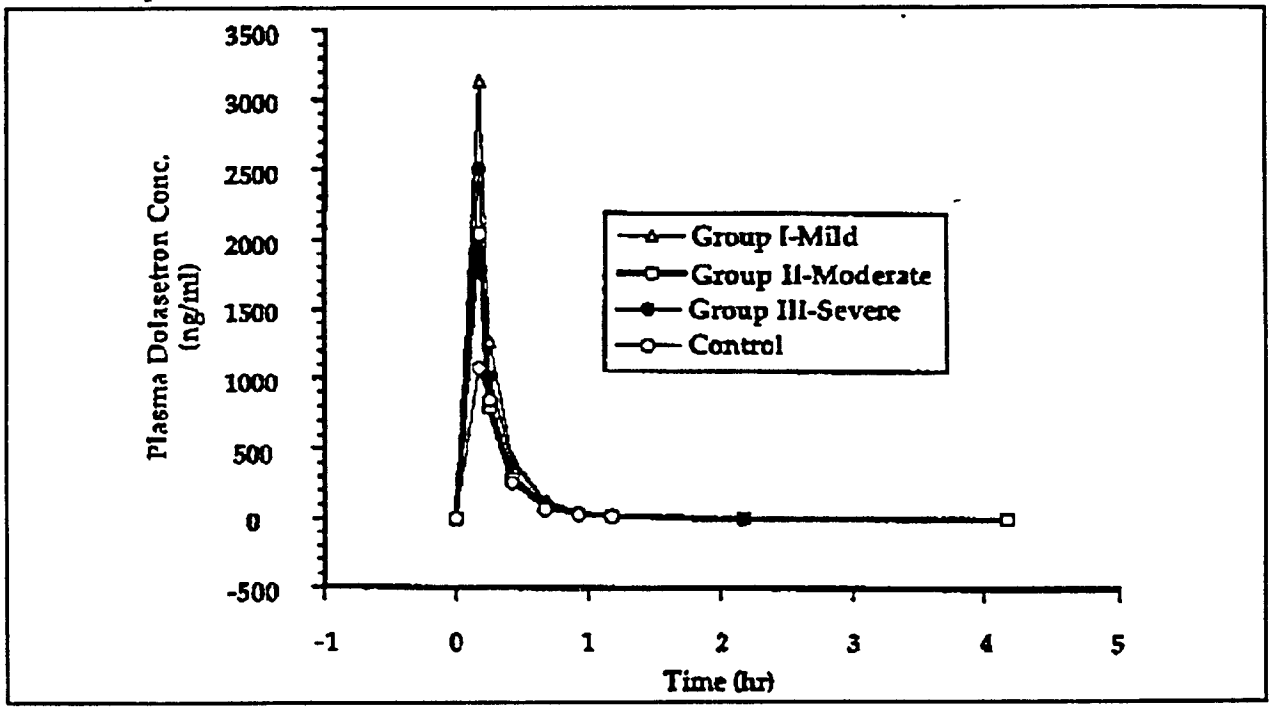
**Study Design and Sampling:** The study was conducted as an open-label, randomized, stratified, two-way complete cross over design. The two treatments were administered to 36 subjects assigned to one of three renal function groups. Renal function was assessed from each subject's 24 hour creatinine clearance. Each group contained 12 subjects with renal function classified as:

Group 1: Mild to moderate renal impairment, 80 ml/min >CrCl > 41 ml/min.
Group 2: Moderate to severe renal impairment, 40 ml/min >CrCl > 11 ml/min.
Group 3: Subjects with end stage disease, CrCl ≤ 10 ml/min.

The data from 24 normal healthy volunteers (age 23.8 ± 5.5 years, body weight 79.6 ± 9.1 kg) obtained from study MCPR0080 was used as the control group. Each subject randomly received a single dose of the following treatments on two different days:
Treatment A: 200 mg single IV dose of DM administered by constant-rate infusion over 10 min.
Treatment B: 200 mg single oral dose of DM in solution.
Serial blood samples were obtained for 60 hours after the drug administration. Urine samples were obtained over three consecutive 24 hour collection intervals for a total of 72 hours after the drug administration.

Blood pressure, heart rate and 12 lead electrocardiogram (ECG) measurements were obtained immediately before each dose and at 1, 6 and 24 hours post dose. Heart rate and PR, QRS, QT and QTc intervals were recorded using

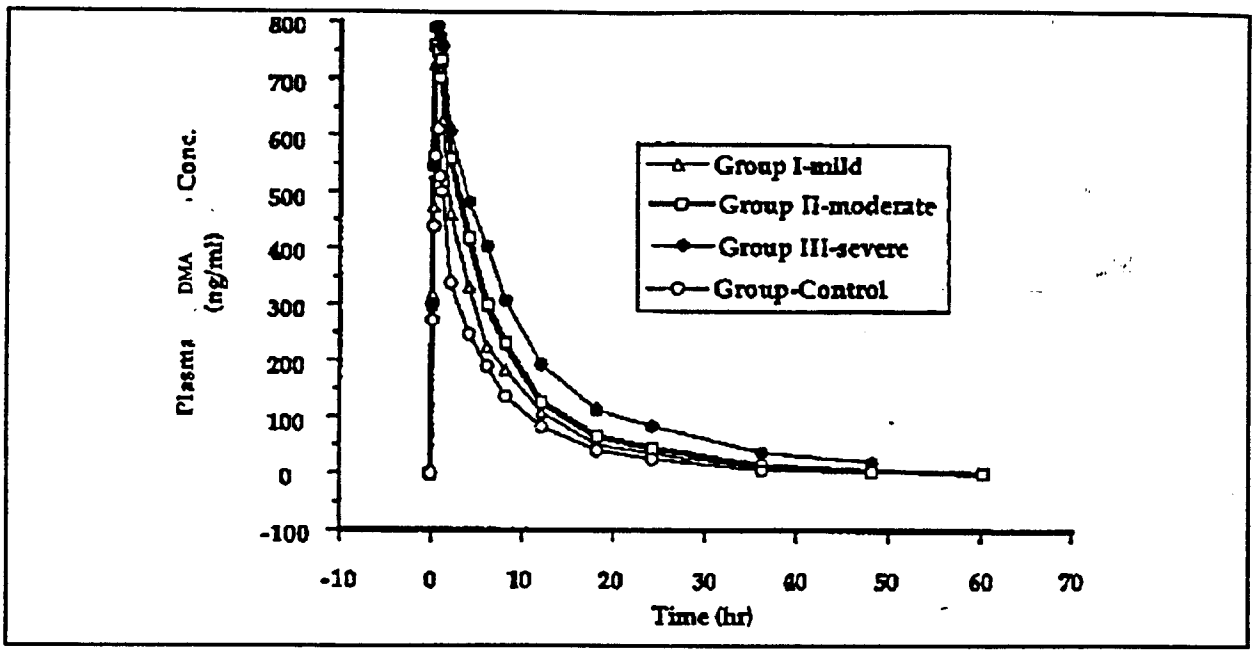
**Results:** Mean plasma DM concentrations after IV administration are shown in the following figure.




Plasma DM PK parameters (mean and %CV), are summarized in the following table.

| Group | Control | Mild | Moderate | Severe |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng.h/ml) | 285.55 (18.94) | 685.90 (45.96) | 426.04 (69.70) | 594.40 (38.93) |
| t1/2 (min) | 8.56 (14.56) | 21.97 (92.83) | 30.11 (138.95) | 11.08 (32.15) |
| CL (ml/min/kg) | 114.86 (30.53) | 55.65 (41.18) | 117.47 (65.93) | 66.13 (36.62) |
| V (L/kg) | 1.397 (26.89) | 1.50 (68.77) | 3.649 (99.49) | 1.028 (36.34) |

Mean plasma concentration-time plots for DMA after IV administration of DM for all three renal impairment groups as well as the control group are shown in following figure.

