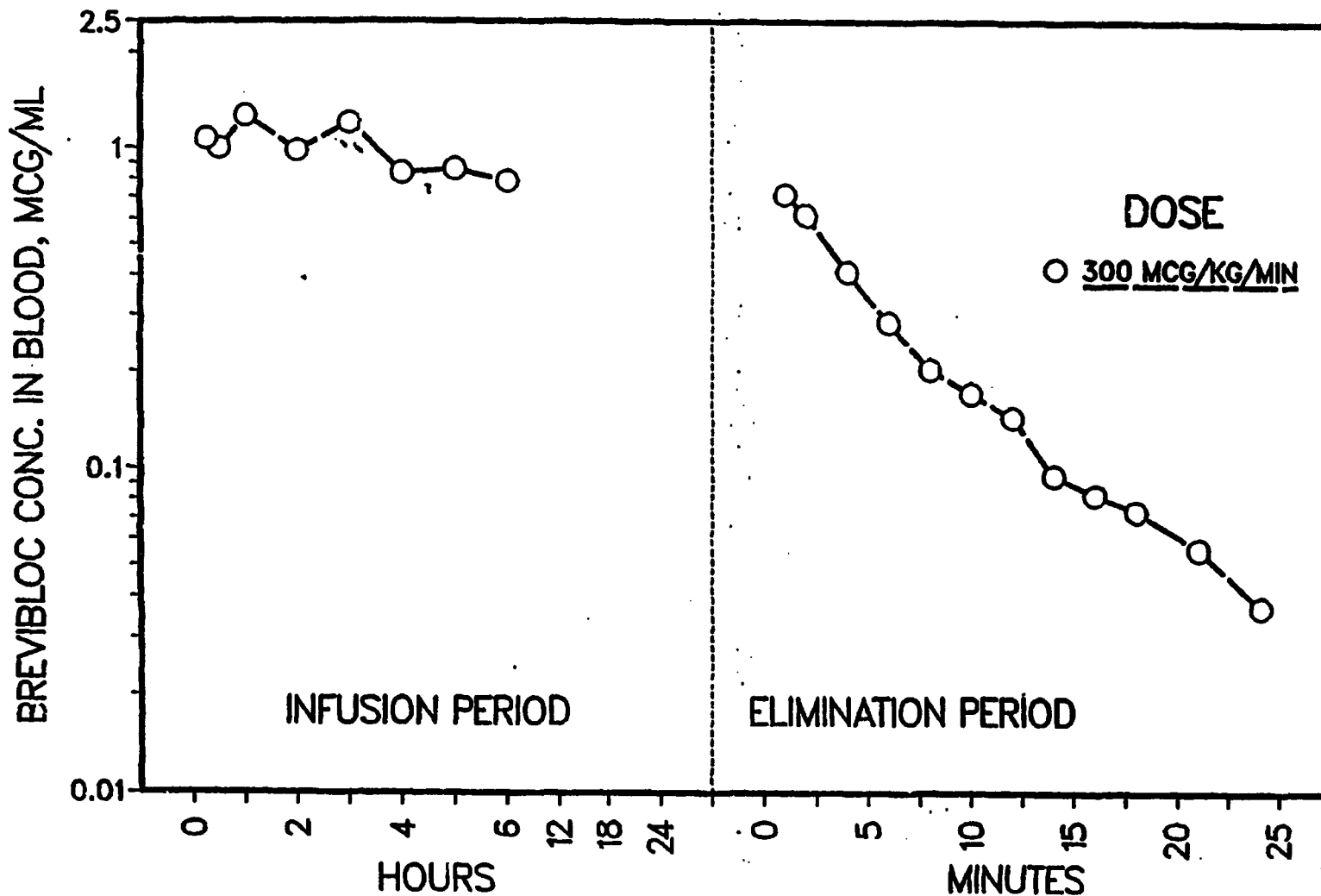
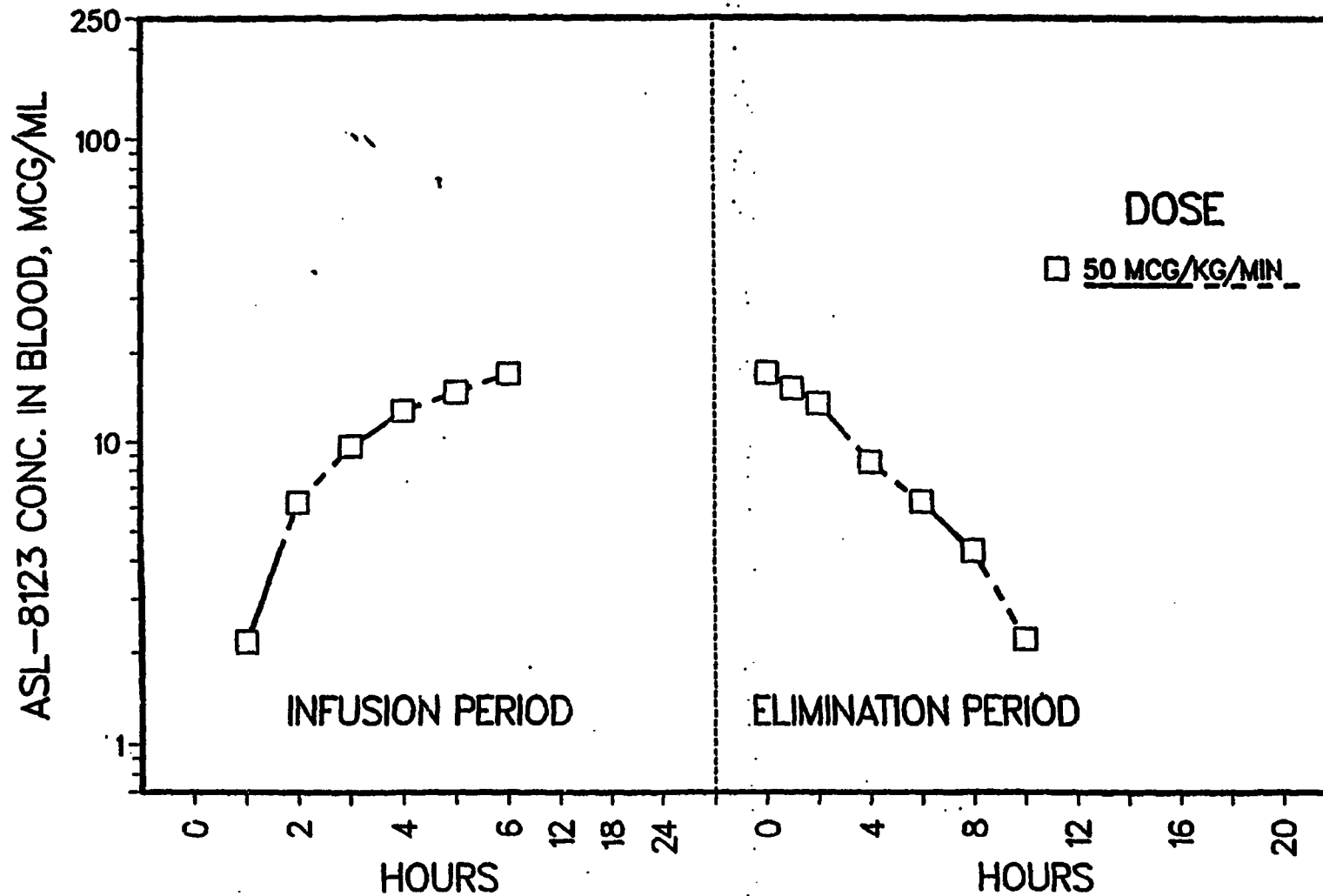


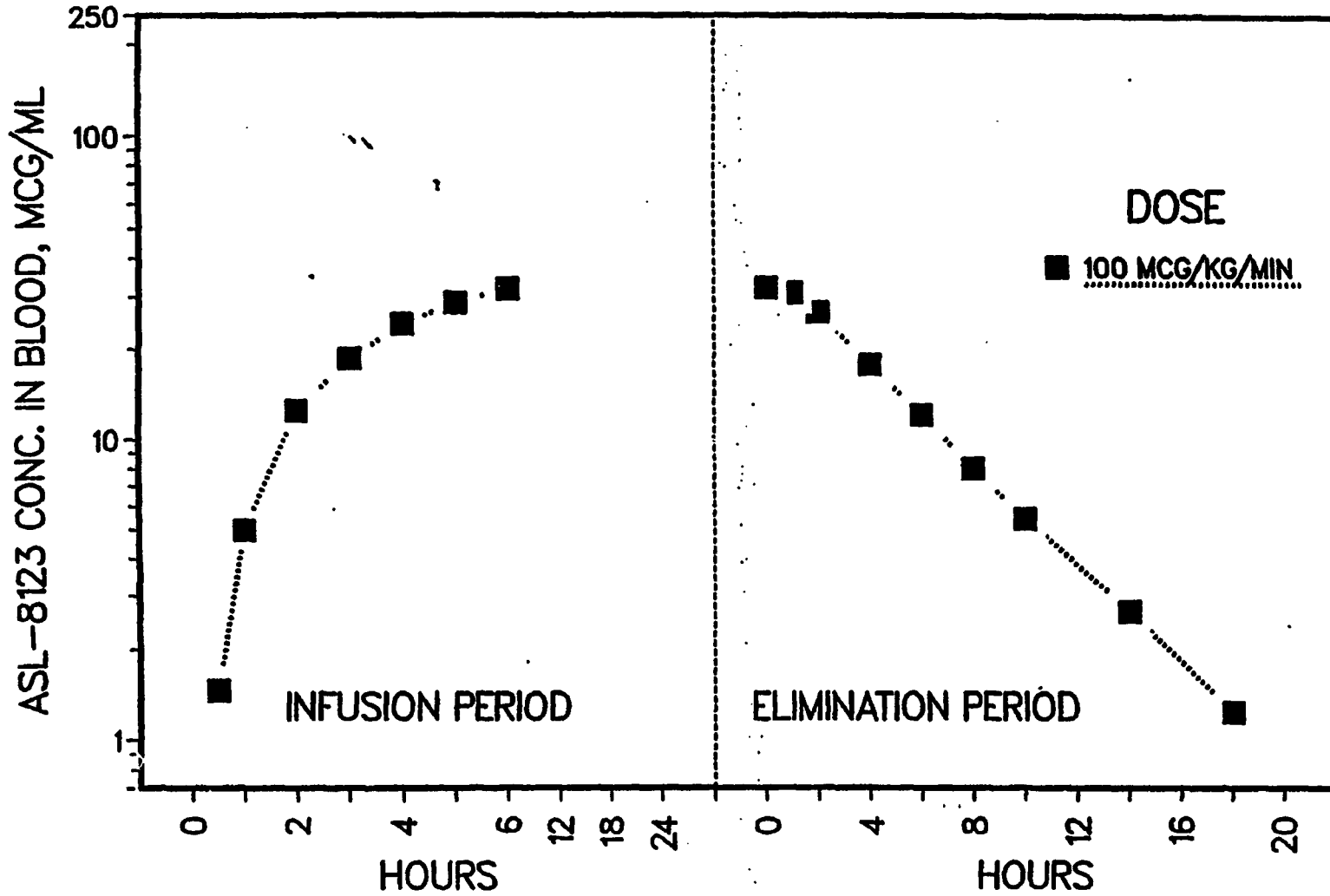
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MEAN OF 8 SUBJECTS



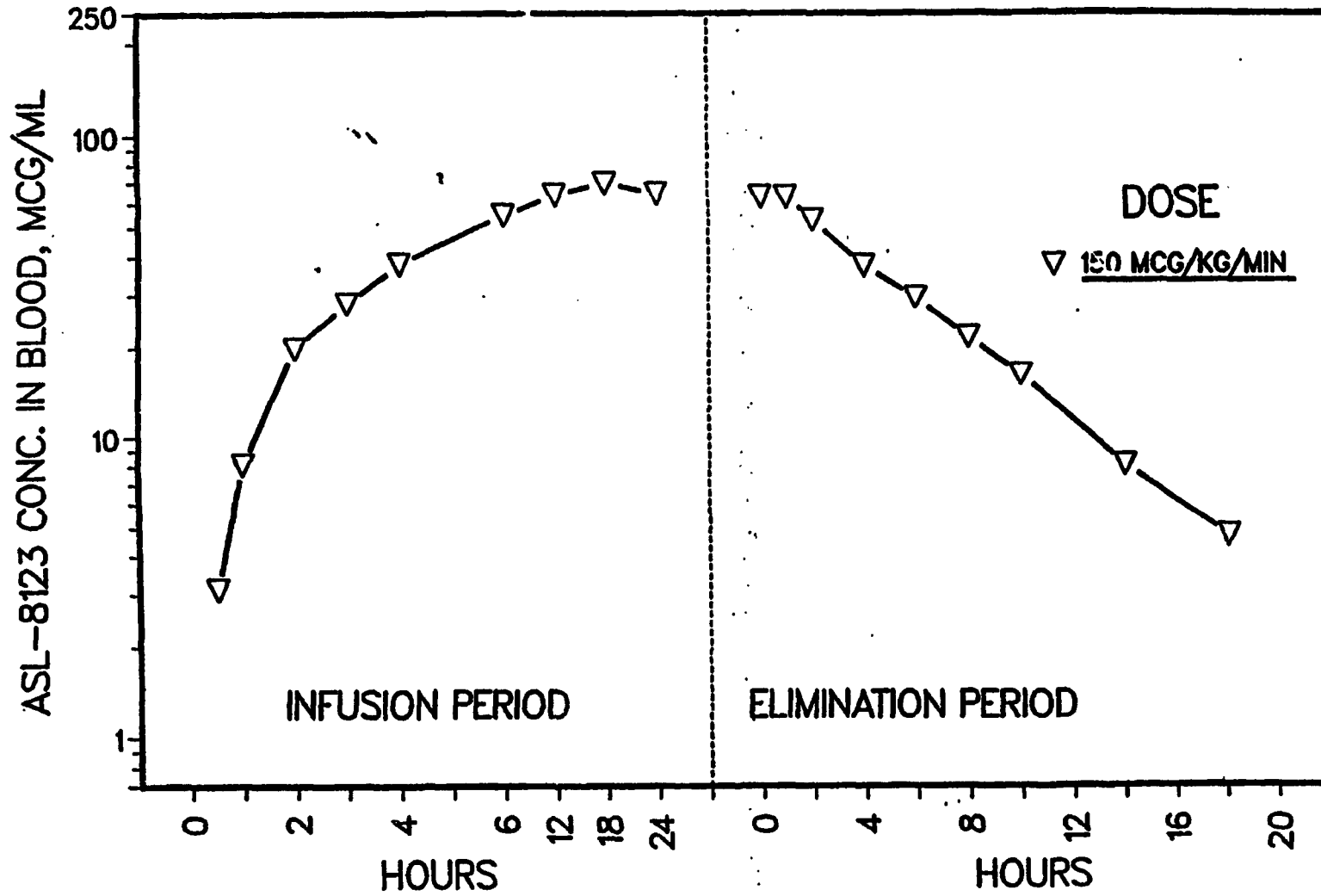
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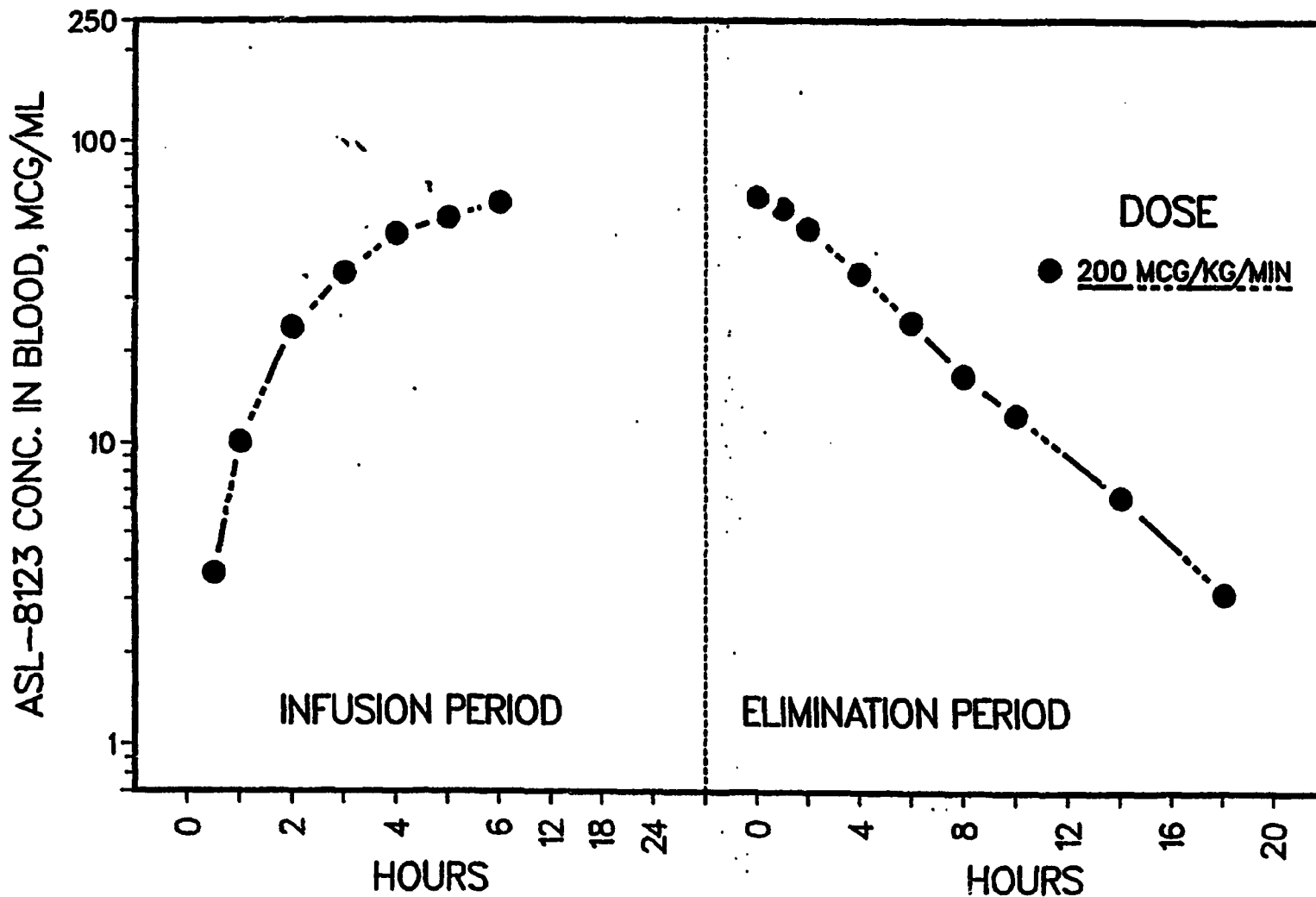
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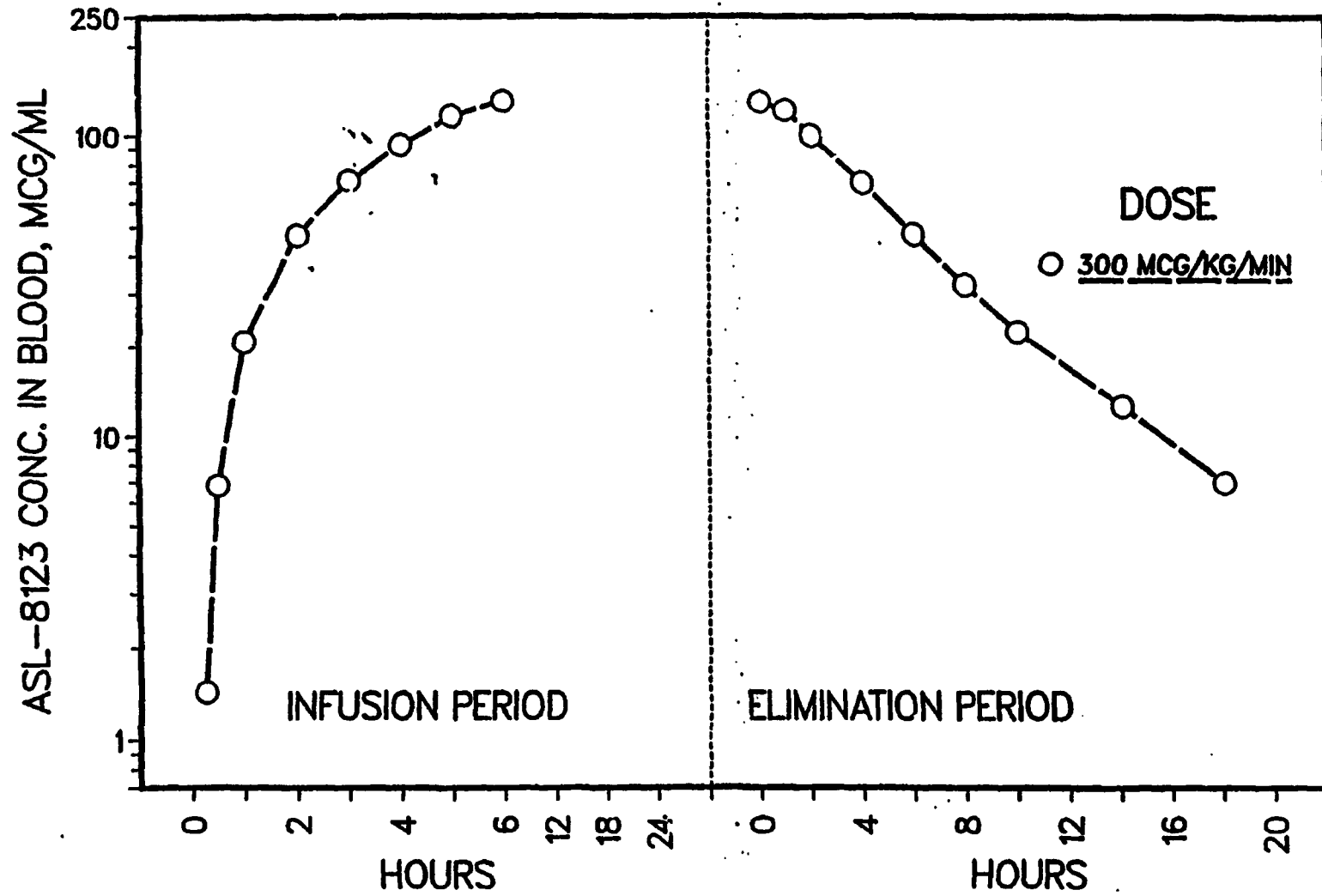
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MEAN OF 8 SUBJECTS