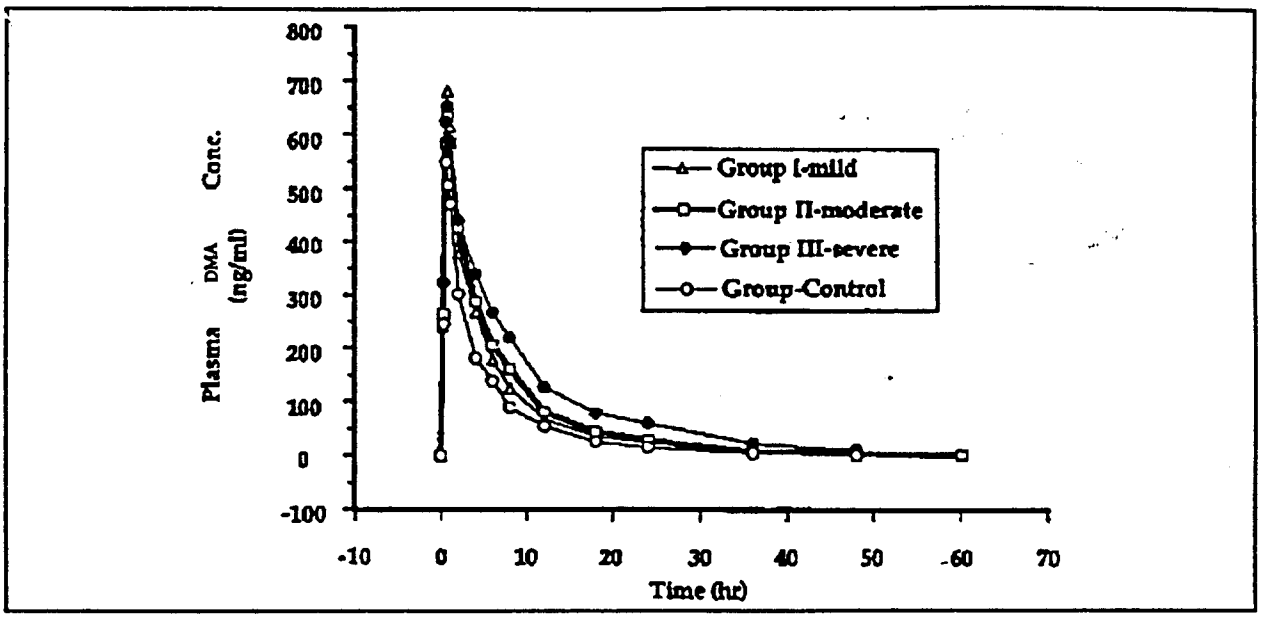



The pharmacokinetic parameters for DMA after IV administration of DM are summarized in the following table.

| Group | Control | Mild | Moderate | Severe |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng.h/ml) | 3637.52 (32.86) | 4770.58 (32.71) | 5832.70 (32.19) | 81.54.97 (55.72) |
| Cmax (ng/ml) | 646.90 (28.68) | 775.71 (39.52) | 812.78 (23.73) | 866.48 (30.60) |
| tmax (hr) | 0.67 (36.66) | 0.72 (30.54) | 0.77 (66.69) | 0.69 (39.21) |
| t1/2 (min) | 7.66 (21.99) | 8.97 (24.35) | 9.51 (44.23) | 10.91 (30.34) |
| CLapp (ml/min/kg) | 9.48 (34.04) | 7.59 (34.36) | 6.20 (37.75) | 4.95 (32.67) |
| CLr (ml/min/kg) | 2.91 (24.72) | 1.61 (52.53) | 0.44 (50.50) | 0.01 (156.05) |
| Vapp (L/kg) | 6.082 (30.15) | 5.802 (38.84) | 5.036 (61.65) | 4.537 (38.85) |

The Cmax was increased by ) in renally impaired subjects compared to the control group. The $AUC_{0-\infty}$ increased with renal impairment from 31.15 % in mild renal impairment to 124.19 % in severe renal impairment compared to AUC for the control subjects.

Mean plasma concentration-time plots for DMA after oral administration of DM for all three renal impairment groups as well as the control group are shown in following figure.




The pharmacokinetic parameters (mean, %CV) for DMA after oral administration of DM are summarized in the following table.

| Group | Control | Mild | Moderate | Severe |
|---|---|---|---|---|
| $AUC_{0-}$ (ng.h/ml) | 2680.28 (30.27) | 3596.69 (27.42) | 4130.9 (32.16) | 5633.22 (35.24) |
| Cmax (ng/ml) | 601.21 (34.62) | 742.7 (40.38) | 680.9 (26.97) | 700.8 (20.96) |
| tmax (hr) | 0.74 (43.99) | 0.81 (23.57) | 0.79 (29.60) | 0.72 (25.69) |
| t1/2 (min) | 8.84 (22.71) | 10.34 (36.88) | 13.15 (55.77) | 10.70 (29.27) |
| CLapp (ml/min/kg) | 12.88 (33.70) | 10.24 (34.55) | 8.79 (37.02) | 7.20 (48.14) |
| CLr (ml/min/kg) | 2.61 (28.09) | 1.67 (60.39) | 0.41 (59.26) | 0.01 (157.85) |
| F | 0.76 (28.30) | 0.77 (23.860 | 0.73 (27.77) | 0.75 (32.10) |

$\frac{12.88-7.2}{12.88} = 44\%$

The Cmax was higher in renal impairment groups compared to the control group. However, this increase in Cmax was not directly proportional to the extent of renal impairment. The area under plasma concentration-time curve was higher in renally impaired groups compared to the control group, and also increased with the degree of renal impairment from mild to severe. A mean increase of 110.17 % in $AUC_{0-}$ occurred with severe renal impairment compared to the control group subjects.

The following table shows the percentage of dose excreted in urine over 72 hours (mean and % cv) after IV and oral administration of DM as DMA (total), R(+) DMA, S(-) DMA, 5'OH-DMA and 6'OH-DMA.

| Group | Total DMA | R(+) DMA | S(-) DMA | 5'OH-DMA | 6'OH-DMA |
|---|---|---|---|---|---|
| Mean (%CV) | **200 mg IV** | | | | |
| Control | 32.76 (28.42) | 29.29 (30.22) | 3.47 (23.05) | 2.80 (32.14) | 7.14 (31.23) |
| I-Mild | 22.80 (41.50) | 20.91 (42.60) | 1.88 (33.11) | 1.85 (44.020 | 5.06 (38.15) |
| II-Moderate | 7.01 (34.92) | 6.43 (36.25) | 0.58 (47.64) | 0.84 (50.91) | 2.23 (43.02) |
| III-Severe | 0.42 (108.47) | 0.40 (108.91) | 0.02 (102.43) | 0.02 (118.76) | 0.12 (110.79) |
| | **200 mg Oral** | | | | |
| Control | 21.62 (30.48) | 18.71 (33.40) | 2.91 (23.37) | 2.60 (30.77) | 6.57 (29.07) |
| I-Mild | 16.76 (49.15) | 14.76 (51.54) | 2.00 (39.26) | 1.71 (27.52) | 4.88 (26.06) |
| II-Moderate | 4.82 (53.43) | 4.11 (57.09) | 0.71 (50.38) | 0.80 (57.55) | 2.09 (55.27) |
| III-Severe | 0.26 (108.15) | 0.24 (106.42) | 0.02 (133.60) | 0.02 (134.58) | 0.07 (119.37) |

The urinary excretion of DMA and hydroxylated metabolites after oral dosing was similar to IV administration of DM and is lower in magnitude due to the bioavailability factor. The urinary excretion ratios of R(+) and S(-) to total DMA following oral and intravenous administration of dolasetron mesylate were similar between healthy male volunteers and renally impaired subjects.

**Conclusion:** As renal function decreased, the renal clearance of DMA and the fraction of dose excreted in the urine decreased. The systemic exposure of major active metabolite, DMA based on AUC increased approximately two fold in patients with end-stage renal function. Renal elimination of metabolic products of DMA also decreased with an increase in degree of renal impairment. However, the ranges of individual apparent oral clearance and apparent clearance values of DMA for renally impaired subjects are not considerably different from those observed in healthy normal volunteers.

Even though, the ranges of individual apparent oral clearance and apparent clearance values of DMA for renally impaired subjects are not considerably different from those observed in healthy normal volunteers, the range of Cmax of DMA for renally impaired subjects for IV administration is greater than those observed for healthy normals. Also, data for cardiac conduction changes showed that frequency of QTc prolongation beyond 440 msec was much higher in severe renal impaired group. The pharmacokinetic and safety results suggest that a dose adjustment may be necessary for renally impaired cancer or surgery patients (reduction of about 30%) .

**Pharmacokinetics of orally and intravenously administered DM in healthy volunteers and in patients with hepatic impairment**

Study: 73147-2-S-085

**Objectives:** To provide an evaluation of the impact of hepatic impairment on the absorption and disposition of DM, as well as on the formation and disposition of DMA when administered orally or intravenously.

**Study Design and Sampling:** This was a two-center, open design study in which subjects received a single 150 mg IV dose and a single 150 mg oral dose of DM. The subjects were randomized to the following treatments:
Treatment A: 150 mg DM infused intravenously over 10 min.
Treatment B: 150 mg DM oral (100 mg tablet + 50 mg tablet)
The wash-out period was 1 week and the doses were administered under fasting conditions.
Group I: A total of 6 healthy subjects
Group II: 7 patients with hepatic impairment of Child-Pugh class A
Group III: 4 patients with hepatic impairment of Child-Pugh class B or C1
Plasma samples were taken over the period 0 to 48 hours after the start of dosing for both treatments, a total of 34 plasma samples per subject. Urine samples were taken over the periods 0-12 hours, 12-24 hours and 24-48 hours after the start of dosing for both treatments.

**Results:**

Table 1 summarizes mean DMA PK parameters and Table 2 summarizes mean percentage of the total unconjugated metabolites over the period 0 to 48 hours post dose. For IV administration the PK parameters for DMA were similar between Group I, II and III. However, $AUC_{0-}$ after oral dosing indicated a increase from group I to III of approximately 70 %. Clearance (normalized to body weight), decreased from group I to group III by about 58 %.

There were no differences observed between groups in the total urinary metabolites excreted over 48 hours after dosing. Subject #6 (a healthy volunteer) was genotypically classified as a poor metabolizer of CYPIID6 substrates. This subject showed reduced urinary excretion of 5-OH and 6-OH-DMA.

Table 1

| Parameter | Treatment | Group | mean | c of v | range |
|---|---|---|---|---|---|
| $C_{max}$ ($ng.ml^{-1}$) | A intravenous | I | 424 | 15.8 | |
| | | II | 473 | 17.0 | |
| | | III | 396 | 45.1 | |
| | B oral | I | 347 | 33.9 | |
| | | II | 387 | 23.8 | |
| | | III | 410 | 11.9 | |
| $T_{max}$ (hr) | A intravenous | I | 0.75(1) | | |
| | | II | 0.50(1) | | |
| | | III | 0.50(1) | | |
| | B oral | I | 1.51(1) | | |
| | | II | 1.02(1) | | |
| | | III | 0.75(1) | | |
| $AUC_{0-\infty}$ ($ng.ml^{-1}.hr$) | A intravenous | I | 2525 | 33.7 | |
| | | II | 2604 | 17.4 | |
| | | III | 2844 | 17.2 | |
| | B oral | I | 1870 | 38.9 | |
| | | II | 2267 | 30.2 | |
| | | III | 3108 | 21.1 | |
| $t_{1/2}$ (hr) | A intravenous | I | 6.87 | 27.2 | |
| | | II | 8.96 | 32.6 | |
| | | III | 11.69 | 21.7 | |
| | B oral | I | 6.95 | 20.4 | |
| | | II | 10.84 | 57.7 | |
| | | III | 11.01 | 35.8 | |
| CLapp ($ml.min^{-1}.kg^{-1}$) | A intravenous | I | 10.77 | 31.8 | |
| | | II | 11.26 | 18.4 | |
| | | III | 9.62 | 18.7 | |
| | B oral | I | 15.25 | 44.6 | |
| | | II | 13.47 | 23.9 | |
| | | III | 8.83 | 57.3 | |
| Vdβ ($l.kg^{-1}$) | A intravenous | I | 6.12 | 25.2 | |
| | | II | 8.60 | 31.4 | |
| | | III | 9.75 | 31.2 | |

*1:Median and not mean

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15.25-8.83 / 15.25 = -2%

Table 2

| Metabolite | Treatment | Group | mean | range |
|---|---|---|---|---|
| MDL 74,156 | intravenous | I | 36.04 | |
| | | II | 33.09 | |
| | | III | 35.28 | |
| | oral | I | 21.91 | |
| | | II | 22.18 | |
| | | III | 33.53 | |
| MDL 102,382 | intravenous | I | 1.70 | |
| | | II | 2.25 | |
| | | III | 1.90 | |
| | oral | I | 1.59 | |
| | | II | 1.70 | |
| | | III | 1.81 | |
| MDL 73,492 | intravenous | I | 6.89 | |
| | | II | 8.17 | |
| | | III | 3.79 | |
| | oral | I | 5.69 | |
| | | II | 6.30 | |
| | | III | 3.65 | |
| Total | intravenous | I | 44.63 | |
| | | II | 43.51 | |
| | | III | 40.96 | |
| | oral | I | 29.19 | |
| | | II | 30.18 | |
| | | III | 38.98 | |



*MDL 74,156 = DMA, *MDL102382 = 5'OH-DMA, *MDL73-492 = 6'OH-DMA

**Conclusions:**

1. The PK of DM and its metabolites were affected by hepatic impairment. The effect of hepatic impairment on PK parameters depends on the route of administration and was most significant in severely impaired subjects.

2. The greatest differences were observed in severely impaired subjects after oral administration and were in mean clearance, 58 % compared to healthy subjects and mean AUC, 170 % compared to the healthy subjects. Where as, for IV administration the PK parameters for DMA were similar between Group I, II and III.

**Bioavailability of DM After Co-Administration with Cimetidine and Rifampin in Normals**

Study: MCPR0083

**Objectives:** To determine if a PK interaction exist after 1 week co-administration of DM with cimetidine or rifampin.

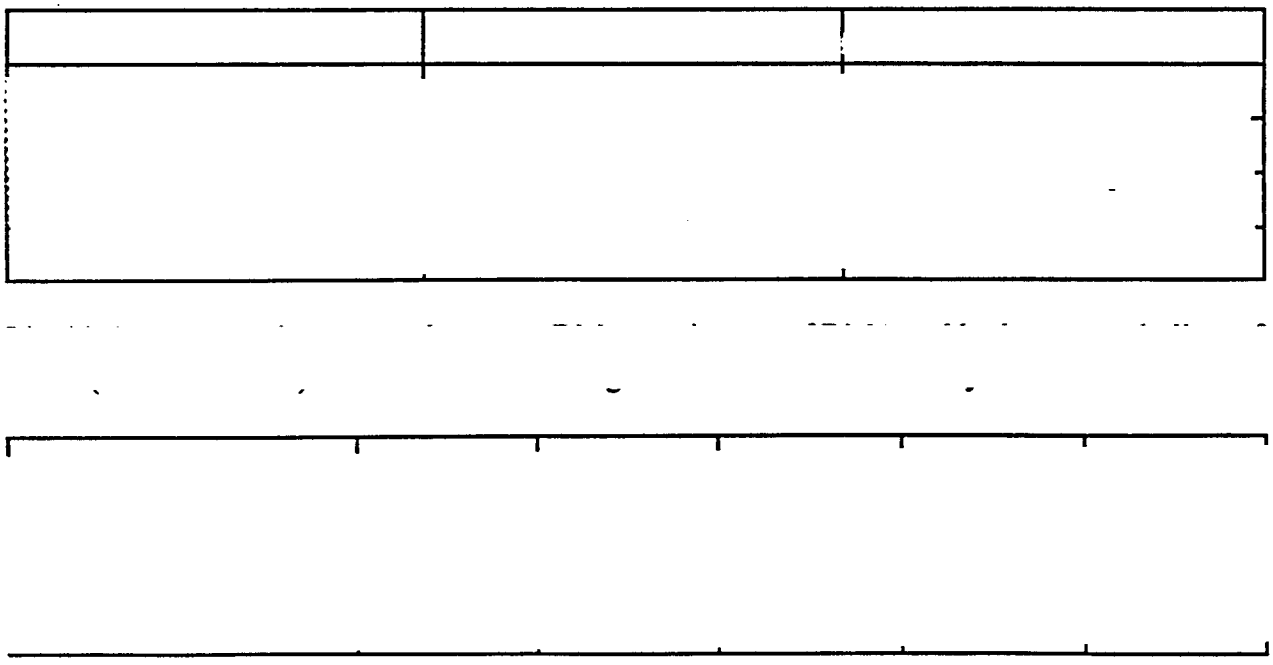
**Study Design and Sampling:** This was an open-label, randomized, three-way cross-over design with 18 healthy, male subjects between the Seventeen subjects completed all study procedures and one subject was dropped after two periods for a non drug-related illness.