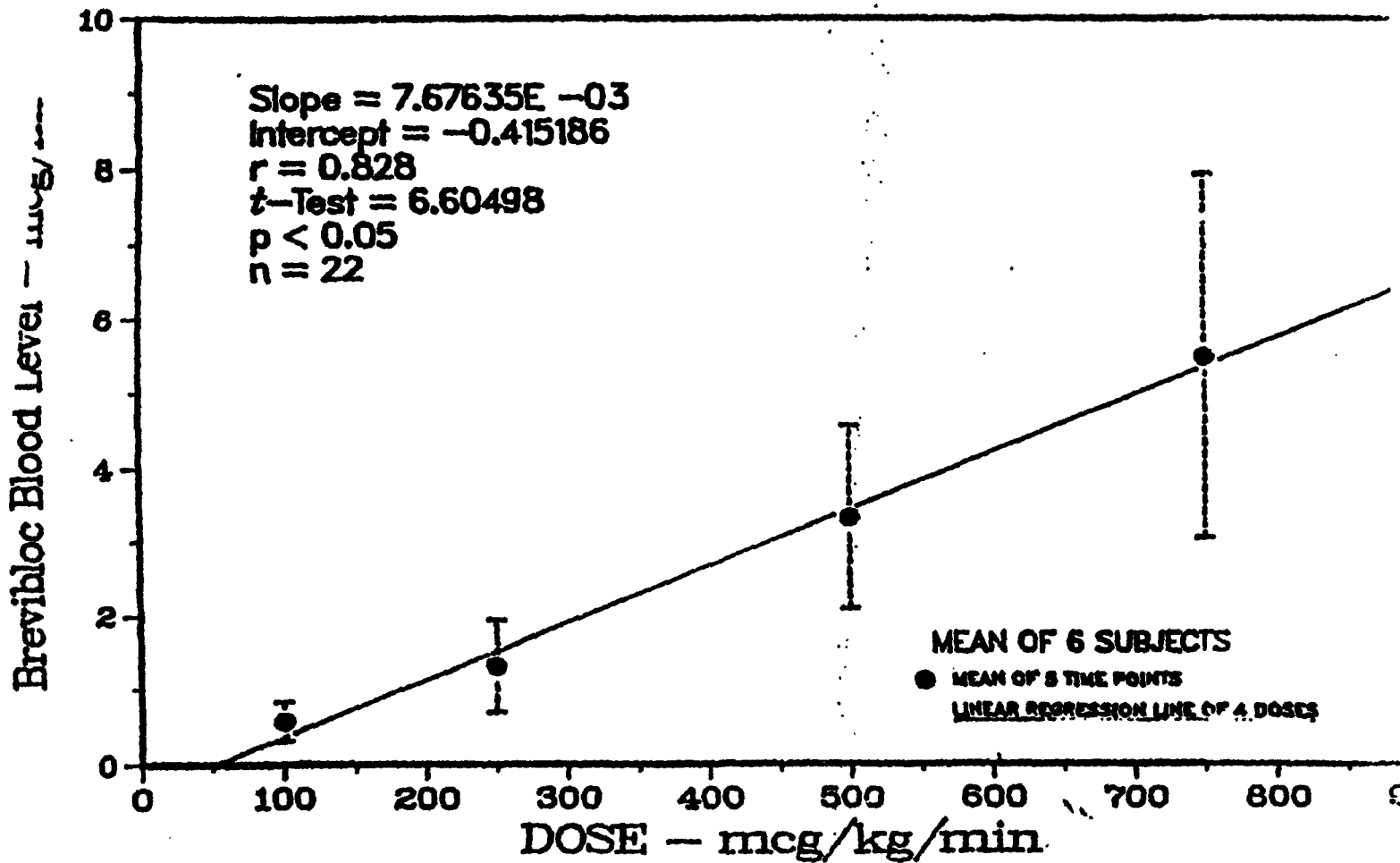
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MEAN OF 8 SUBJECTS



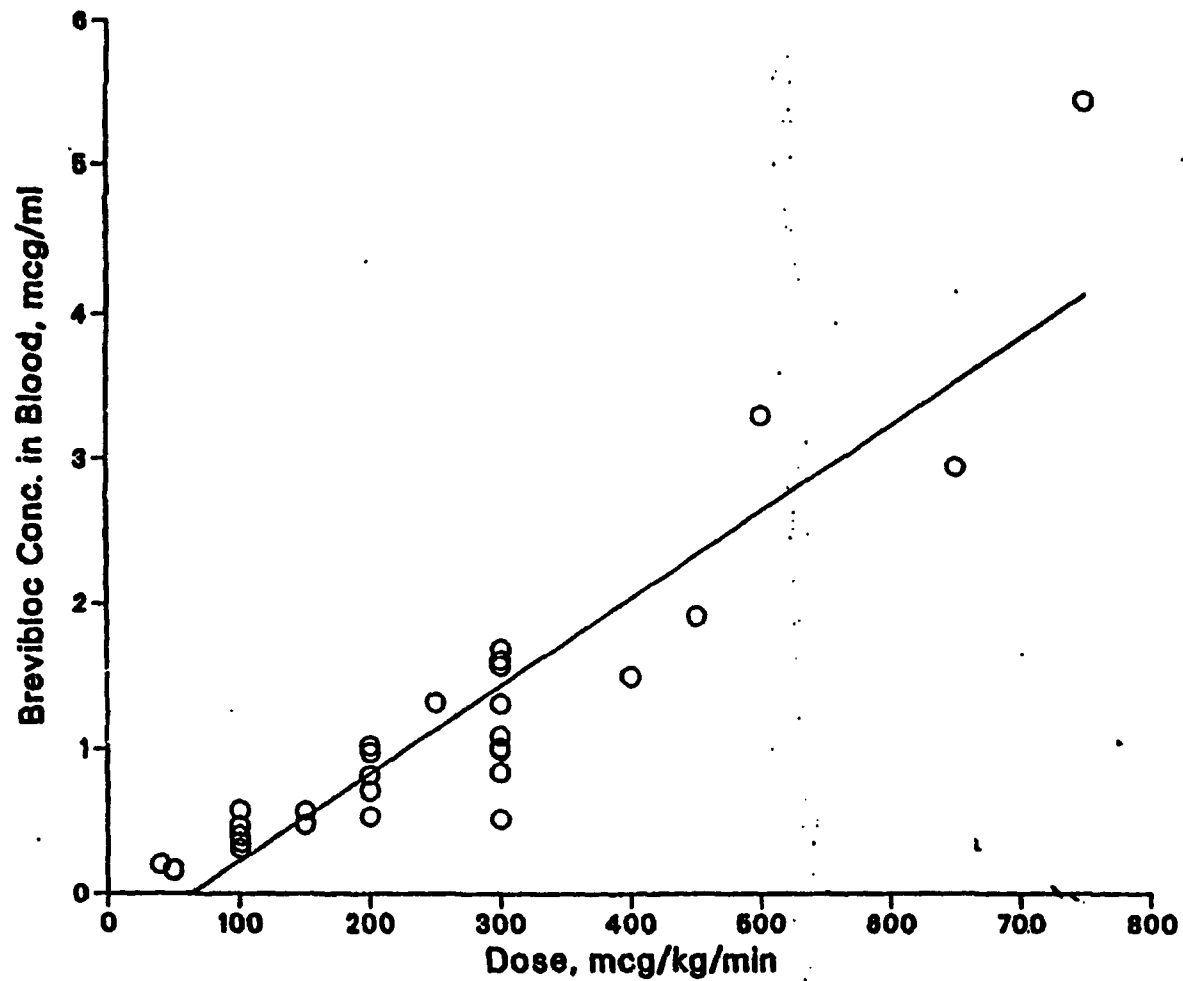
BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS



STUDY NO. 8052-83-43
STEADY STATE BREVIBLOC BLOOD LEVELS



Steady State Brevibloc Blood Levels Scatter Plot of Mean Venous Levels From All Studies



Appendix 1C - Blood Concentration X Time Plots for Esmolol and Its Acid Metabolite

Study No 1

12 Pages

Redacted

Study # 2

16 Pages

Redacted

Study #3

23 Pages

Redacted

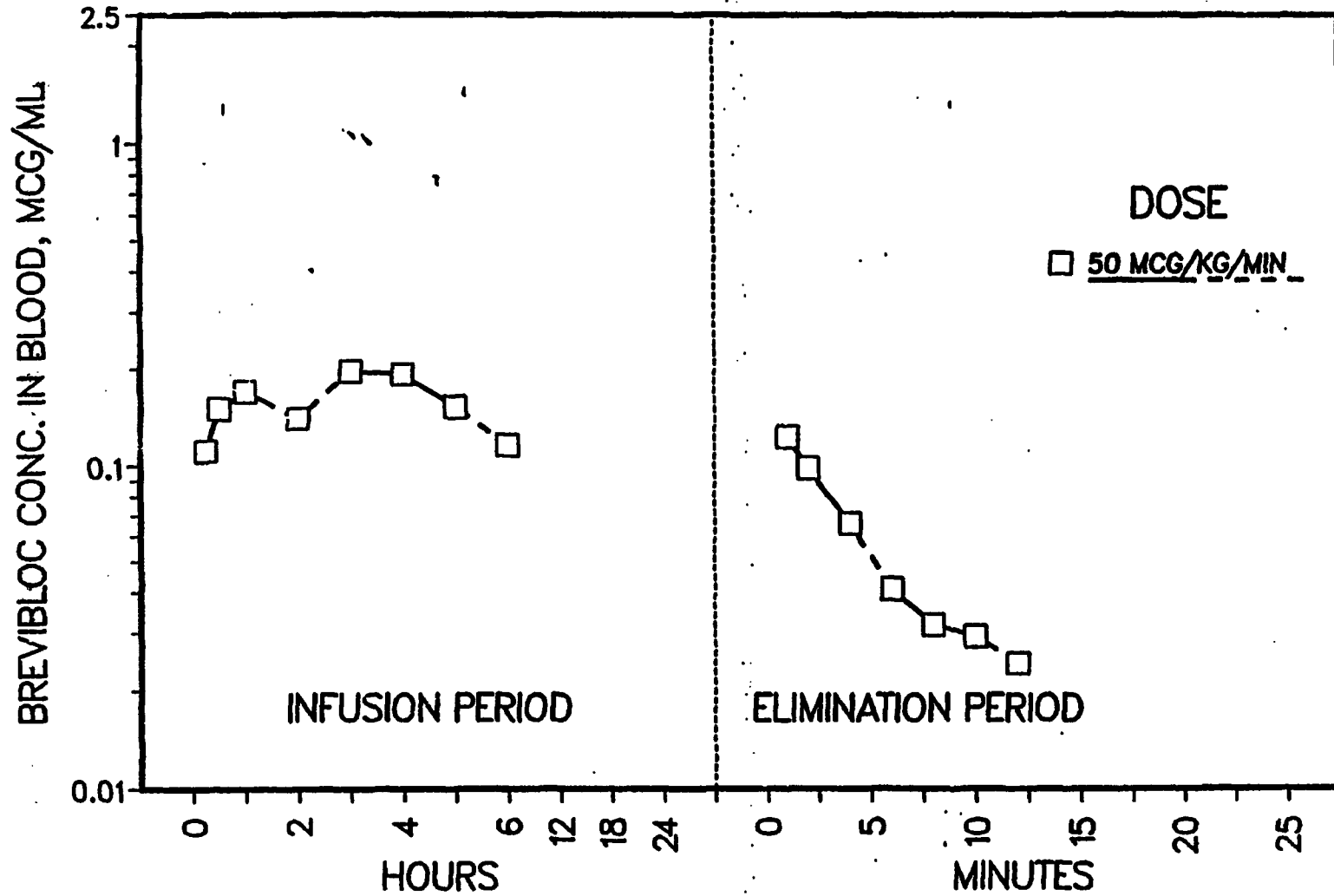
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73 Pages