Treatment A: 200 mg DM oral solution given at 8 AM on days 1 through 7.

Treatment B: 200 mg DM oral solution given at 8 AM on days 1 through 7 and one 300 mg cimetidine tablet given at 2 AM, 8 AM, 2 PM and 8 PM starting at 8 AM on day 1 through 2 AM on day 8.

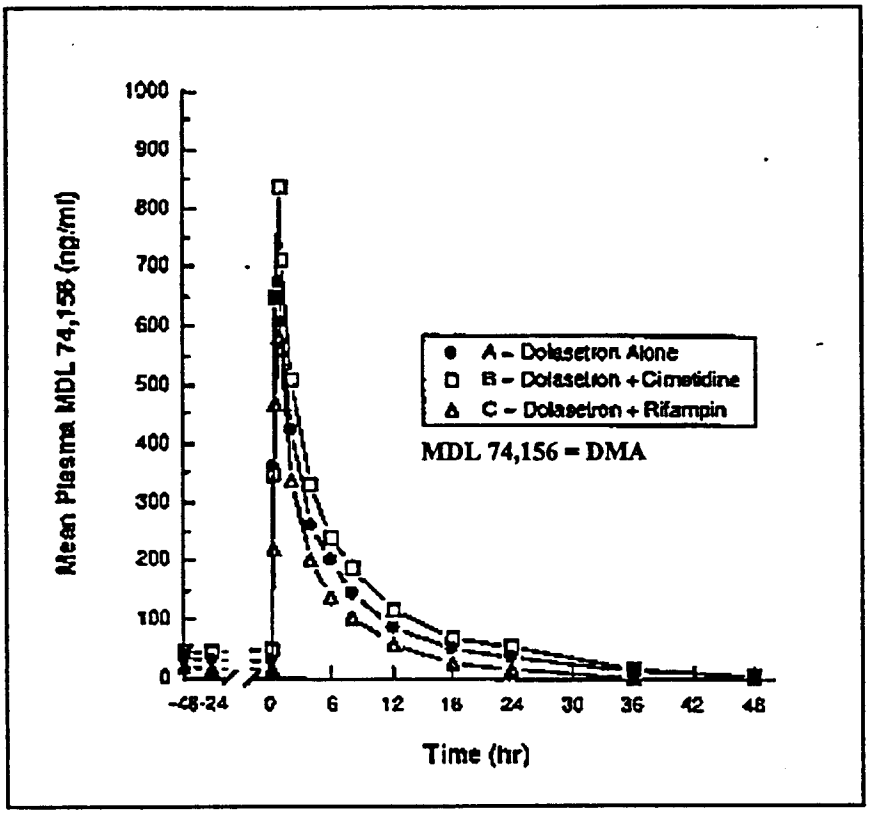
Treatment C: 200 mg DM oral solution and two 300 mg rifampin capsules given at 8 AM on days 1 through 7.

Serial blood and urine samples were collected up to 48 hours after the day 7 at 8 AM dose. Also, trough blood samples were collected on days 6 and 7 of each period.



**Results:**

Figure 1 presents the mean plasma concentration-time plots for DMA for the three treatments.






The following table summarizes mean PK parameters for DMA.



| Parameter | TRT | Mean (% CV) |
|---|---|---|
| AUCss (0-24 hr) (ng.h/ml) | A | 3654 (31) |
| | B | 4551 (33) |
| | C | 2682(31) |
| Cmax ss (ng/ml) | A | 732.7 (24) |
| | B | 842.2 (31) |
| | C | 614.3 (23) |
| tmax (hr) | A | 0.67 (29) |
| | B | 0.78 (10) |
| | C | 0.82 (18) |

| | | |
|---|---|---|
| CLapp.po (ml/min/kg) | A | 10.5 (29) |
| | B | 8.4 (28) |
| | C | 14.4 (30) |
| t1/2 (hr) | A | 8.8 (19) |
| | B | 8.4 (18) |
| | C | 7.4 (20) |
| CLr (ml/min/kg) | A | 2.15 (48) |
| | B | 2.00 (33) |
| | C | 2.58 (38) |

The following table shows mean percent of dose excreted in urine for 0 - 24 hr on day 7 as total, R(+), S(-) DMA, 5'-OH and 6'-OH DMA.

| Parameter | TRT | Mean (% CV) |
|---|---|---|
| R(+)-DMA | A | 19.33 (49) |
| | B | 22.59 (39) |
| | C | 17.58 (52) |
| S(-)-DMA | A | 2.35 (43) |
| | B | 2.55 (95) |
| | C | 2.21 (62) |
| Total DMA | A | 21.68 (47) |
| | B | 25.15 (37) |
| | C | 19.79 (52) |
| 5'OH-DMA | A | 1.38 (61) |
| | B | 1.22 (54) |
| | C | 1.32 (60) |
| 6'OH-DMA | A | 4.21 (59) |
| | B | 4.55 (61) |
| | C | 4.99 (51) |

The urinary excretion ratios of R(+) and S(-) to total DMA following oral and intravenous administration of dolasetron mesylate were not affected by coadministration of a cytochrome P450 inhibitor (cimetidine) or inducer (rifampin).

**Conclusion:**

1. When DM (200 mg oral solution) was co-administered with cimetidine (300 mg bid), AUCss (0-24 hr) and Cmaxss or DMA were increased by 24% and 15% respectively, CLapp,po of DMA decreased by about 19%.
2. When DM (200 mg oral solution) was co-administered with rifampin (300 mg QD), AUCss (0-24 hr) and Cmaxss or DMA were decreased by 28% and 17% respectively, CLapp,po of DMA increased by about 39%.
3. The renal clearance of DMA was not influenced by either cimetidine or rifampin co-administration.

**A five Arm Double-Blind Randomized Dose-Response Study of the Antiemetic Effectiveness of IV DM in Patients Receiving Cisplatin Chemotherapy: Population Pharmacokinetic and Pharmacodynamic Analysis**

Study: MCPR0032

**Objectives:**

1. Characterize pharmacokinetics (PK) of DMA in patients undergoing chemotherapy
2. Characterize pharmacodynamics (PD) of DMA in patients undergoing chemotherapy
3. Determine the influence of demographic variables, underlying disease and concomitant medications on the PK and PD of DMA in patients receiving chemotherapy.

**Study Design and Sampling:**

This was a five arm, double-blind, randomized, stratified, parallel, multicenter, dose-response study in which patients cancer received intravenously either a 0.6, 1.2, 1.8, 2.4 or 3.0 mg/kg dose of DM. Three hundred cancer patients

of either sex and any race were enrolled.

Blood: 7 ml blood samples was collected 15 minute prior to the administration of DM infusion and at 2, 4, 8, 12 and 24 hour after the start of cisplatin infusion 930 min after DM dose). Plasma samples were assayed to quantitate DMA by LC-MS method.

Electrocardiogram (ECG): Twelve-lead ECGs were obtained at pretreatment and at 1-2 and 24 hours after the start of cisplatin infusion.

**Data Analysis:**

Plasma concentration-time data for DMA were analyzed by nonlinear mixed effect modeling (NONMEM). The change in ECG parameters from the pretreatment value (ΔPR and ΔQRS intervals) and plasma concentrations were fitted to pharmacodynamic models using NONMEM. The covariates included in the PK/PD analysis were: demographics (patient age, weight, body surface area, gender and race), serum creatinine, albumin, disease, DM dose level, chemotherapy and concomitant medications.

A two-compartment model with elimination from central compartment was used. The parameters were apparent clearance (CLapp) and apparent volume of distribution of central compartment (V), and apparent intercompartmental clearance (Q) and apparent volume of distribution at steady state (Vs). The proportional error model in CLapp and V was used for interindividual variability.

From NONMEM analysis, the patient covariates such as body weight, serum creatinine, race (1=black, 0=others) and atenelol (ATEN; 1=yes, 0=no) when included in CLapp, and body weight in V and Vs significantly influenced the objective value function. The final model was as follows:

$CLapp\ (l/hr) = [\theta_1 * WGT\ (kg) * (1 + \theta_2 * Race + \theta_3 * ATEN) + \theta_4 * CRET\ (\mu mol/L)] * (1 + \eta_j)$
$V\ (L) = \theta_5 * WGT\ (kg) * (1 + \eta_j)$
$Q\ (L/hr) = \theta_6$
$Vs\ (L) = \theta_7 * WGT\ (kg)$

where $\eta_j$ represent persistent differences between the jth individual's 'true' parameter and the typical value for parameter, and are independent, identically distributed random errors with a mean of 0 and a variance of $\omega^2$.

The residual error or intrasubject variability in concentration of DMA was also modeled as proportional error model.

$$Cp_{ij} = C'p_{ij} * (1 + \varepsilon_{ij})$$

where, $Cp_{ij}$ is the ith measured DMA concentration in the jth individual, $C'p_{ij}$ is the predicted concentration and $\varepsilon_{ij}$ are independent, identically distributed errors with a mean of 0 and a variance of $\sigma^2$.

**Results:**
The parameter estimates, relative standard errors (CV %) and 95 % confidence intervals of the parameter estimates are summarized in the following table.

| Parameter | Description | Estimate | % CV | Lower 95 % CI | Upper 95 % CI |
|---|---|---|---|---|---|
| θ1 | L/hr/kg | 0.607 | 7.68 | 0.514 | 0.700 |
| θ2 | Coefficient for Race | 0.303 | 31.85 | 0.110 | 0.496 |
| θ3 | Coefficient for Atenolol | -0.184 | 43.64 | -0.345 | -0.0234 |
| θ4 | $L^2/\mu mol/hr$ | -0.090 | 34.11 | -0.151 | -0.0286 |
| θ5 | V (L/kg) | 1.56 | 8.14 | 1.306 | 1.814 |
| θ6 | Q (L/hr) | 39.0 | 5.59 | 34.64 | 43.36 |
| θ7 | Vs (L/kg) | 4.10 | 4.56 | 3.726 | 4.474 |
| $\omega^2_{CL}$ | interindividual variability | 0.209 | 11.34 | 0.162 | 0.256 |
| $\omega^2_V$ | interindividual variability | 0.327 | 24.13 | 0.169 | 0.485 |
| $\sigma^2$ | intraindividual variability | 0.0815 | 10.39 | 0.0646 | 0.0984 |

**Pharmacodynamics:**
ΔPR interval: Plasma DMA concentration and baseline PR interval (BPR) when included in a linear model significantly influenced the objective value function. The predicted ΔPR at the ith

concentration of DMA and for the jth subject in the final model is as follows:

$\Delta PR_{ij} = \theta_1 * Cp + \theta_2 * BPR + \theta_3 + \eta_j$

where $\eta_j$ represent persistent differences between the ith and jth individual's 'true' slope and the typical value for slope and are independent, identically distributed random errors with a mean of 0 and a variance of $\omega^2$.

The additive error for residual variability was used in observed change in PR interval:

$(\Delta PR_{ij})obs = \Delta PR_{ij} + \varepsilon_{ij}$

where, $(\Delta PR_{ij})obs$ is the measured change in PR interval in the jth individual, $\Delta PR_{ij}$ is the predicted value, and $\varepsilon_{ij}$ are independent, identically distributed errors with a mean of 0 and a variance of $\sigma^2$.

The estimated parameters, relative standard errors (% CV) and 95 % CI of the parameters are summarized in the following table.

| Parameter | Description | Estimate | % CV | Lower 95% CI | Upper 95 % CI |
|---|---|---|---|---|---|
| $\theta_1$ | Slope (msec/(ng/ml)) | 0.0353 | 9.41 | 0.0287 | 0.0419 |
| $\theta_2$ | Coefficient of BPR | -0.159 | 25.09 | -0.239 | -0.0792 |
| $\theta_3$ | Intercept (msec) | 29.0 | 20.90 | 16.88 | 41.12 |
| $\omega^2$ slope | Interindividual Variability $(msec)^2$ | 98.0 | 16.02 | 66.6 | 129.4 |
| $\sigma^2$ | Residual Variability $(msec)^2$ | 125 | 14.48 | 88.8 | 161.2 |

ΔQRS Width

The predicted ΔQRS at ith concentration of DMA and for the jth subject in the final model is as follows:

$\Delta QRSij = \theta_1 * Cp + \theta_2 + \eta_j$

where $\eta_j$ represent persistent differences between the ith and jth individual's 'true' slope and the typical value for slope and are independent, identically distributed random errors with a mean of 0 and a variance of $\omega^2$.
The additive error for residual or intrasubject variability was used in observed change in QRS interval:

$(\Delta QRS_{ij})obs = \Delta QRS_{ij} + \varepsilon_{ij}$

where, $(\Delta QRS_{ij})obs$ is the measured change in QRS interval in the jth individual, $\Delta QRS_{ij}$ is the predicted value, and $\varepsilon_{ij}$ are independent, identically distributed errors with a mean of 0 and a variance of $\sigma^2$.

| Parameter | Description | Estimate | % CV | Lower 95% CI | Upper 95 % CI |
|---|---|---|---|---|---|
| $\theta_1$ | Slope (msec/(ng/ml)) | 0.0139 | 16.98 | 0.00918 | 0.01862 |
| $\theta_2$ | Intercept (msec) | 1.05 | 34.10 | 0.334 | 1.766 |
| $\omega^2$ slope | Interindividual Variability $(msec)^2$ | 15.3 | 24.38 | 7.84 | 22.76 |
| $\sigma^2$ | Residual Variability $(msec)^2$ | 38.1 | 25.91 | 18.36 | 57.84 |

**Conclusions:**

Pharmacokinetics of DMA in patients receiving IV dose of DM was described by 2 compartment model.

Patient body weight, serum creatinine, race and atenelol for apparent systemic clearance and body weight in apparent volume of distribution were significant covariates in the model.

The intersubject variability in apparent systemic clearance and volume of distribution of DMA was 45.7 and 57.2 %, respectively. The residual variability was 28.5 %.

The changes in PR interval were linearly related to plasma DMA concentrations and baseline PR interval.

The changes in QRS width were linearly related to plasma DMA concentrations.

The intersubject variability in ΔPR interval and ΔQRS width was 9.9 and 3.9 msec, respectively.

The residual variability in ΔPR interval and ΔQRS width was 11.2 and 6.2 msec, respectively.

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**Population Pharmacokinetics of DM in Patients Receiving IV Cyclophosphamide and/or Doxorubicin Containing Chemotherapy**

Study: MCPR0048

**Objectives:** To provide recommended doses for the prevention of acute emesis due to cyclophosphamide and/or doxorubicin-containing chemotherapy by estimating the nature of the dose response curves across 25, 50, 100 and 200 mg single oral doses of dolasetron mesylate

To characterize the population pharmacokinetic parameters of active metabolite DMA

**Study Design:** This was a four-arm, parallel group, double-blind, randomized study testing dose-response of oral DM doses 25, 50, 100 and 200 mg. DMA plasma concentration time data from 61 patients were used in the population pharmacokinetic and pharmacodynamic analysis. Patients included both males and females in the age range of years who were receiving IV cyclophosphamide and /or doxorubicin-containing chemotherapy.

Serial blood samples were obtained at the following time points: 45 minutes prior to the administration of IV chemotherapy and at 2, 4, 8, 12 and 24 hours after start of chemotherapy infusion.

**Data Analysis and Results:** Pharmacokinetic parameters for DMA were calculated from plasma concentration-time data by model-dependent methods using NONMEM. The potential impact of patient demographics (age, weight, height, body surface area, gender and race), serum creatinine, albumin, DM dose and dose of chemotherapeutic agents on the PK parameters of DMA was investigated.

| PK Parameters (mean, %CV) | Chemotherapy Patients Study 0048 | Healthy Male Volunteers |
|---|---|---|
| CL (ml/min/kg) | 12.9 (49) | 12.3 (34) |
| CL range | | |
| Half-life (h) | 7.88 (43) | 8.0 (37) |
| V (l/kg) | 2.52 (19) | - |
| Vss (l/kg) | 5.10 (33) | - |

**Comments:** Out of all the covariates tested, only race and "DM dose" came out as covariates responsible for significantly affecting DMA apparent clearance. The sponsor did not find influence of other covariates on DMA clearance (similar to study 0032) because of the limited number of patients in this study. However, use of "DM dose" as a covariate on clearance is surprising as the drug has exhibited linear PK in several other studies. The clearance of DMA is an apparent clearance and influenced by fraction of DM absorbed and/or extend of DMA formed. A possibility of drug-interaction between DM or DMA and chemotherapeutic agent can not be ruled out.