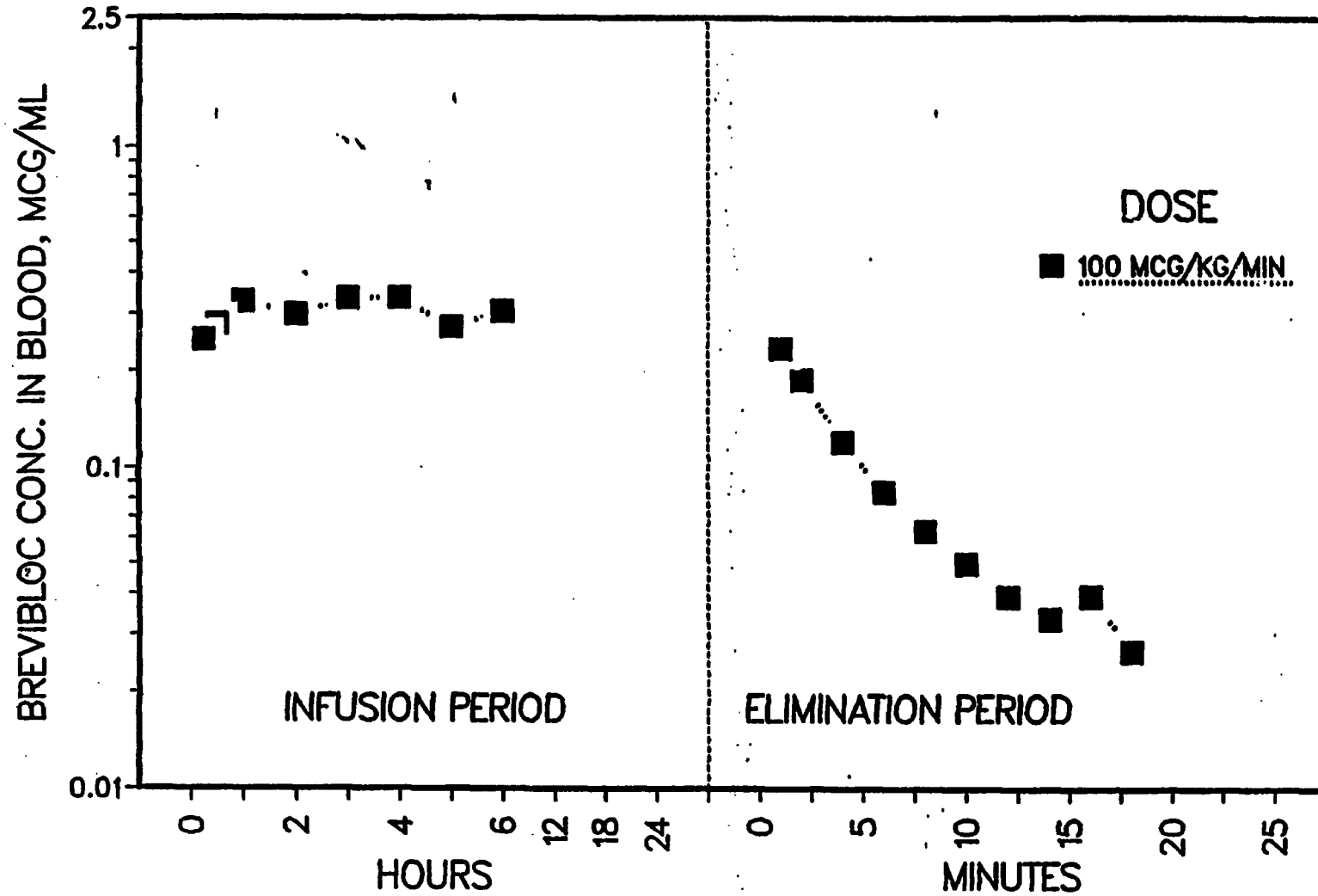
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Study 09

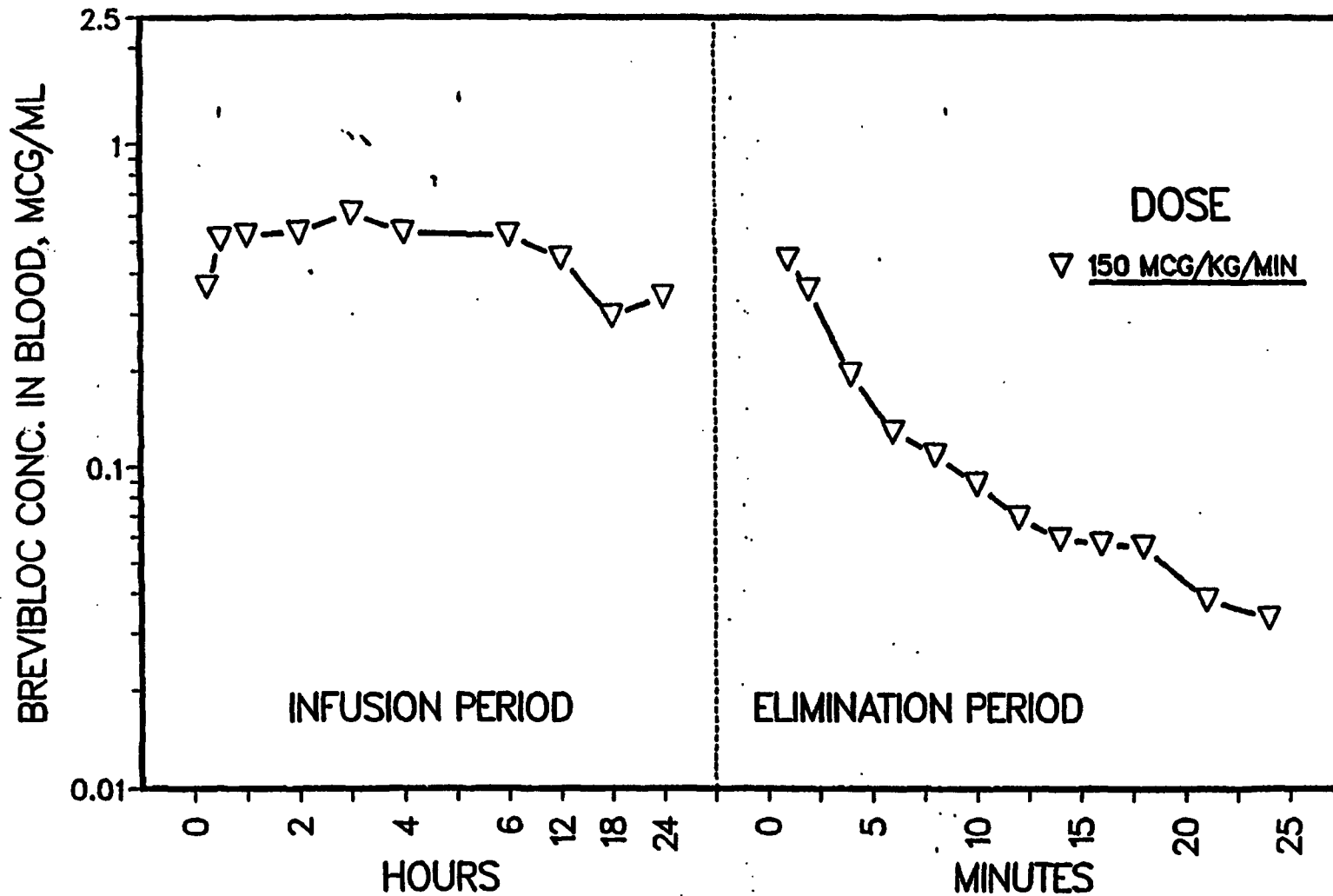
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MEAN OF 8 SUBJECTS