**Conclusion:**
The population pharmacokinetics of DMA after oral administration of DM was best characterized by a two-compartment model with first-order input for the rate of DMA formation. The overall mean oral apparent clearance and terminal half-life were similar between patients and normal subjects. However, the oral apparent clearance showed dependence on DM dose level. Such trend towards nonlinearity was not seen in other studies.
Other than race, identification of any other covariates that influenced the PK of DMA such as body weight and serum creatinine, was not achieved for this study data.

**Clinical Interpretation of a Population Analysis of ECG Parameters (QTc interval, JT interval and heart rate) in Normal Volunteers and Cancer Patients Following DM Administration**

**Objectives:**
To characterize the clinical implications of the relationship between plasma concentrations of DMA and changes in heart rate, QTc interval and JT interval in healthy normal subjects and cancer patients,
To identify demographic, drug or disease covariates which may affect changes in these variables in a clinically meaningful way

**Methodology:**
Plasma samples were collected from 42 healthy male volunteers (Study MCPR0080 and MCPR 0081) and 408 cancer patients (Study MCPR 0032, MCPR0043 and MCPR0048) after oral or IV administration of DM. Each subject/patient had one or more post-treatment 12-lead ECGs recorded at times specified in respective protocols. These ECGs were centrally read by a cardiologist who was blinded to dose/treatment. Pharmacodynamic analysis were performed using NONMEM.

**Results:**
**A QTc interval**
NONMEM analysis indicated that a plasma DMA concentration-effect relationship better predicted changes in QTc than did DM dose and that this relationship was non-linear: the rate of QTc interval increase diminishes as DMA plasma concentration increases. This is in contradiction with the linear relationship between plasma concentration and increases in PR interval and QRS duration. This may be because QTc is a function of measure of repolarization, depolarization and heart rate, while PR and QRS are indices of depolarization.

The DMA concentration vs $\Delta$QTc curve for cancer patients closely parallels that for healthy

subjects, with the curve for cancer patient having slightly higher y-intercept. This suggests that, in addition to the effect of DMA, chemotherapy contributes to the increase in QTc interval in these patients. Those patient who received doxorubicin had a higher y-intercept than cancer patient on other chemotherapy.

In addition to plasma DMA concentration and doxorubicin, the baseline (pretreatment) QTc interval significantly correlated with QTc interval. Larger increases in QTc interval were associated with lower baseline QTc intervals (a regression to mean phenomenon). The PK-PD model predicts that healthy subjects and cancer patients would experience QTc interval increases of 4.1 to 10.0 msec and 6.5 to 17.2 msec, respectively. The PK-PD modelling was done with data from IV and oral high doses of 3.0 mg/kg and 200 mg, respectively. In other dose tolerance studies, doses four-fold of what studied here, did not show adverse clinical consequence associated with the acute, transient increases in QTc interval.

The fully parameterized model equations for Model 7 are shown below.

Healthy Subjects: $\Delta QTc = 108 - 0.315 \cdot BQ + 23.1 \cdot C/[100+C]$

Patients not receiving doxorubicin: $\Delta QTc = 131 - 0.315 \cdot BQ + 36.4 \cdot C/[411+C]$

Patients receiving doxorubicin chemotherapy: $\Delta QTc = 140 - 0.315 \cdot BQ + 36.4 \cdot C/[411+C]$

The following table shows population PD parameters for ΔQTc (combined data)

| PD Parameter | Description | Parameter Estimate | Standard Error of Parameter Estimate | 95% Confidence Interval on the Estimate | SD ($=\sqrt{\omega^2}; =\sqrt{\sigma^2}$) |
|---|---|---|---|---|---|
| $\theta$I-PD | Covariate intercept for anthracycline chemotherapy (msec) | 140 | 19.0 | 102.7 - 177.2 | - |
| $\theta$I-S | Covariate intercept for healthy normal subjects (msec) | 108 | 16.9 | 74.9 - 141.1 | - |
| $\theta$I-PN | Covariate intercept for patients not receiving doxorubicin (msec) | 131 | 18.8 | 94.2 - 167.8 | - |
| $\theta$EM-P | Emax - Patients (msec) | 36.4 | 8.07 | 20.6 - 52.2 | - |
| $\theta$EM-S | Emax - Subjects (msec) | 23.1 | 3.22 | 16.8 - 29.4 | - |
| $\theta$EC-P | EC50 - Patients (ng/mL) | 411 | 145 | 127 - 695 | - |
| $\theta$EC-S | EC50 - Subjects (ng/mL) | 100 | 31.5 | 38 - 161 | - |
| $\theta$BQ | Covariate slope for baseline QTc | -0.315 | 0.0453 | (-0.404) - (-0.226) | - |
| $\omega^2$EM | Intersubject variability for Emax ($\omega^2$) (msec)$^2$ | 218 | 75.1 | 70.8 - 365.2 | 14.8 |
| $\omega^2$EC | Intersubject variability for EC50 ($\omega^2$) (ng/mL)$^2$ | 24800 | 15500 | 0* - 55180 | 157 |
| $\omega^2$BQ | Intersubject variability for the slope associated with BQTC ($\omega^2$) | 0.00112 | 0.000146 | 0.00083 - 0.00141 | 0.033 |
| $\sigma^2$ | Residual error - $\sigma^2$ (msec$^2$) | 239 | 16.7 | 206 - 272 | 15.5 |

0* Negative intervals of the variability estimates were set at zero due to inability to interpret negative results
$\omega^2, \sigma^2$ Variance
SD: Standard Deviation

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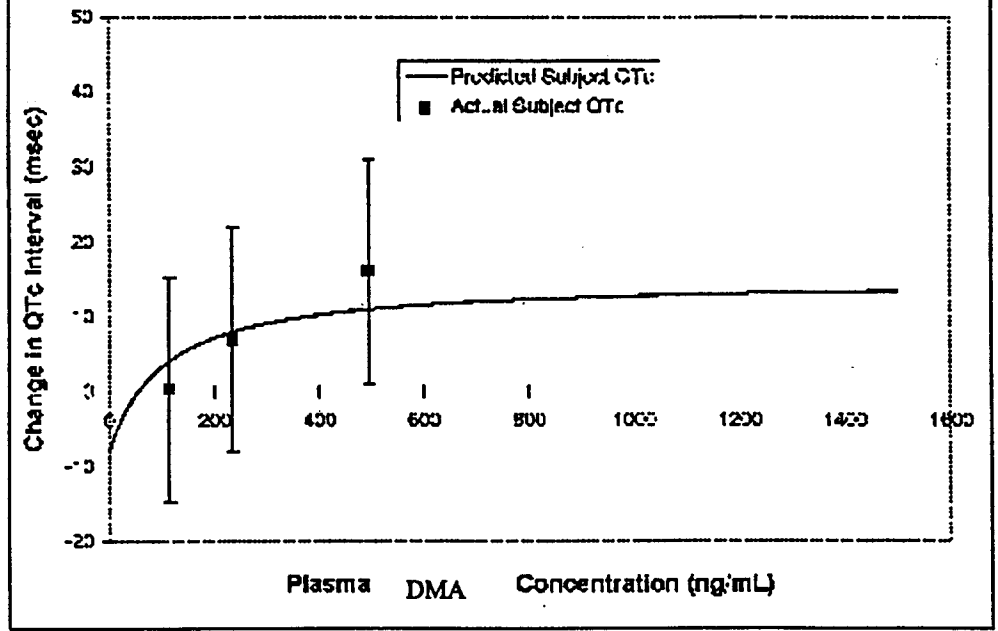


Predicted and Mean Observed Changes in QTc Interval for Healthy Subjects As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 50, 100 and 200 mg IV and Oral Doses

**Outliers:** The sponsor looked at outliers in following ways.
The upper 5% of plasma levels in this analysis (606 to 1282 ng/ml): Baseline QTc intervals for these 19 patients ranged The acute ΔQTc ranged from -22 msec (baseline= 420 msec) to 83 msec (baseline= 412 msec). Approximately 1/2 of these patients were taking concomitant cardiovascular medicines.
Patients from this analysis who showed acute ΔQTc>50 msec: Baseline QTc intervals for these 20 patients ranged from 362 to 437 msec. Acute plasma levels of DMA ranged
Approximately 1/2 of these patients were taking concomitant cardiovascular medicines.
Patients with highest baseline QTc intervals: Those patients who had high baseline QTc and would presumably be at higher risk from an agent that would further prolong QTc interval were chosen for this outlier analysis. Baseline QTc intervals for these 20 patients . The acute ΔQTc ranged from -59 msec (baseline= 481 msec) to 40 msec (baseline= 475 msec). Acute plasma levels of DMA
Seven of the 20 were taking concomitant cardiovascular medicines.

**Summary:** Increases in QTc interval were significantly correlated with plasma concentrations of DMA, the relationship being non-linear with the rate of increases in QTc decreasing with increasing concentration. Cancer chemotherapy, particularly doxorubicin, contributed to the increases observed in patients. The increase was inversely related to baseline QTc. Review of data from outlier patients indicates large variability among acute QTc interval changes, plasma DMA levels and baseline QTc intervals. There was no evidence in the 450 patients and subjects in this analysis, that the acute, transient increases in QTc interval following drug administration result in any adverse clinical consequences.

## B JT Interval

The relationship between plasma concentrations of DMA and changes in JT interval differed between healthy subjects and cancer patients. In healthy subjects, the data fit an Emax model, with an inverse relationship, indicating that the change in JT interval became less as DMA plasma concentration increased. In cancer patients, the change in JT interval appeared to increase linearly with increasing plasma concentrations of DMA, the slope was not steep, indicating that large changes in plasma concentration are associated with only small increases in JT interval in these patients (8.5 msec increase with 500 ng/mL increase in plasma concentration of DMA). Based on the high patient variability and the lack of clinical consequences, the changes in JT interval do not appear to be of clinical importance. The only variable other than plasma level of DMA significantly correlated with JT interval increases was baseline JT interval. As seen with the QTc interval, larger increases in JT interval were associated with lower baseline JT intervals. This, again, may merely represent regression to the mean.

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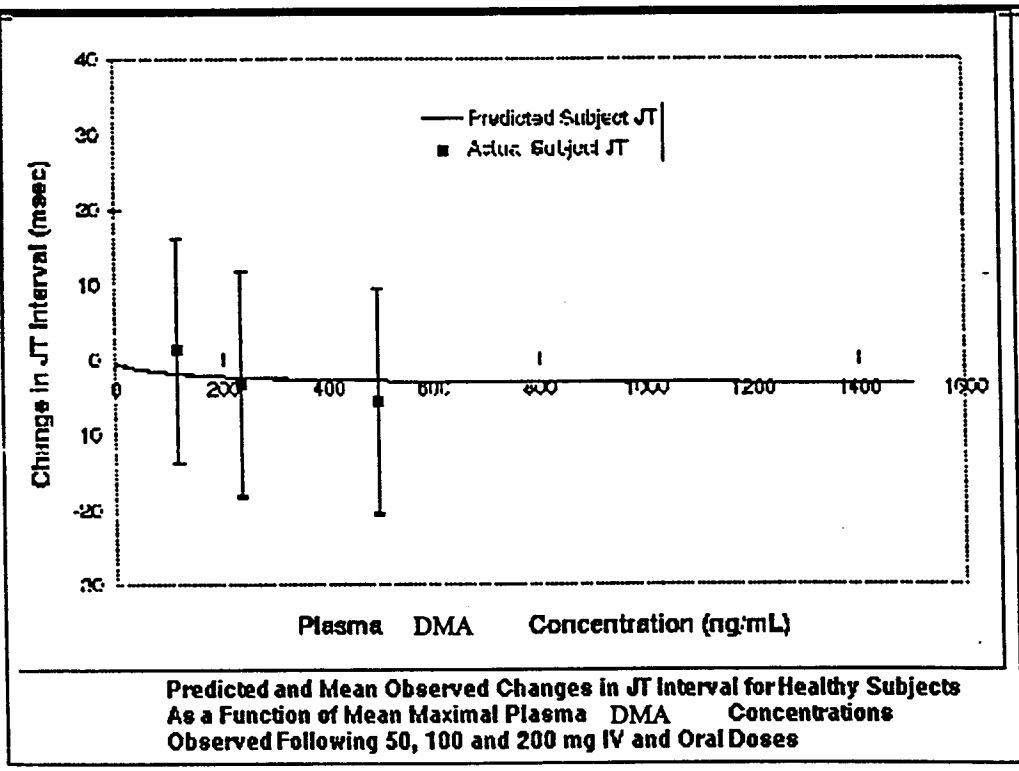
The following table shows population PD parameters for ΔJT(combined data)

| PD Parameter | Description | Parameter Estimate | Standard Error of Parameter Estimate | 95% Confidence Interval on the Estimate | SD (=√ω2; =√σ2) |
|---|---|---|---|---|---|
| θ | Population Estimate for Intercept (msec) | 74.2 | 8.21 | 58.1 - 90.3 | - |
| θBS | Population estimate for the slope associated with baseline JT (BST) | -0.254 | 0.0294 | (-0.312) - (-0.196) | - |
| θEM-S | Population estimate for the Emax Parameter associated with healthy subjects (msec) | -2.95 | 3.73 | (-10.3) - 4.4 | - |
| θEC-S | Population estimate for the EC50 parameter associated with healthy subjects (ng/mL) | 141 | 43.1 | 57 - 225 | - |
| θC-P | Population estimate for the slope associated with patient concentration (msec/ng/mL) | 0.0168 | 0.00466 | 0.0077 - 0.0259 | - |
| ω2I | Inters ubject variability for the intercept (ω2: msec2) | 20.0 | 127 | 0* - 269 | 4.47 |
| ω2BS | Inters ubject variability for the slope parameter (ω2) | 0.000605 | 0.000475 | 0* - 0.00154 | 0.025 |
| ω2EM-S | Inters ubject variability for the Emax parameter (ω2: msec2) | 47.4 | 95.1 | 0* - 234 | 6.88 |
| ω2EC-S | Inters ubject variability for the EC50 parameter (ω2: [ng/mL]2) | 5190000 | 10200000 | 1.5 • 10^7 - 2.5 • 10^7 | 2278 |
| ω2C-P | Inters ubject variability for concentration parameter (ω2: [msec/ng/mL]2) | 0.00331 | 0.00174 | 0* - 0.0067 | 0.058 |
| σ2 | Residual error - σ2 (msec2) | 238 | 14.2 | 210 - 265 | 15.4 |

0* Negative intervals of the variability estimates were set at zero due to inability to interpret negative results
ω2,σ2 Variance
SD: Standard Deviation






**Predicted and Mean Observed Changes in JT Interval for Healthy Subjects As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 50, 100 and 200 mg IV and Oral Doses**

In healthy subjects, the data fit an Emax model, with an inverse relationship and in cancer patients, the change in JP interval appear to increase linearly with increasing plasma concentrations. However, comparing the magnitude of the change in JT interval is within the predictable patient variability. Based on the high patient variability in ΔJT interval and the lack of clinical consequences, the changes in JT interval do not appear to be of clinical importance.