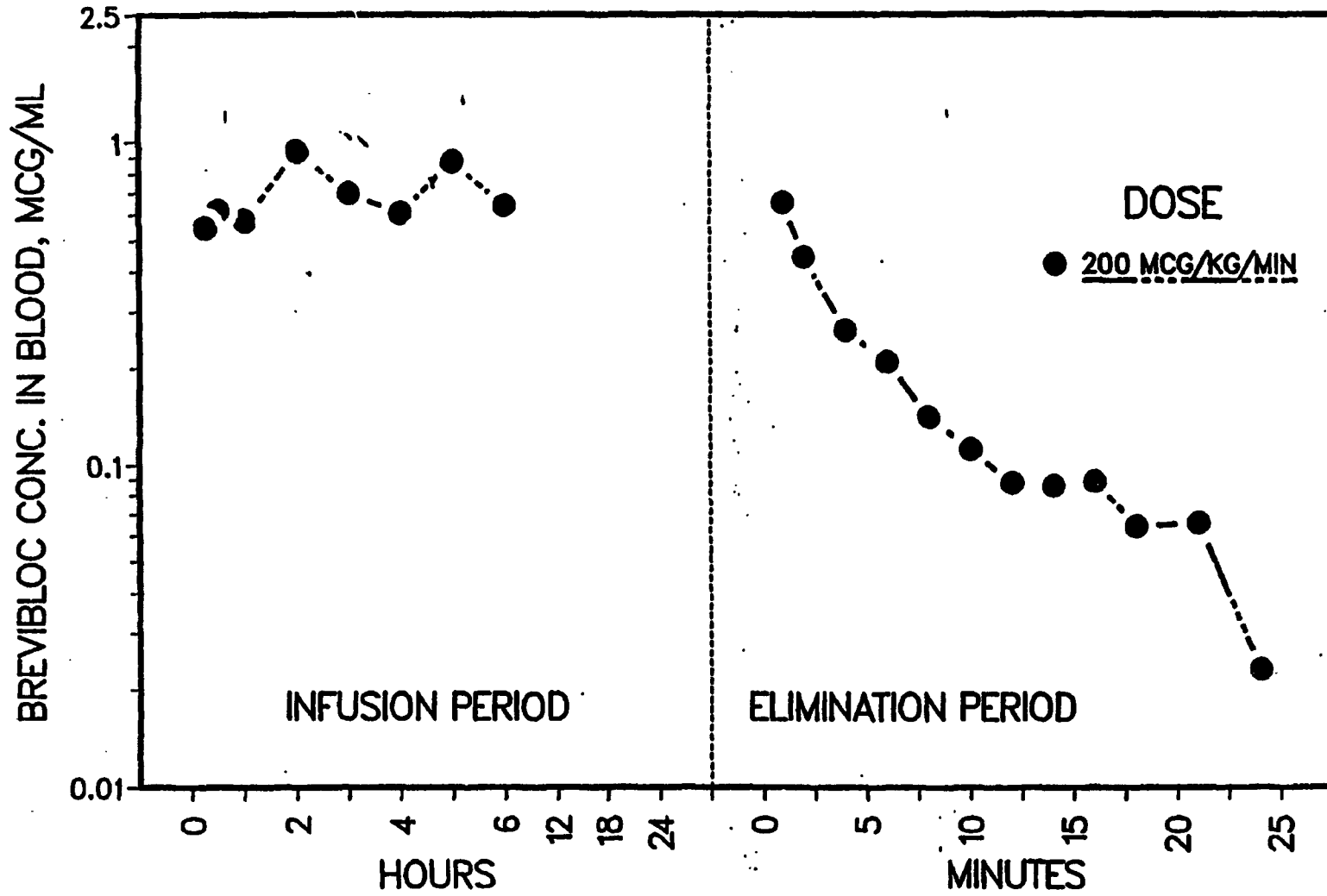
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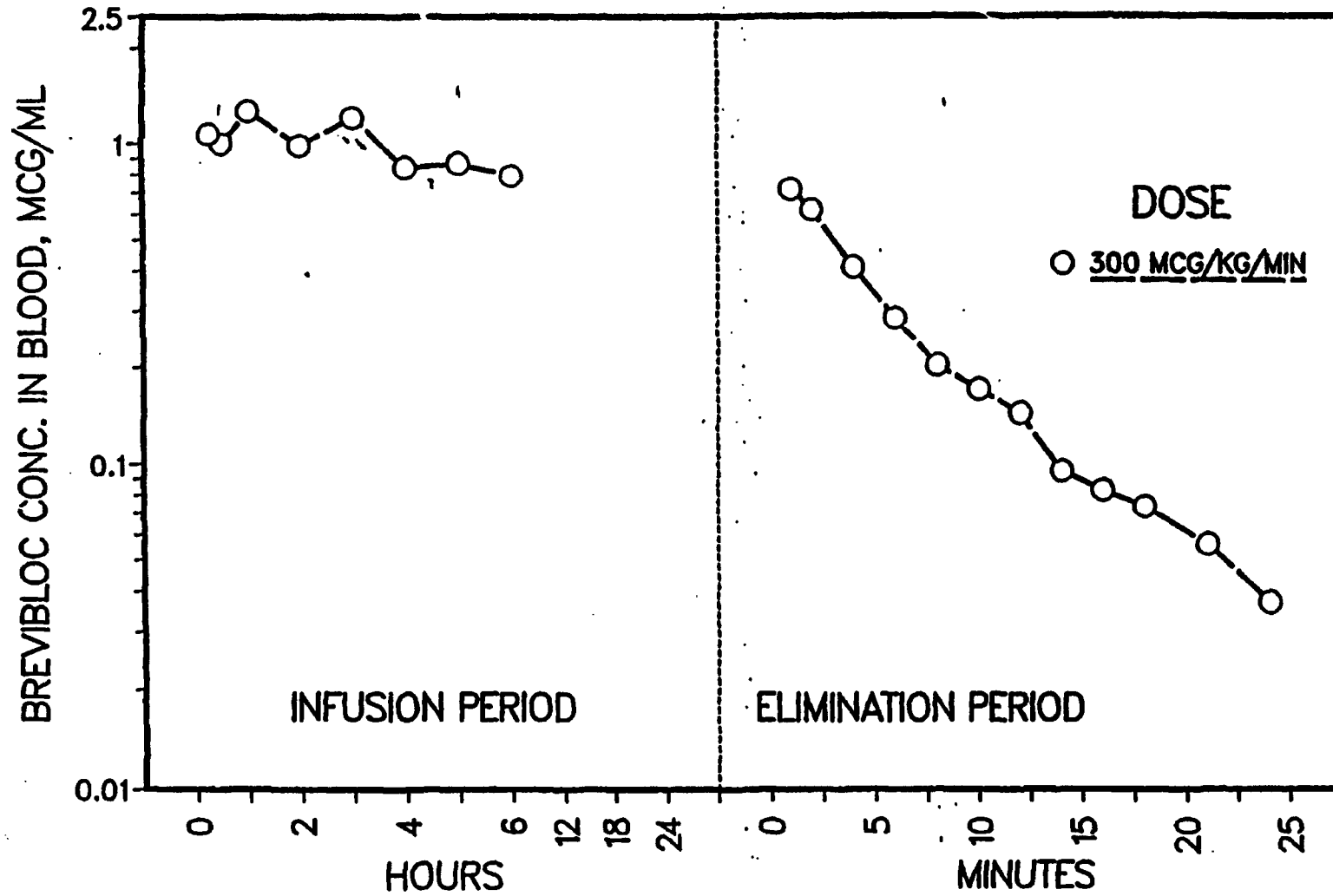
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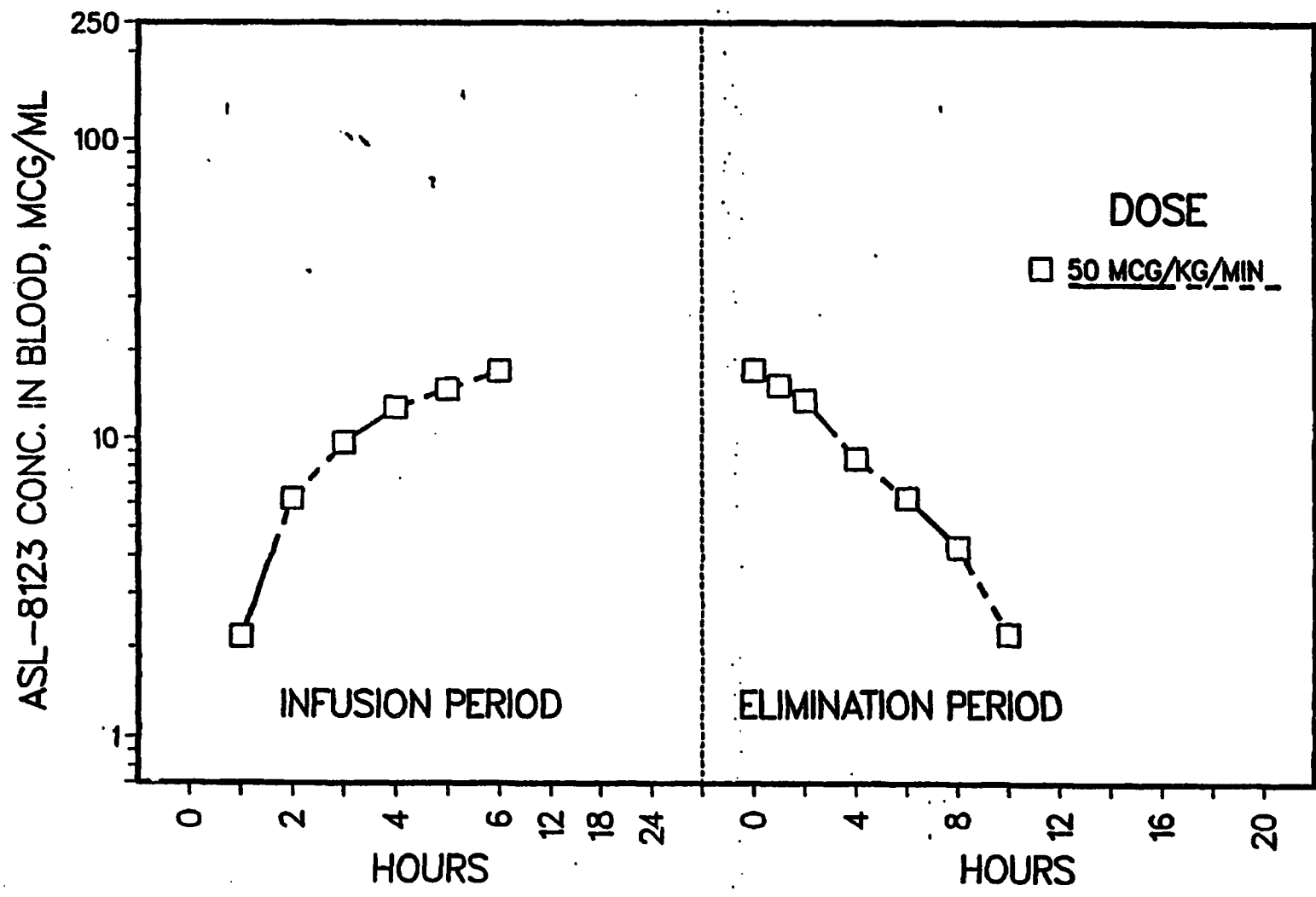
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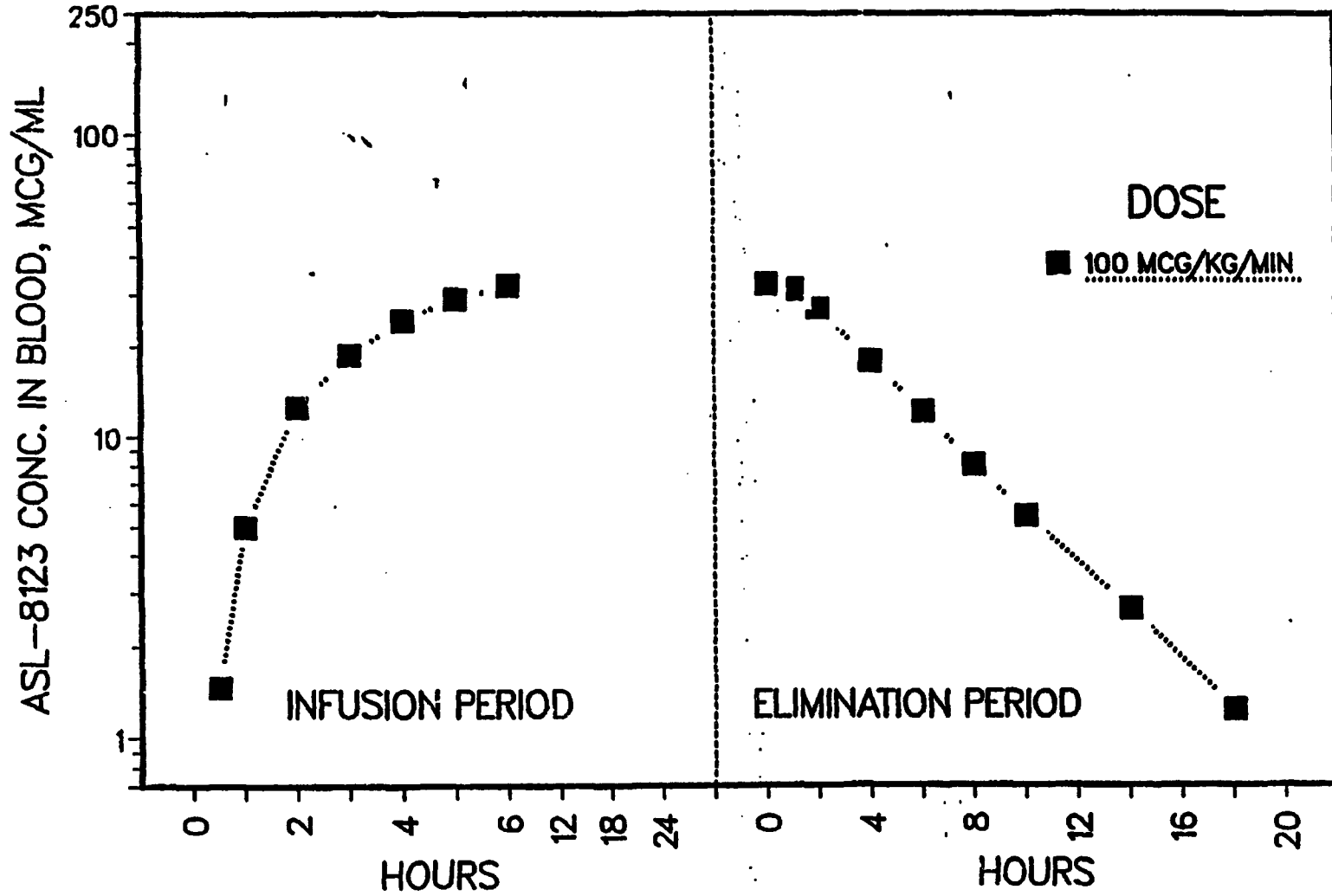
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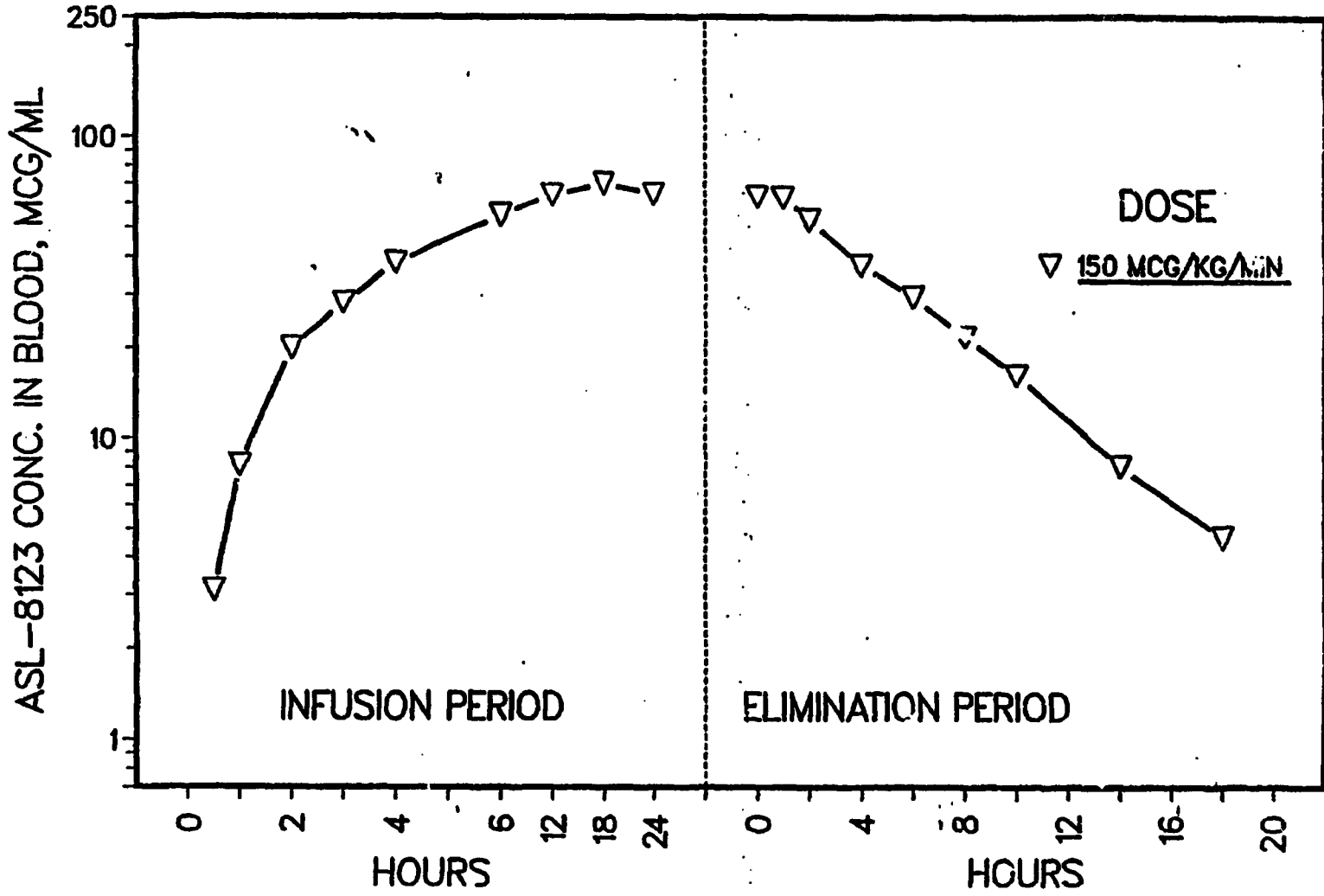
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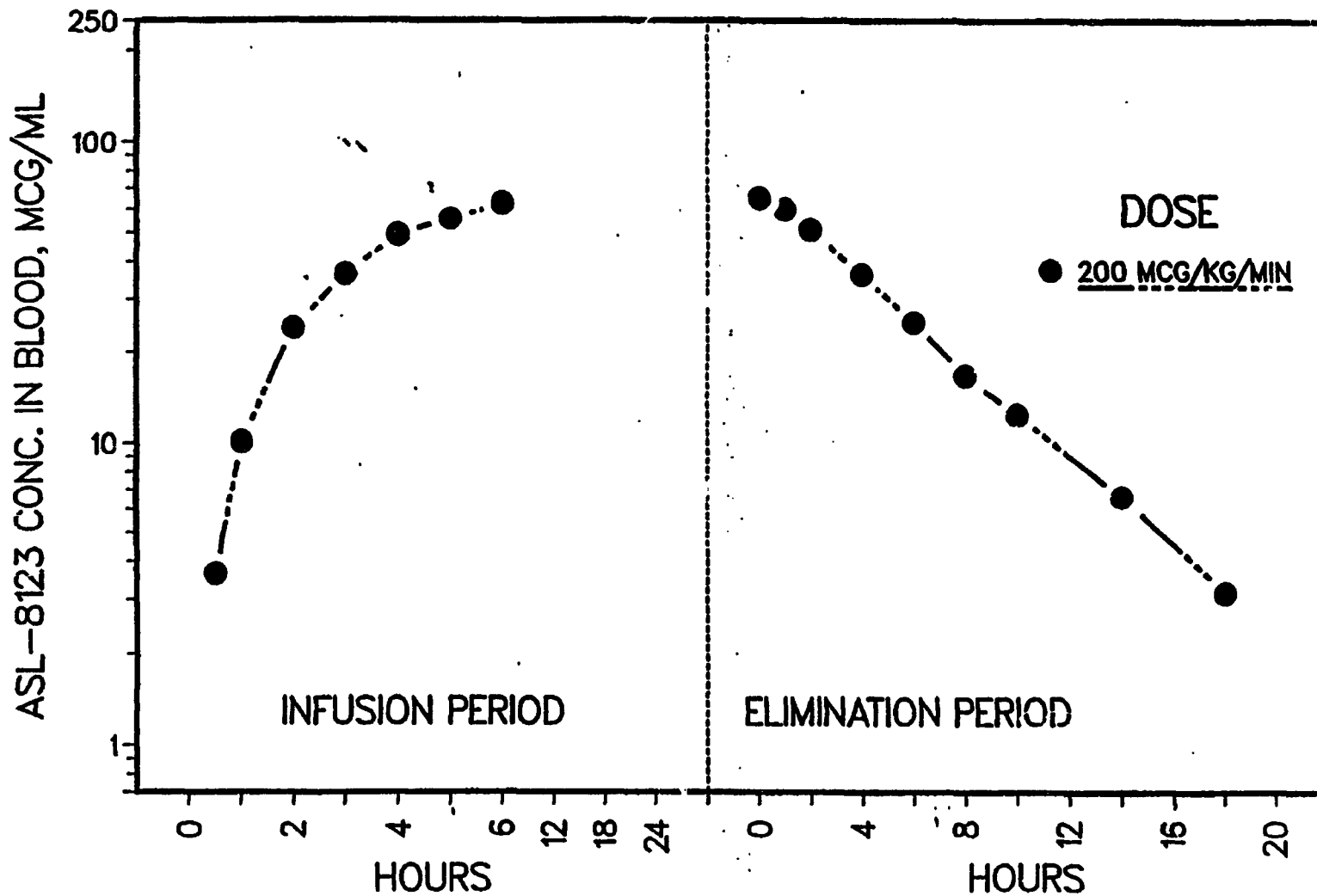
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MEAN OF 8 SUBJECTS



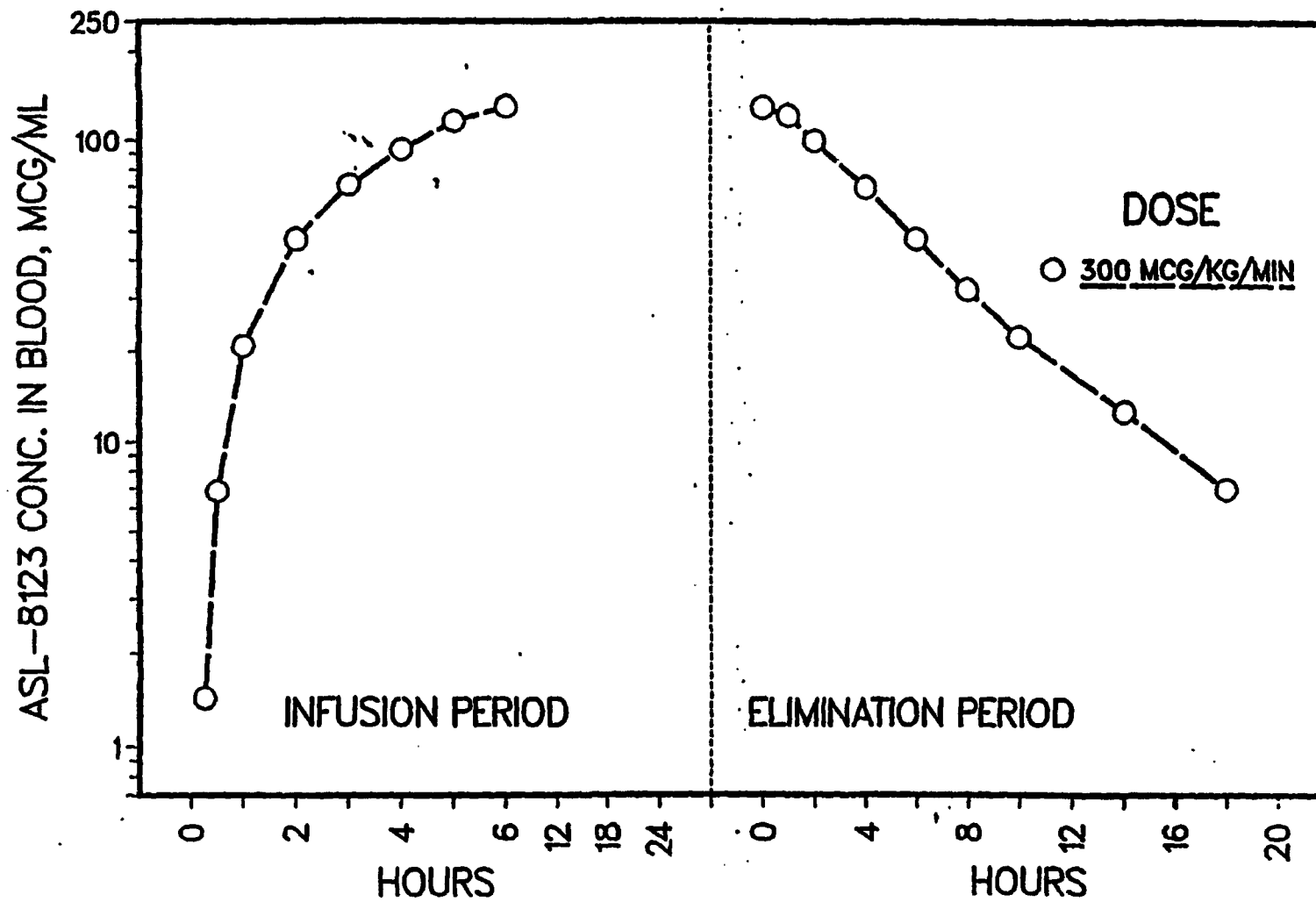
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MEAN OF 8 SUBJECTS



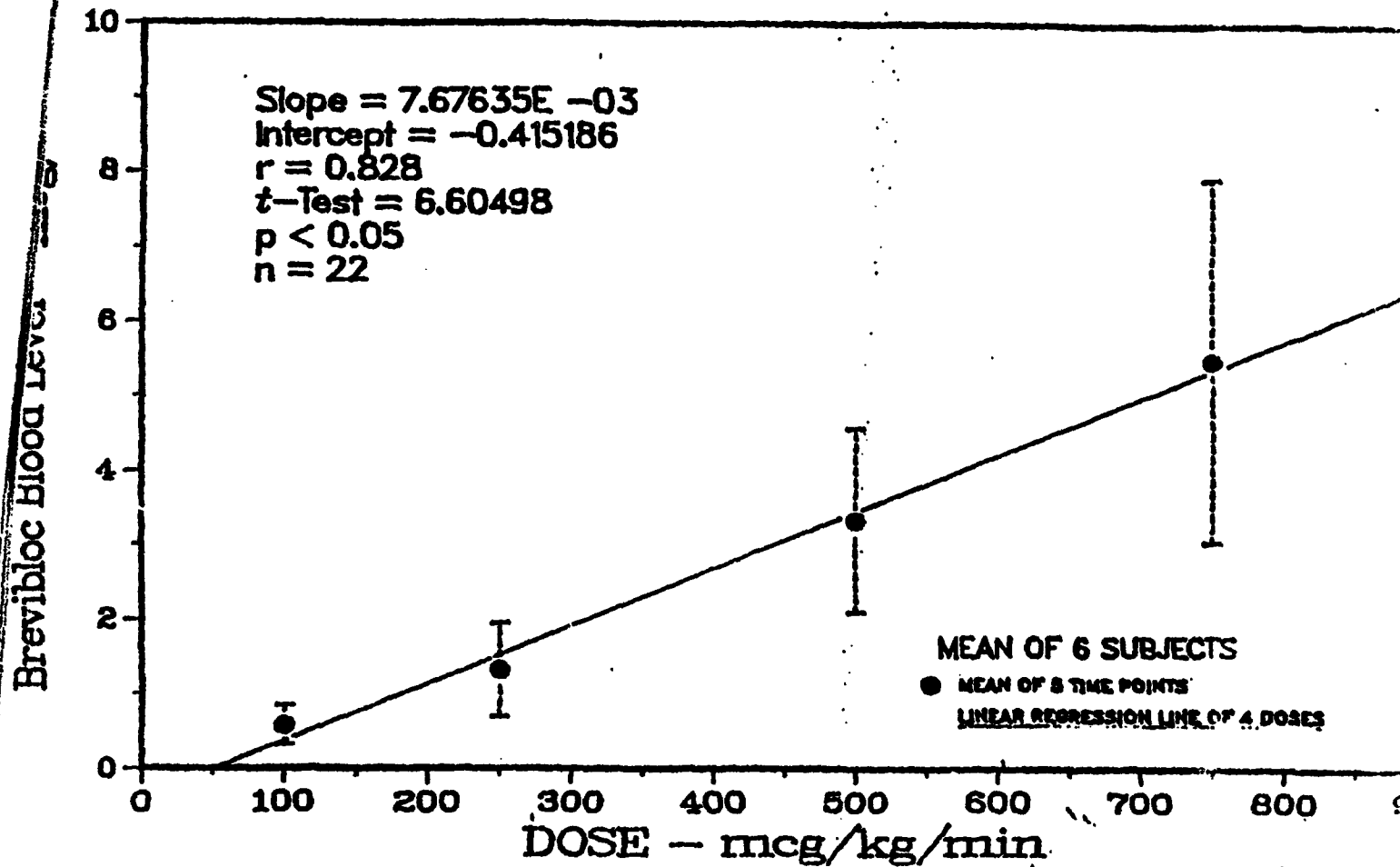
BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS



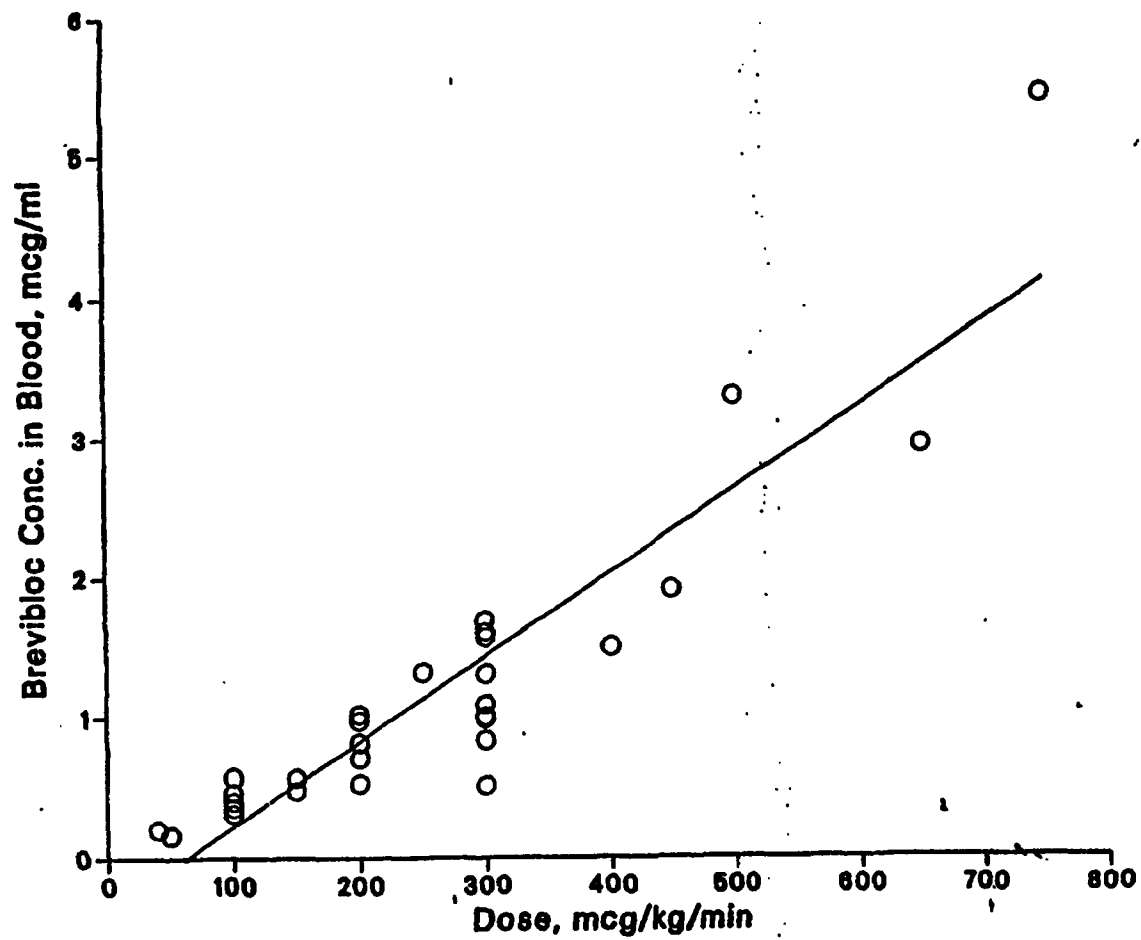
BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS



STUDY NO. 8052-83-43
STEADY STATE BREVIBLOC BLOOD LEVELS

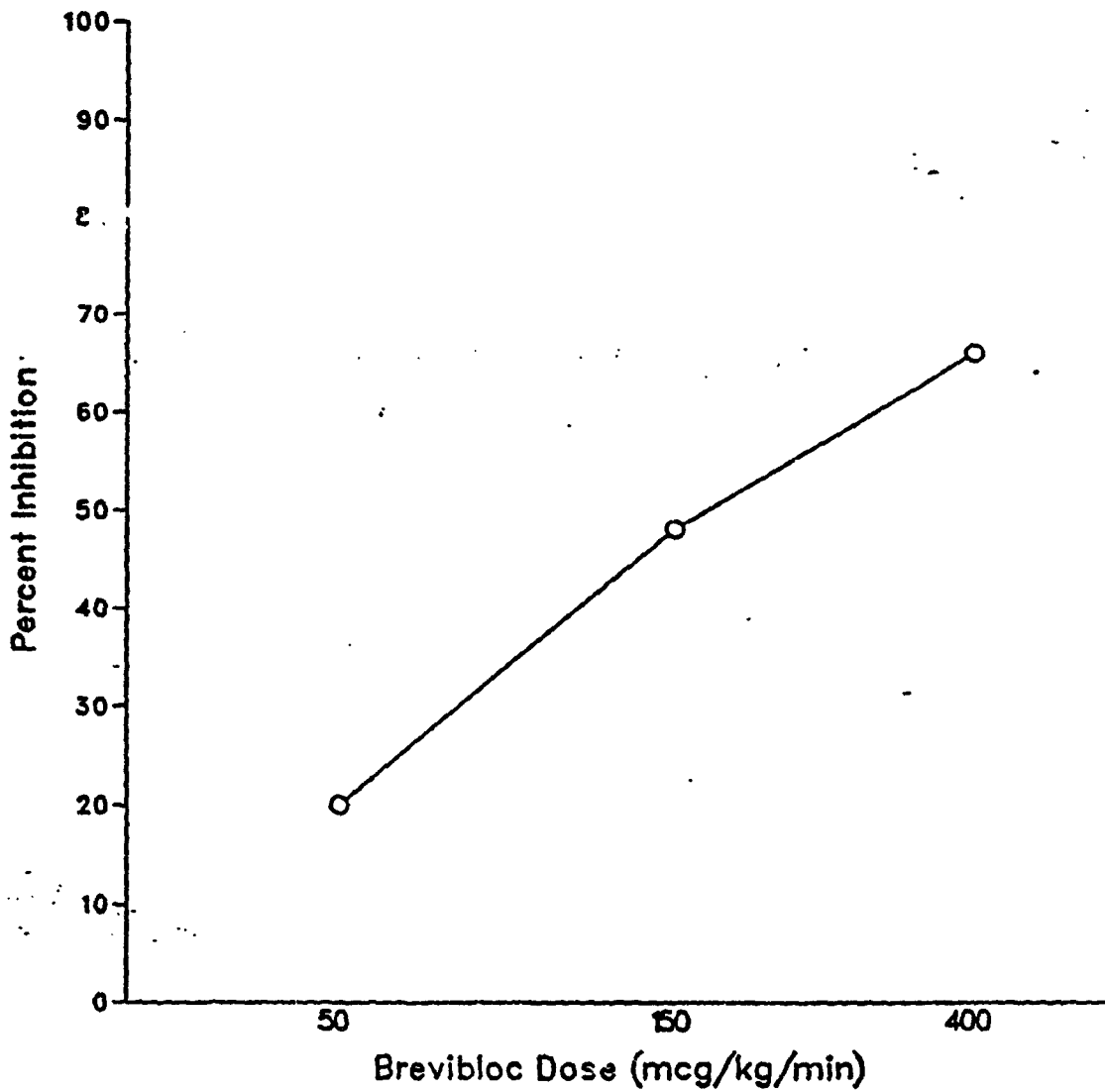


Steady State Brevibloc Blood Levels Scatter Plot of Mean Venous Levels From All Studies

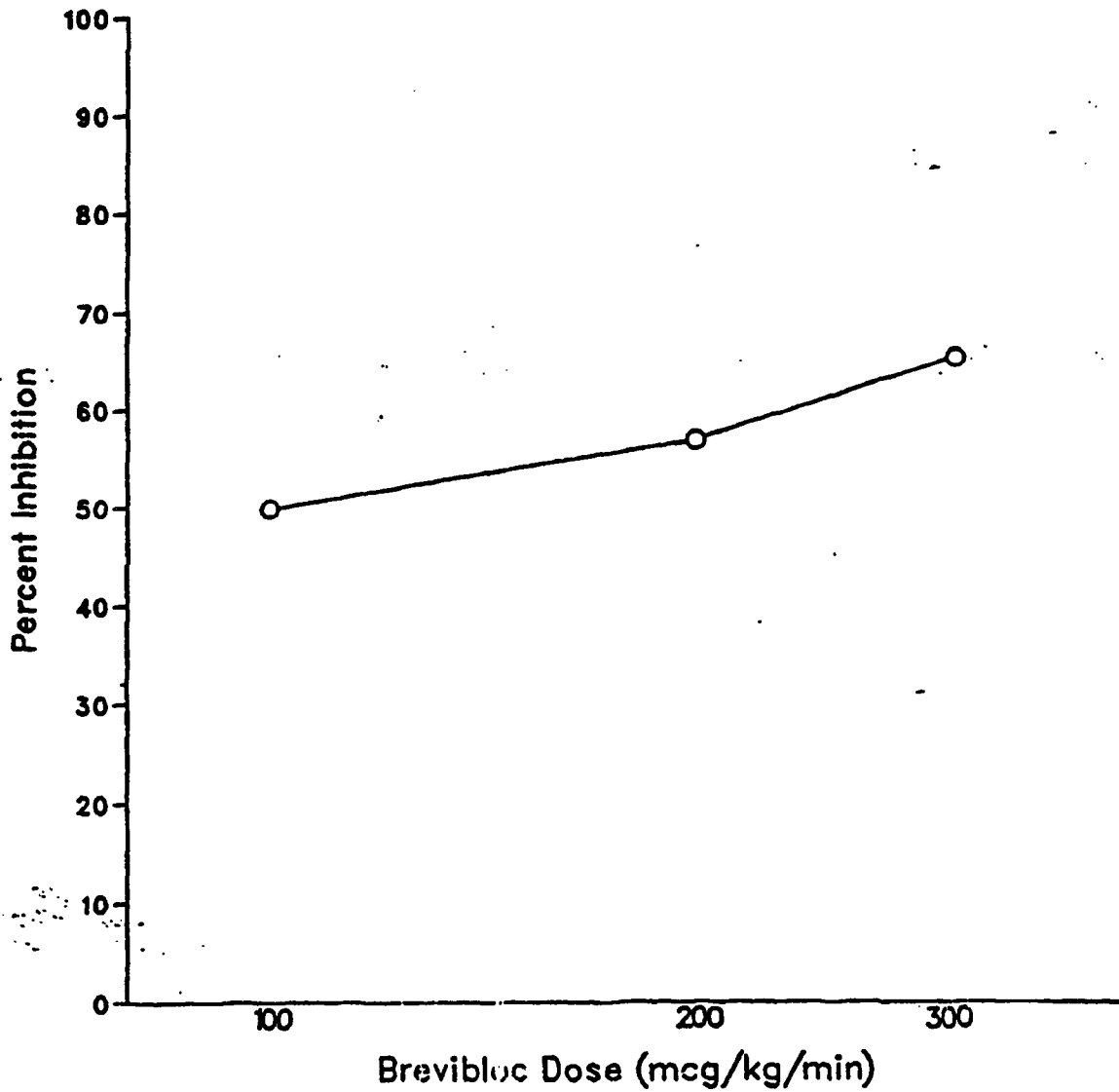


Appendix 10 - Dose Response Relationship Between Percent of Beta Blockade and Dose of Esmolol

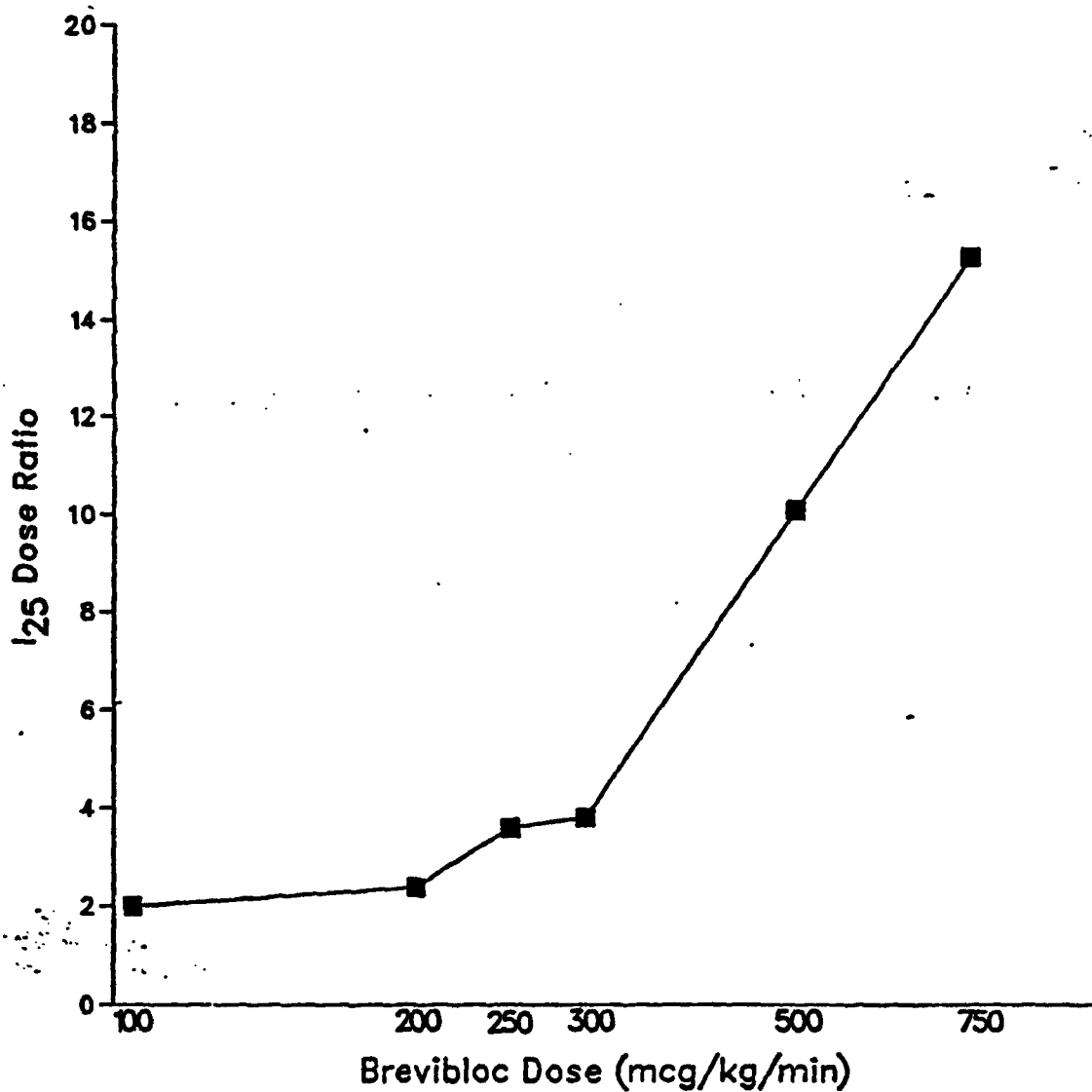
Relationship Between Percent Inhibition
and Dose of Brevibloc (Log Scale)
Schnelle 8052-81-02