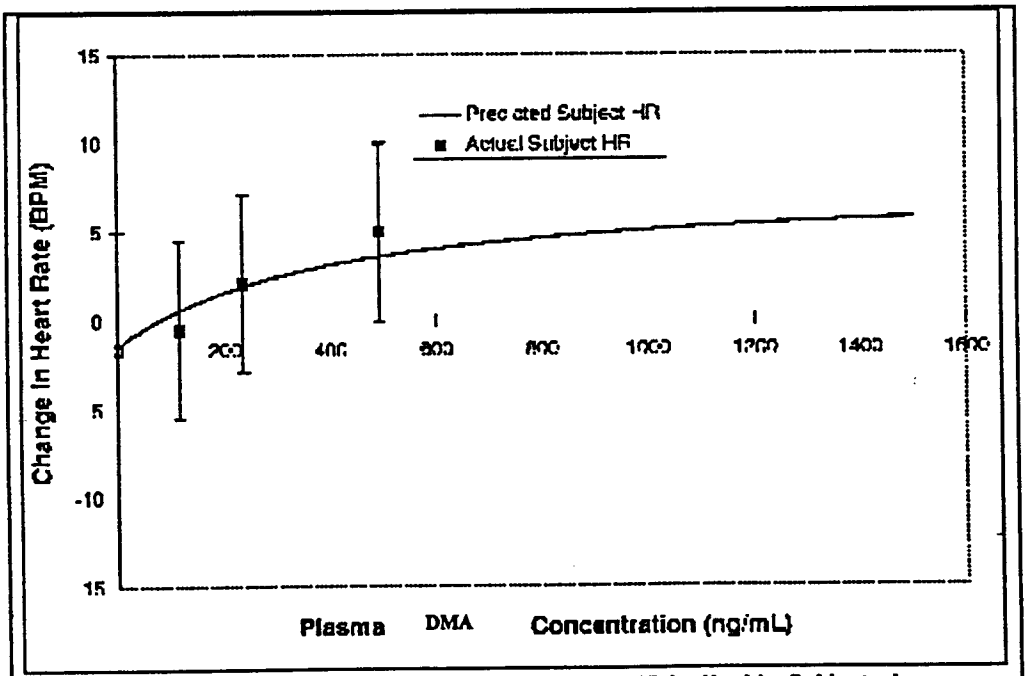
**Summary:** Increases in JT interval were not meaningfully related to plasma concentrations of DMA. The relationship was fitted to an Emax model and a linear model in healthy subjects and cancer patients, respectively. Overall, any change in JT interval which may be correlated to plasma levels of DMA would be expected to be minimal, and obscured by the inherent within patient variability of the JT interval.

### C Heart Rate

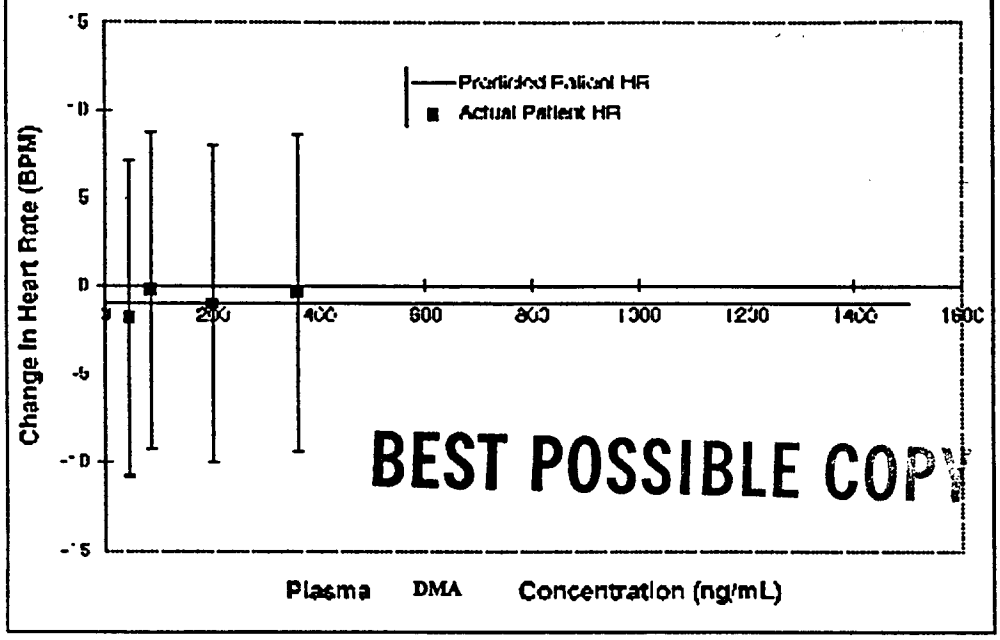
The sponsor carried out the PD analysis of HR as changes in HR could influence QTc interval changes. The analysis used HR recorded on ECG tracings. The relationship between plasma concentrations of DMA and changes in HR differed between healthy subjects and cancer patients. NONMEM analysis indicated that in cancer patients changes in HR were independent of plasma DMA concentration. In healthy subjects, a non-linear plasma DMA concentration/effect relationship was predicted, however, over the observed plasma DMA range (<1300 mg), the maximum change predicted was small (6 bpm) and variable (standard deviation=6 bpm). Additionally, there were large differences in **mean baseline HR** between healthy subjects and patients (57 bpm for subjects and 80 bpm for patients) which most likely contributed to the differences in the model intercept for patients and subjects.

| PD Parameter | Description | Parameter Estimate | Std Error of Parameter Estimate | 95% CI on the Estimate | SD ($=\sqrt{\omega^2}$; $=\sqrt{\sigma^2}$) |
|---|---|---|---|---|---|
| $\theta_{I\text{-}P}$ | Population Estimate for Patient Intercept (BPM) | 20.8 | 2.03 | 16.2 - 24.8 | - |
| $\theta_{I\text{-}S}$ | Population Estimate for Subject Intercept (BPM) | 13.9 | 1.49 | 11.0 - 16.8 | - |
| $\theta_{EM\text{-}S}$ | Population estimate for the EMAX parameter associated with concentration in healthy subjects (BPM) | 9.01 | 2.39 | 4.3 - 13.7 | - |
| $\theta_{EC\text{-}S}$ | Population estimate for the EC50 parameter associated with concentration in healthy subjects (ng/mL) | 391 | 193 | 13 - 769 | - |
| $\theta_{BH}$ | Population estimate for the slope associated with baseline HR | -0.269 | 0.0252 | (-0.318) - (-0.220) | - |
| $\omega^2_{EC\text{-}S}$ | Intersubject variability for the EC50 parameter associated with subject concentration ($\omega^2$: [ng/mL]$^2$) | 393000 | 284000 | 0* - 949640 | 627 |
| $\omega^2_{BH}$ | Intersubject variability for the slope associated with BHR ($\omega^2$) | 0.00659 | 0.000839 | 0.0049 - 0.0082 | 0.081 |
| $\sigma^2$ | Residual error - $\sigma^2$ (BPM$^2$) | 40.9 | 2.16 | 36.6 - 45.2 | 6.40 |

The above table shows population PD parameters for ΔHR(combined data).




**Predicted and Mean Observed Changes in HR for Healthy Subjects As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 50, 100 and 200 mg IV and Oral Doses**






**Predicted and Mean Observed Changes in HR for Cancer Patients Receiving Chemotherapy As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 25, 50, 100 and 200 mg IV and Oral Doses**

Summary: Changes in heart rate were not related to plasma concentrations of DMA in cancer patients. In healthy subjects, there was a non-linear relationship with positive, but modest maximum effects (6 bpm). Overall, any change in heart rate which may be correlated to plasma levels of DMA would be expected to be minimal, and obscured by the inherent within-patient variability of heart rate. Review of data from outlier patients indicates large variability among acute heart rate changes, plasma DMA levels and baseline heart rates.

## Conclusion

Increases in QTc intervals after dolasetron mesylate administration to healthy subjects or cancer patients are related to plasma concentrations of DMA. Patients/subjects with high pretreatment QTc intervals had relatively smaller increases than patients/subjects with lower pretreatment QTc intervals. There is no evidence these increases are associated with significant clinical consequences.

Changes in JT interval were, at most, marginally related to plasma concentrations of DMA and confounded by intrasubject variability in the measurements. The same was true for changes in heart rate. The relationship of plasma concentrations of DMA to increases in QTc interval was clear in this analysis, and a significant linear relationship has previously been shown between plasma concentrations of DMA and increases in QRS duration. Taken together, these results support the conclusion that increases in QTc interval after dolasetron mesylate are the result of increases in QRS duration (depolarization), not because of any prolongation of JT interval (repolarization) or heart rate.

Even though probability of prolongation in ventricular repolarization is less with DM and it is acknowledged that there were no instances of Torsades des pointes reported in clinical trials, prolongation of QTc interval raises questions about the 'practicality of use' of this drug. For instance, giving a second or a third dose of DM to treat vomiting (as is possible for DM Injection) will increase the risk for QTc prolongation and possibly the risk of Torsades des pointes. This risk is even greater for patients with reduced clearance of the active metabolite, viz. renal impairment.

The submitted PK-PD analysis were reviewed by the DPE-II with the assumption that QRS, PR and QT intervals were recorded/measured accurately. Also, most ECG recordings were carried out near the peak concentration of DMA (tmax). The paucity of PD data covering the entire corresponding concentration time profile is also a limitation of the submitted PK-PD analysis.