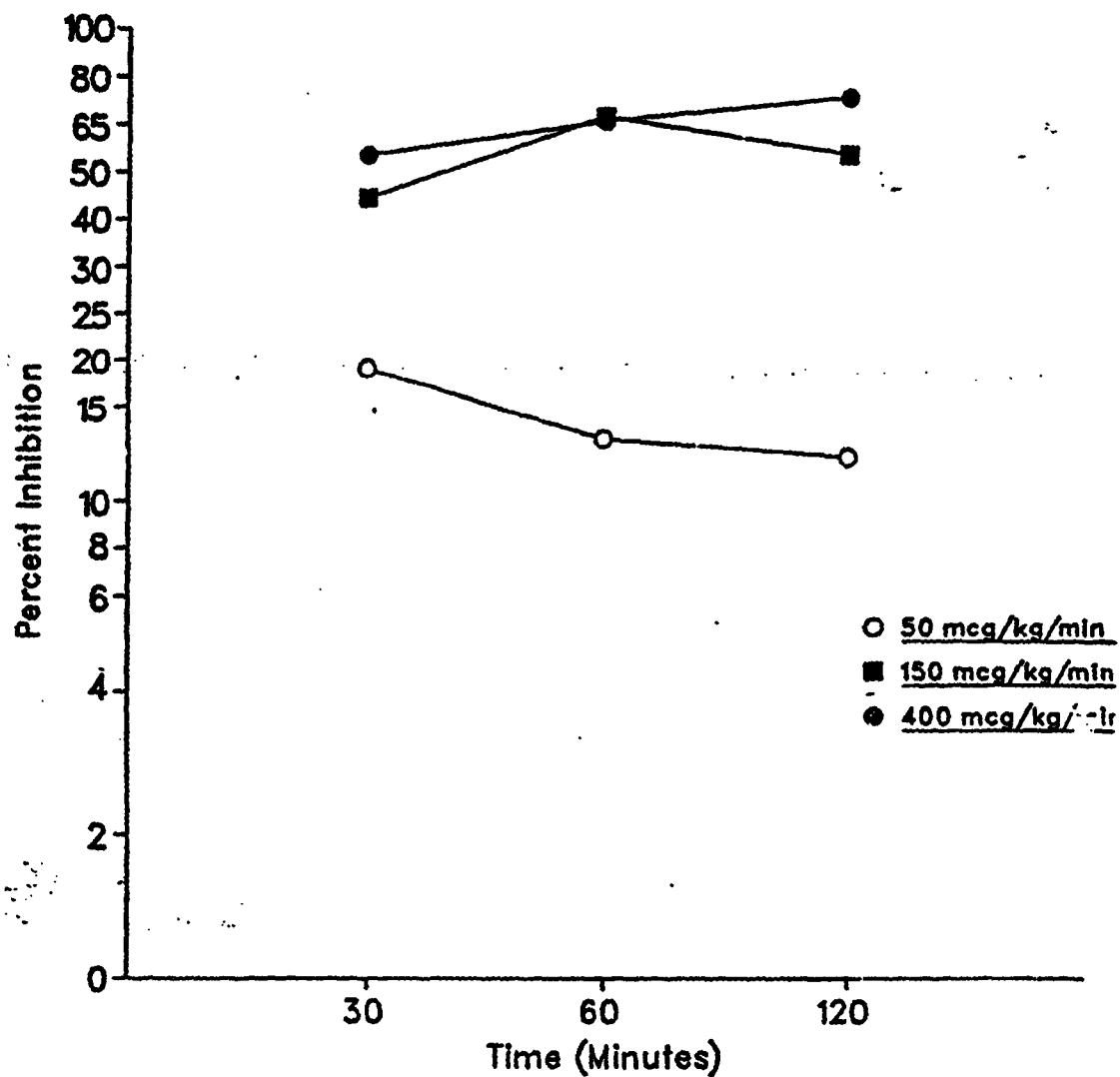
Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Dose of Brevibloc (Log Scale)
Williams 8052-84-58



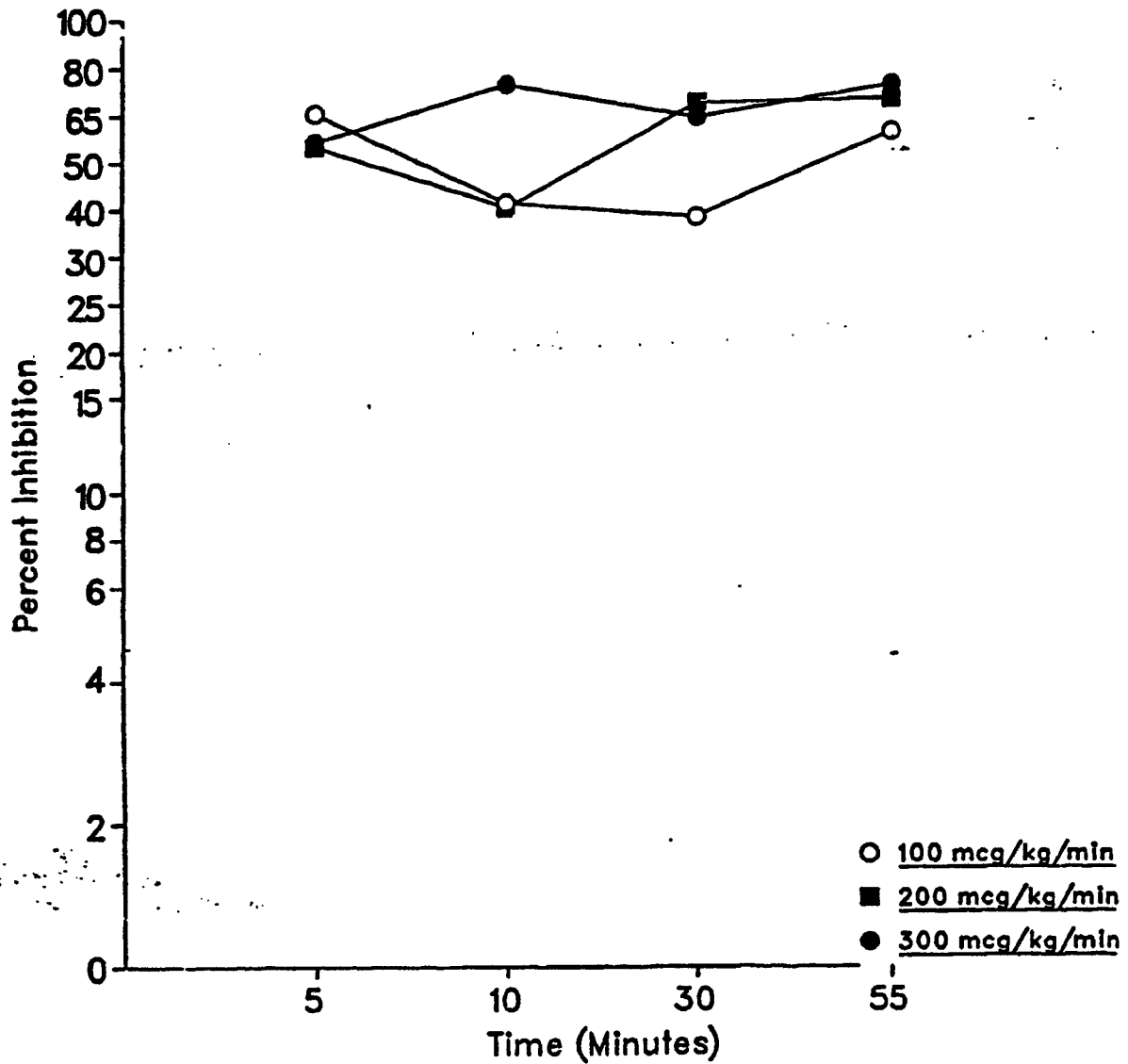
Relationship Between I₂₅ Dose Ratio
and Dose of Brevibloc (Log Scale)
Wood 8052-83-43



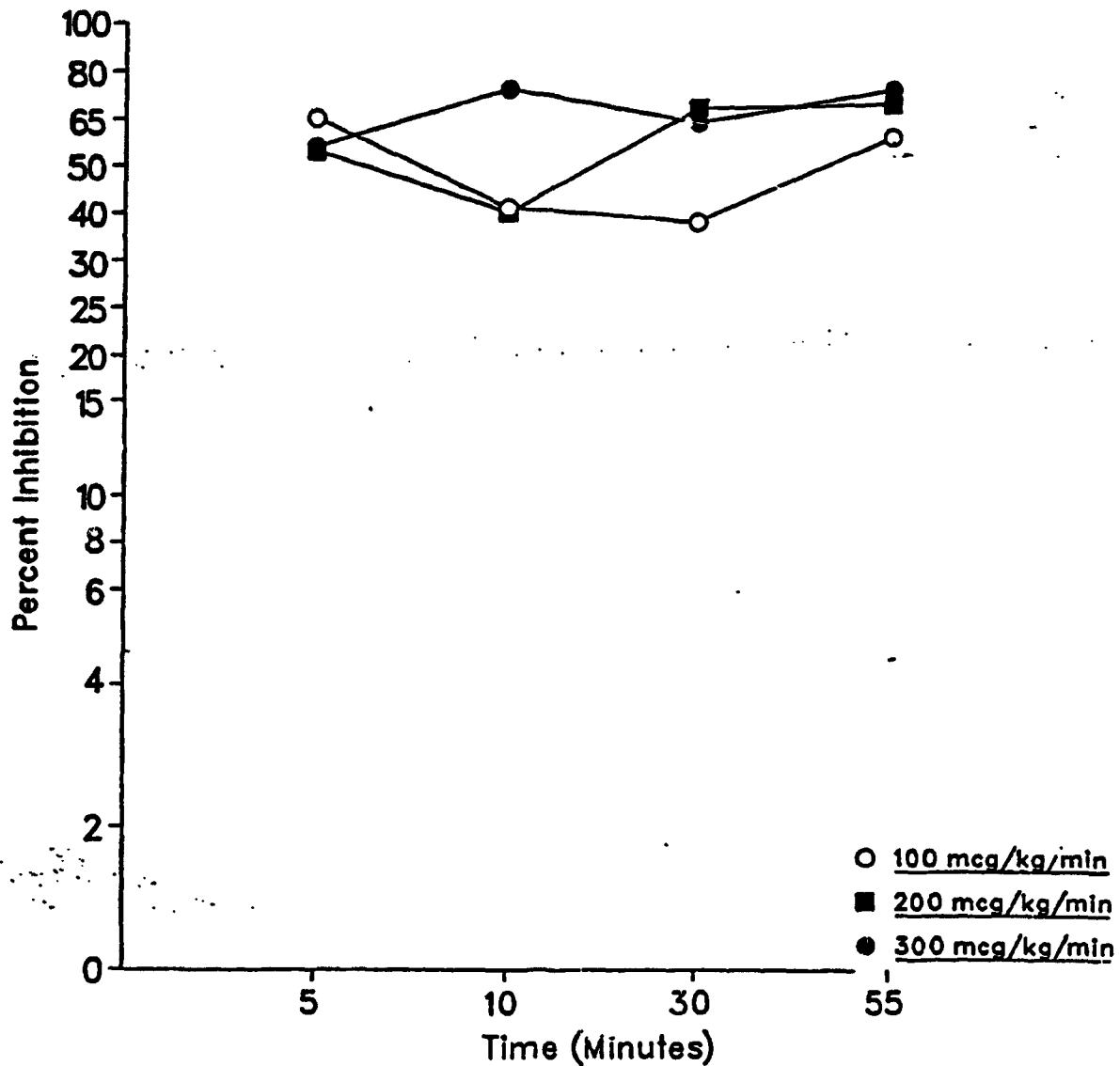
Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time At Various Dose Levels
Schnelle 8052-81-02



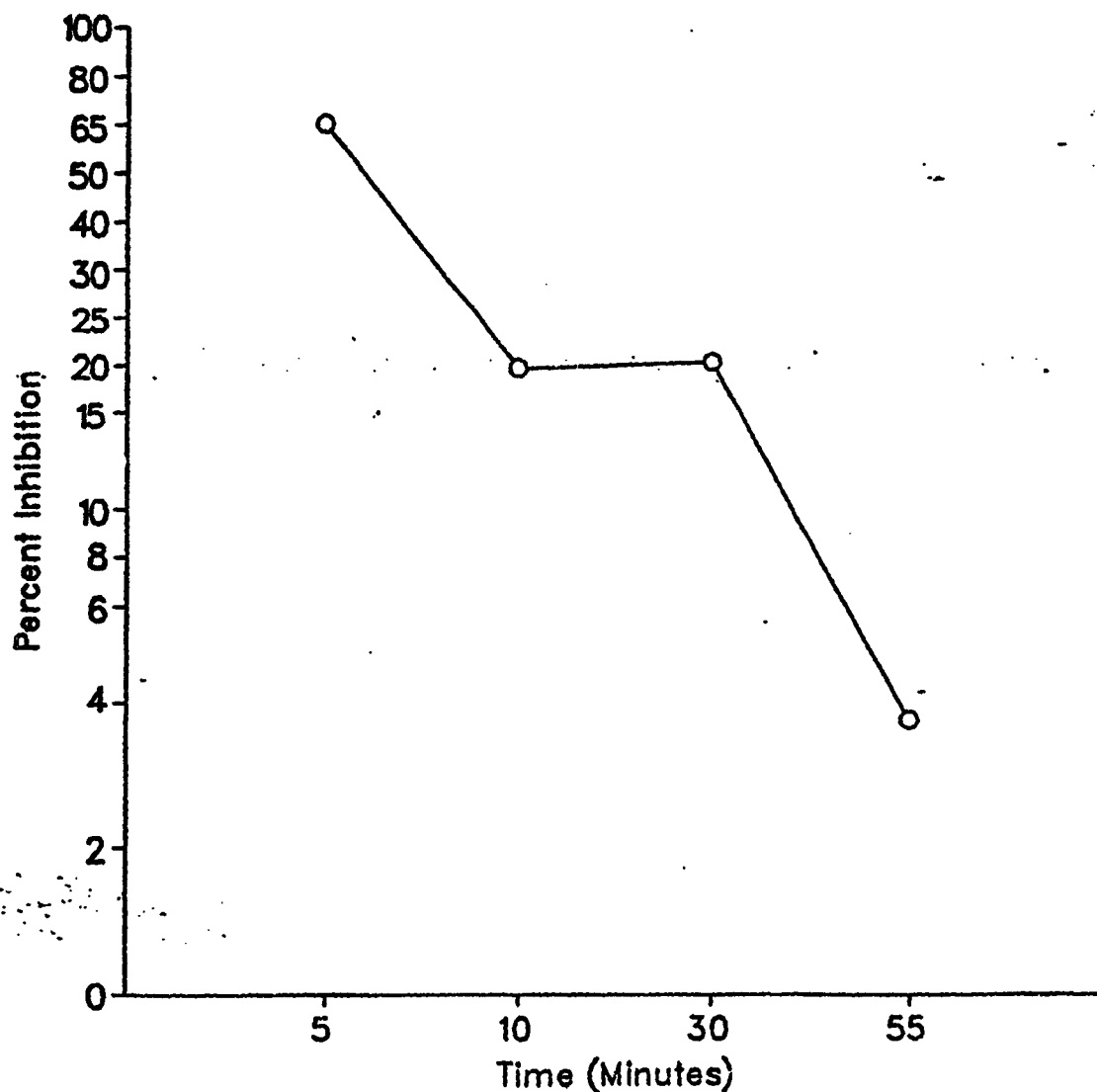
Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time at Various Dose Levels
Williams 8052-84-58



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time at Various Dose Levels
Williams 8052-84-58



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time During Follow-Up Period
Williams 8052-84-58



Wood 8052-83-43

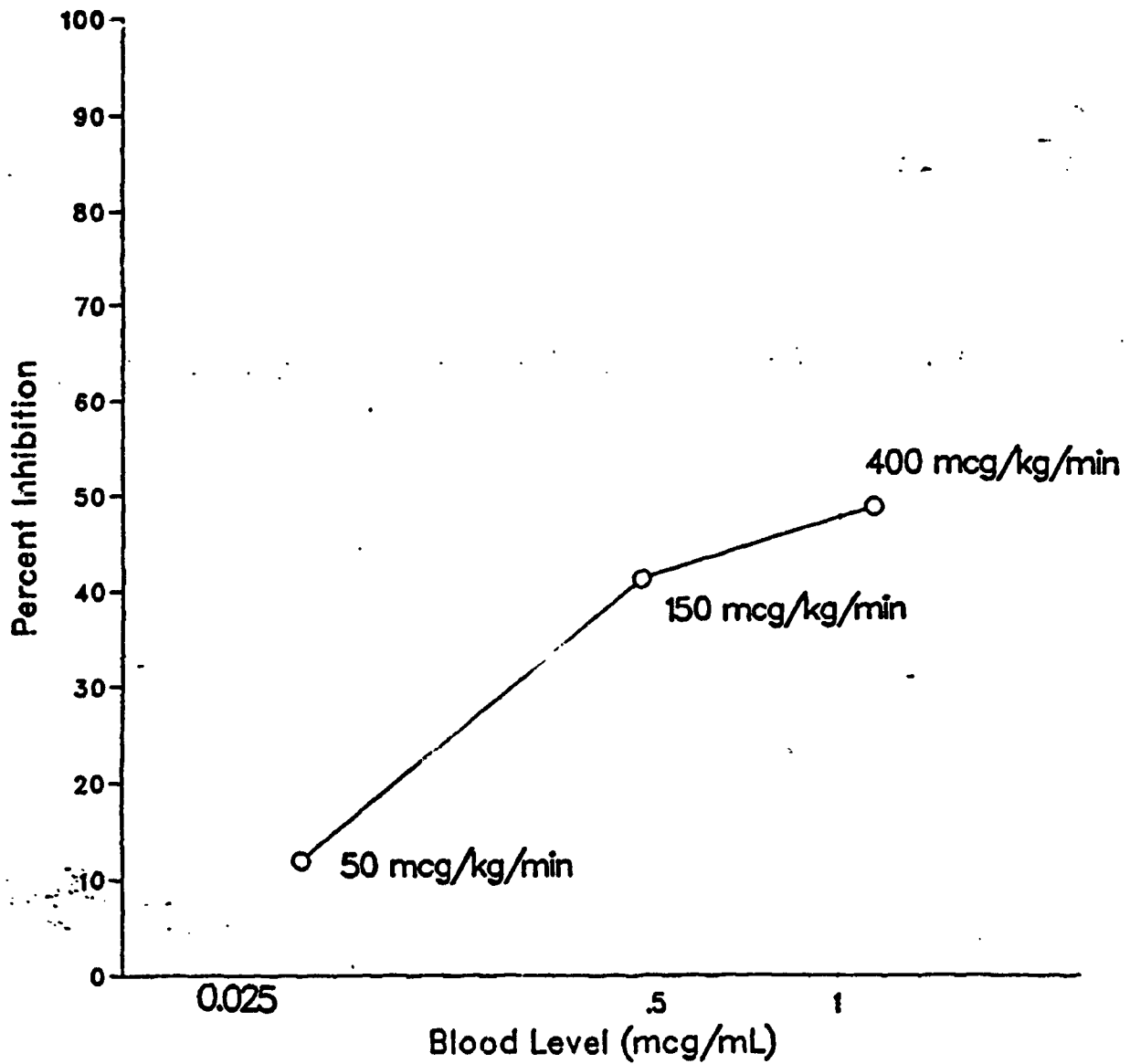
COMPARISON OF HEART RATE RESPONSE
TO ISOPROTERENOL AT 5 AND 25 MINUTES
DURING EACH ESMOLOL INFUSION RATE¹

Dose Esmolol mcg/Kg/min	N	Mean (s.e.) Dose of Isoproterenol ²	Time of Infusion	
			5 Minutes	25 Minutes
			Mean (s.e.) HR Increase	Mean (s.e.) HR Increase
100	12	1.18 (0.07)	16.17 (0.89)	17.67 (0.57)
200	7	2.16 (0.16)	18.43 (0.61)	19.86 (0.70)
250	4	1.28 (0.17)	8.25 (2.21)	11.00 (3.81)
300	7	3.09 (0.29)	18.14 (0.74)	19.00 (0.93)
500	4	4.73 (0.24)	11.25 (1.03)	13.25 (3.75)
750	3	9.83 (1.59)	13.67 (4.48)	14.67 (2.40)

¹ There were no significant differences (at $\alpha = 0.05$ level) between the means at 5 and 25 minutes at each dosing level.

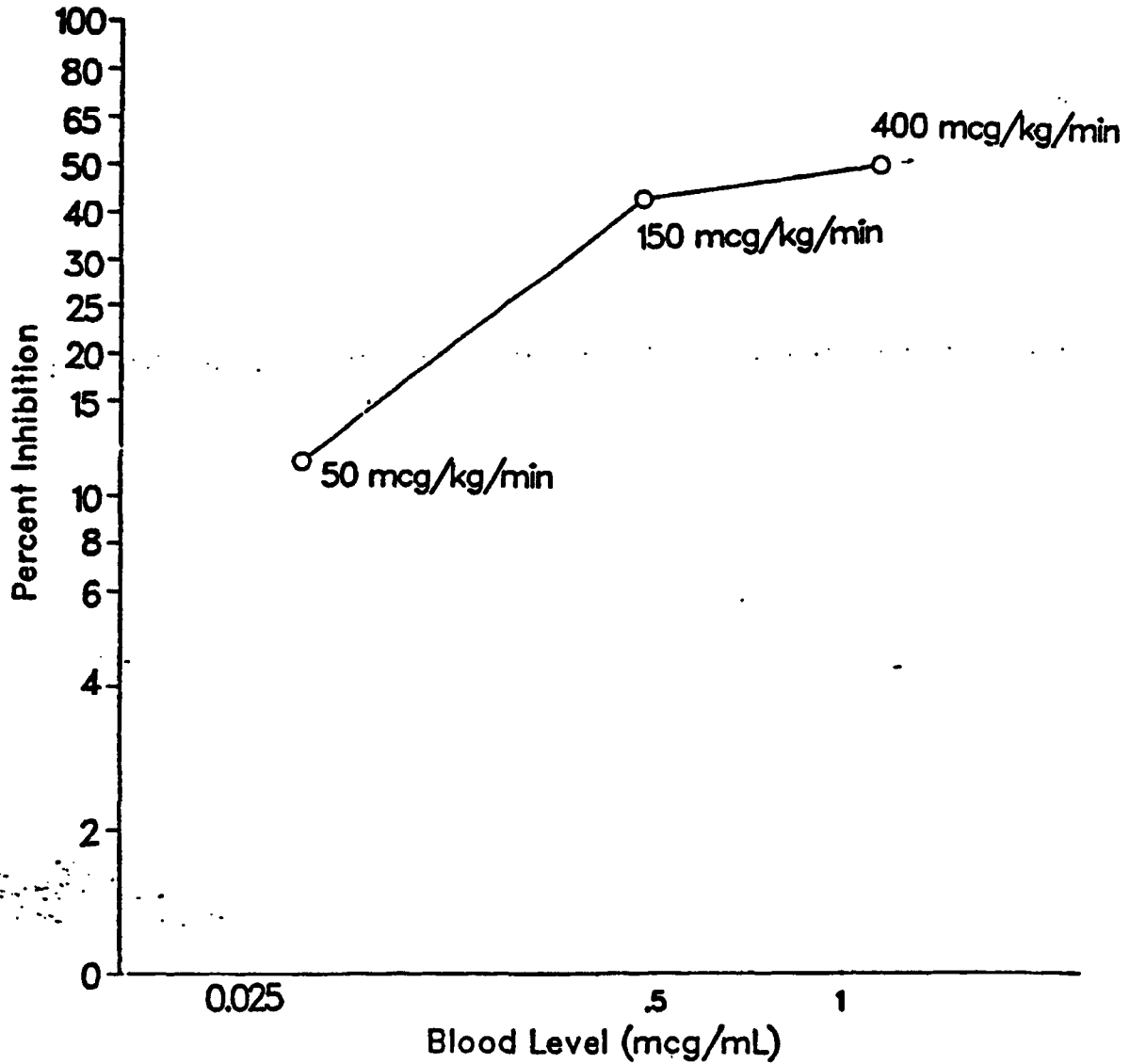
² In each subject the dose of isoproterenol administered was the I_{25e} determined during the previous (lower) esmolol infusion (or in the absence of esmolol infusion for the 100 mcg/Kg/min dose). The I_{25e} was defined as the estimated dose of isoproterenol, determined from the isoproterenol heart rate dose response curve, that would increase heart rate by 25 beats/minute.

Relationship Between the Mean Percent Inhibition
of Isoproterenol Heart Rate Response
and Mean Blood Level of Esmolol (Log Scale)
at Each Dose
Schnelle 8052-8102

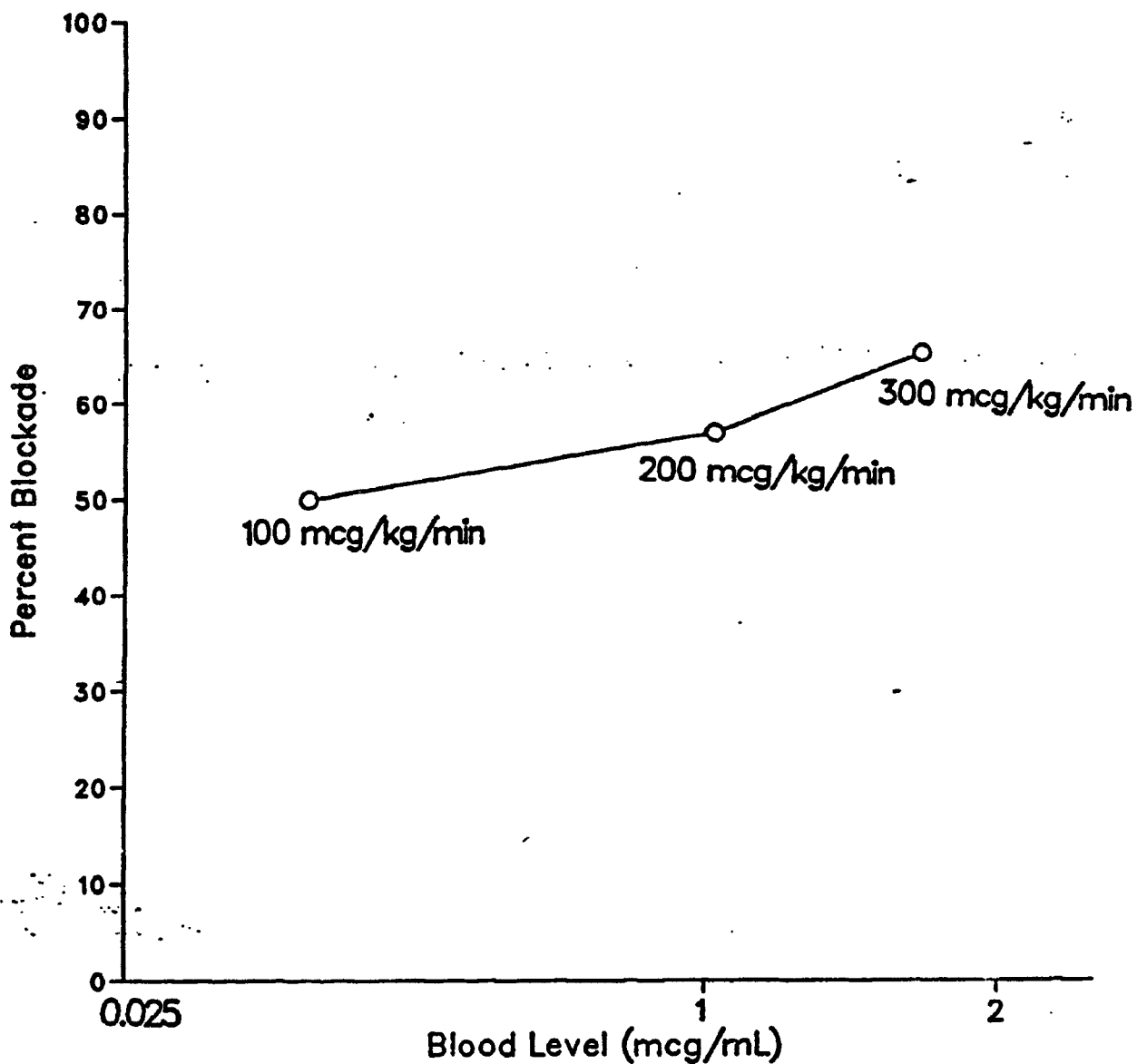


Relationship Between Mean Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Mean Blood Level of Esmolol (Log-Scale)
at Each Dose

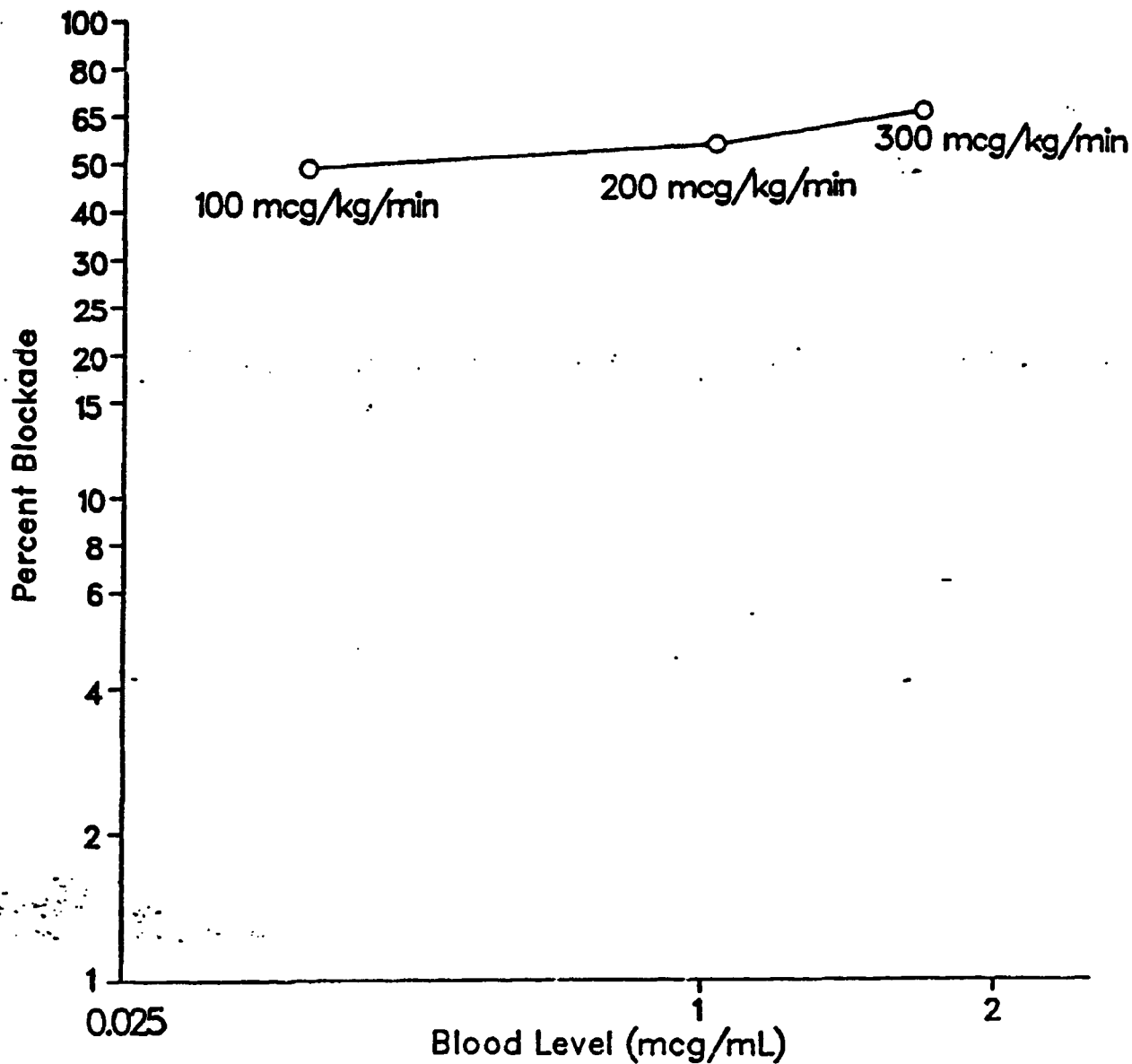
Schnelle 8052-81-02



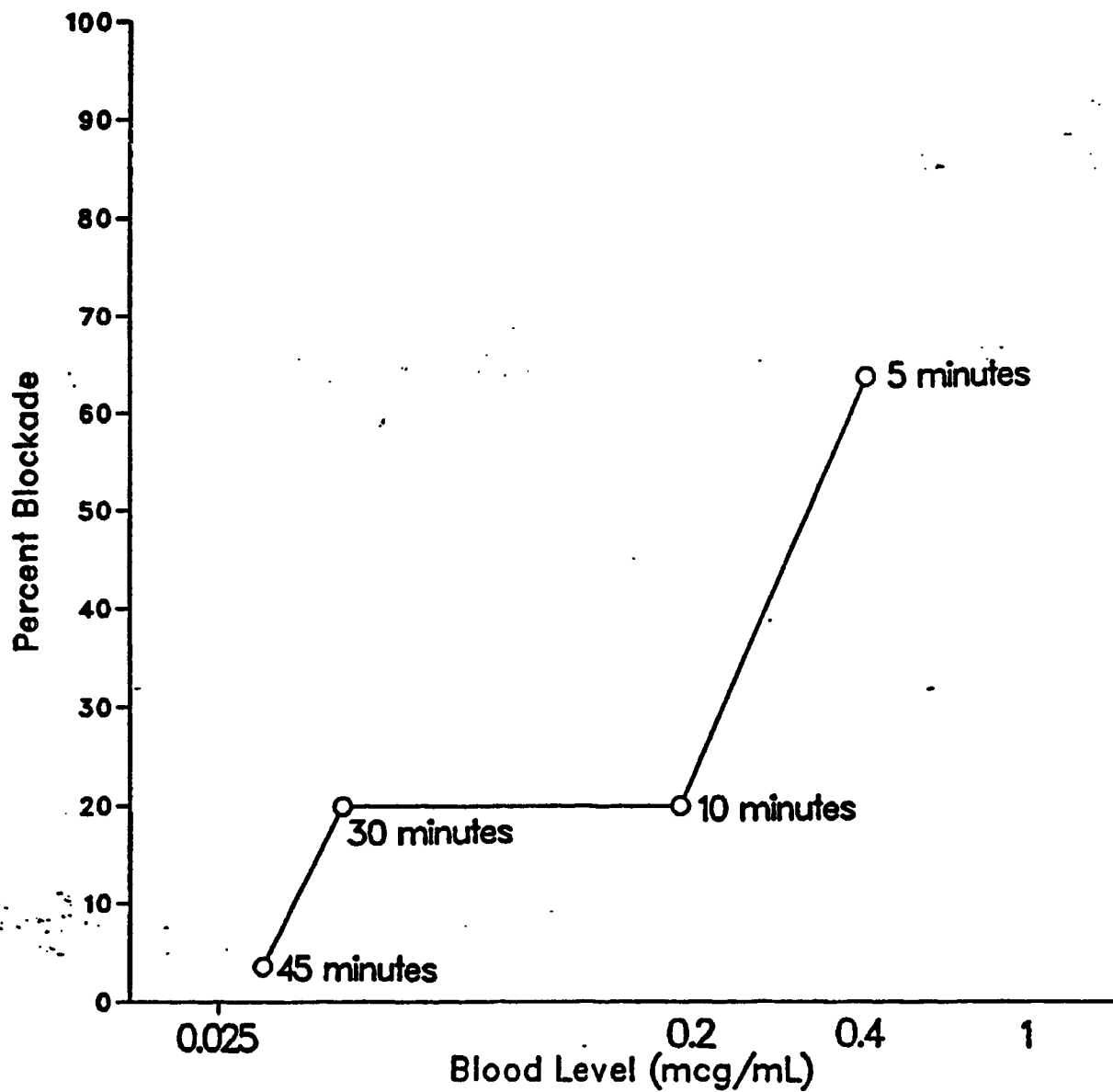
Relationship Between Mean Percent Inhibition
of the Isoproterenol Heart Rate Response and
Mean Blood Level of Esmolol (Log Scale) at Each Dose
Williams 8052-84-58



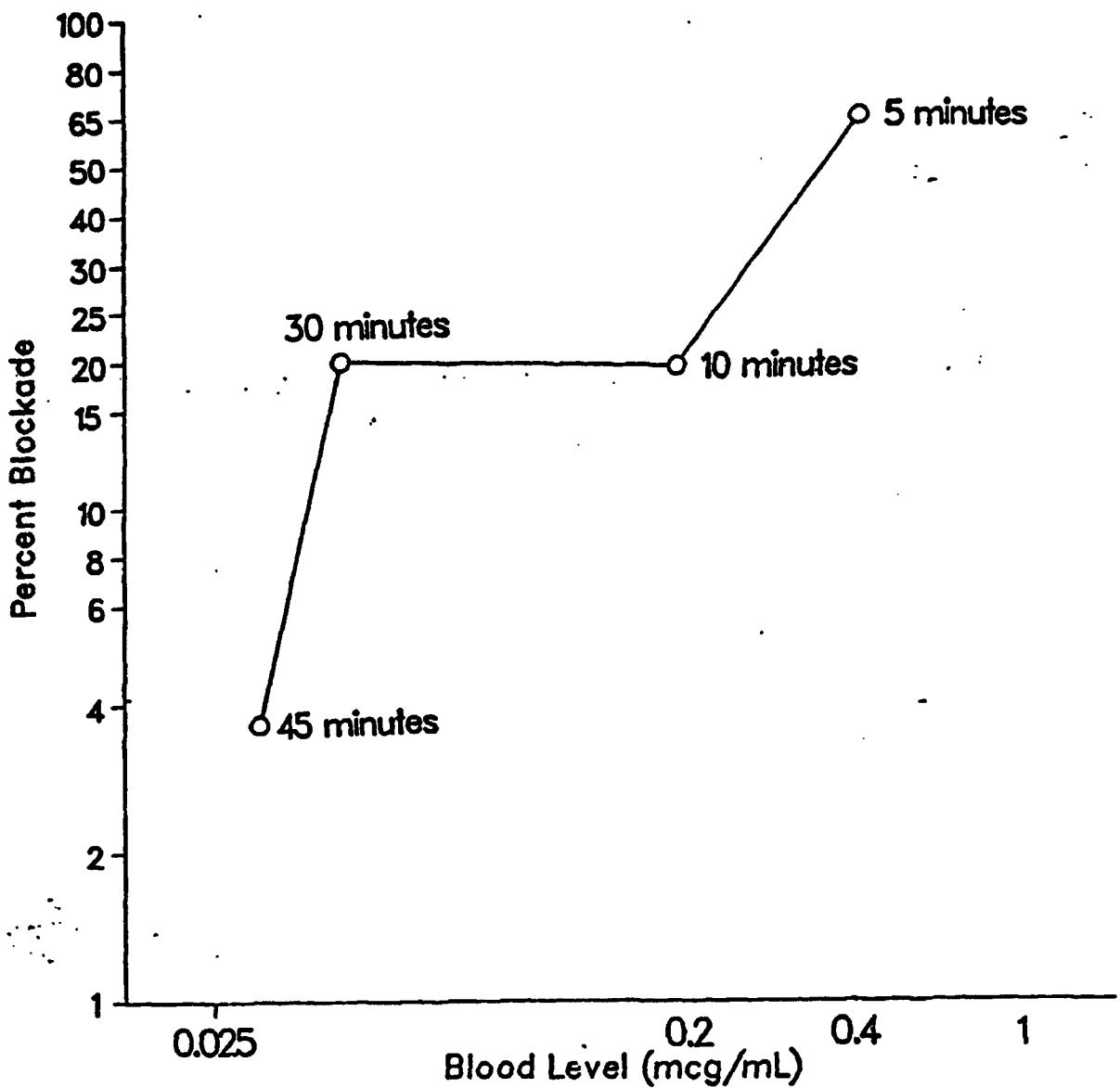
Relationship Between Mean Percent of
Beta Blockade (Log Scale)
and Mean Blood Level of
Esmolol (Log Scale) at Each Dose
Williams 8052-84-58



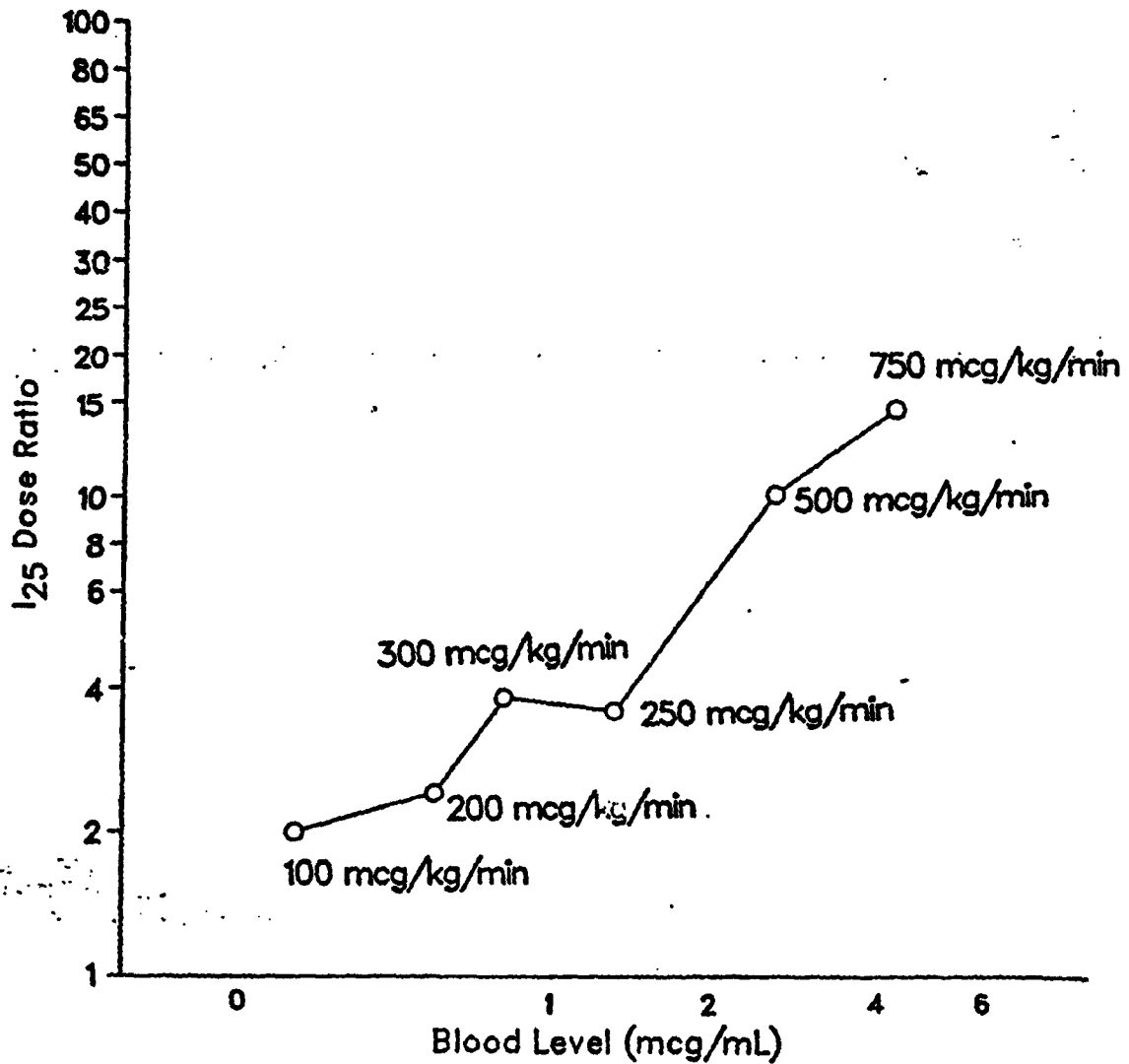
Relationship Between Percent Inhibition
of the Isoproterenol Heart Rate Response
and Blood Level of Esmolol (Log Scale) at Follow-Up
Williams 8052-84-58



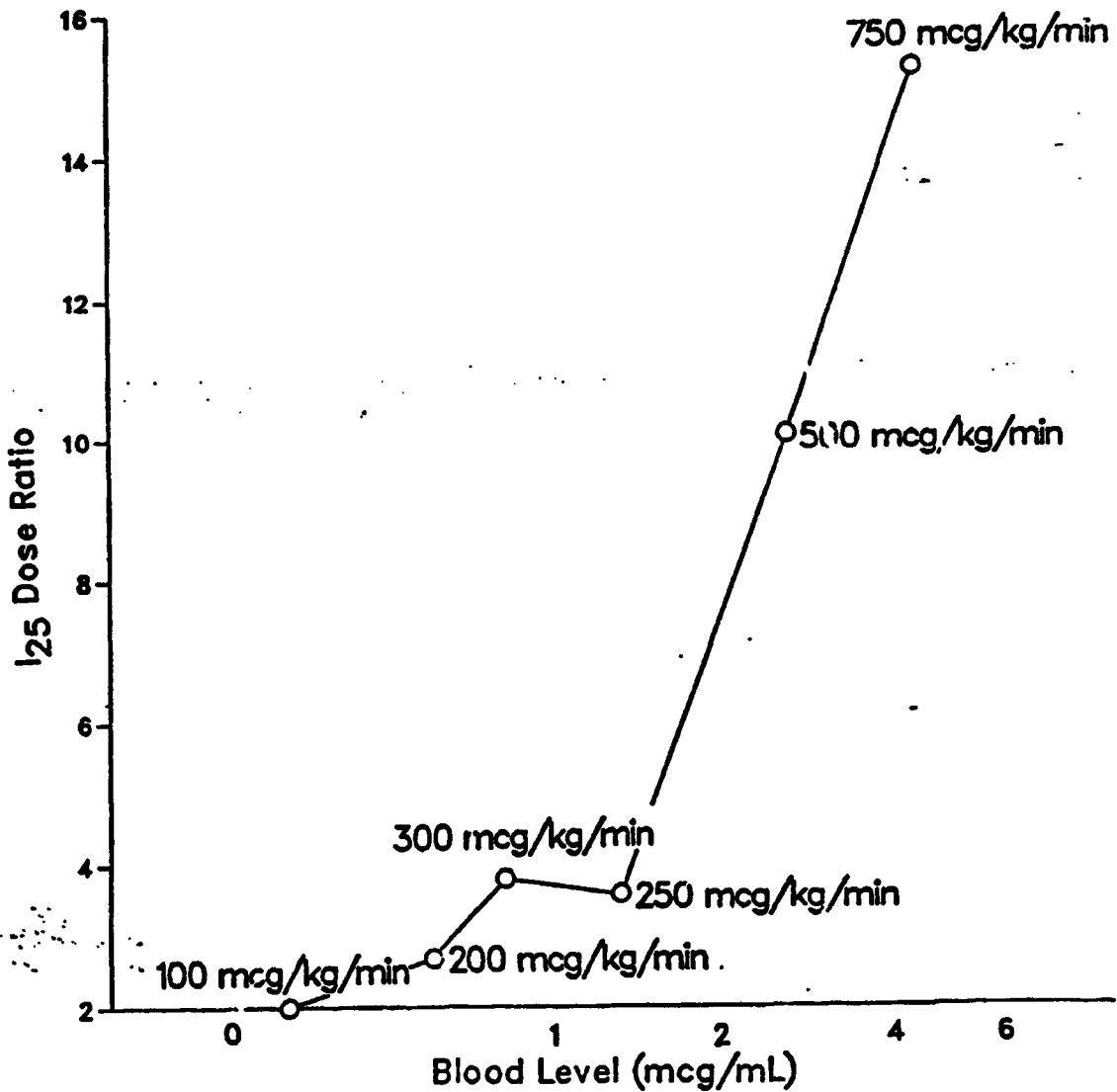
Relationship Between Percent of Beta Blockade (Log Scale)
and Blood Level of Esmolol (Log Scale) at Follow-Up
Williams 8052-84-58



Relationship Between I₂₅ Dose Ratio (Log Scale)
and Blood Level of Esmolol (Log Scale)
Wood 8052-83-43

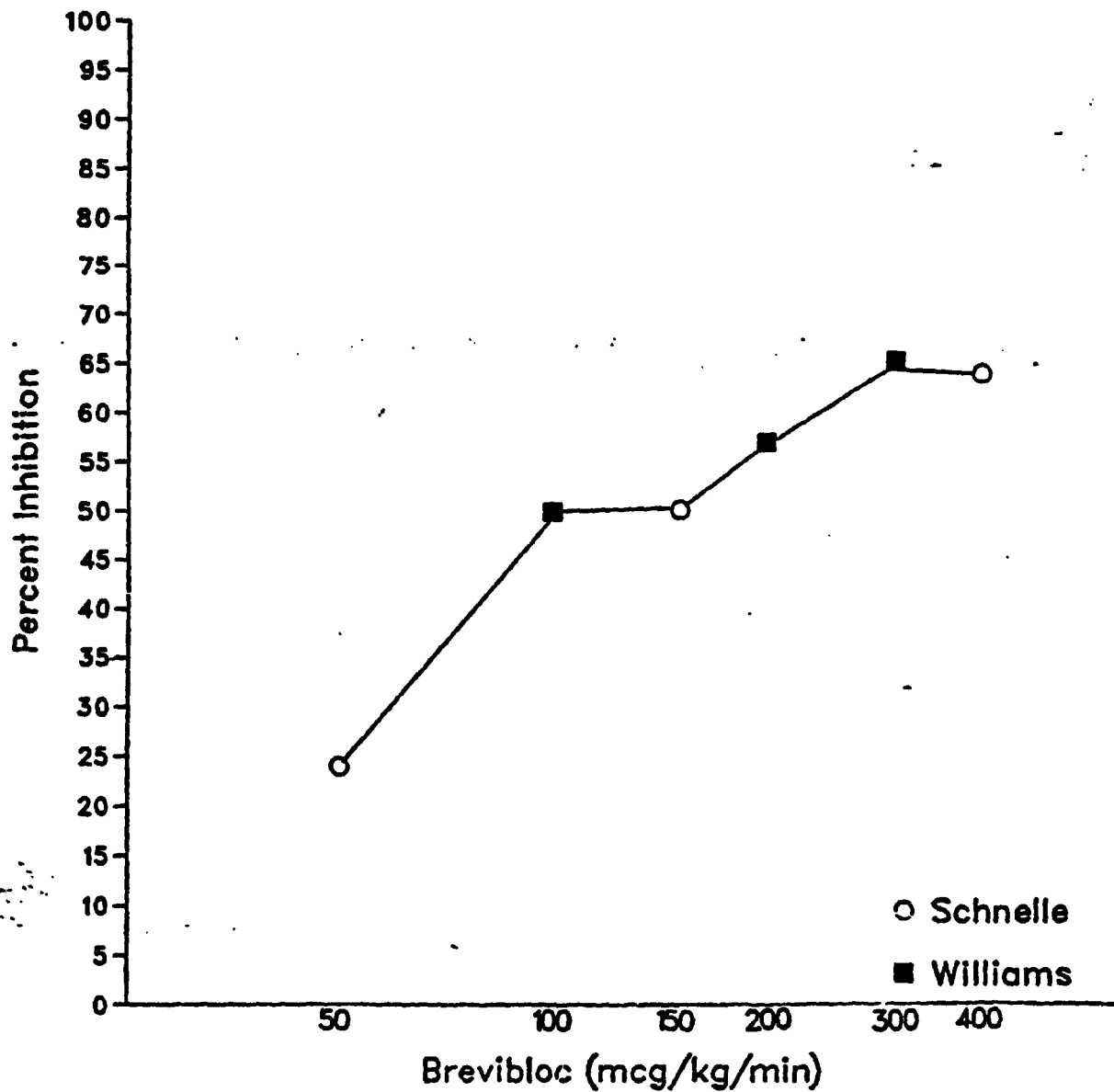


Relationship Between I₂₅ Dose Ratio
and Blood Level of Esmolol (Log Scale)
Wood 8052-83-43

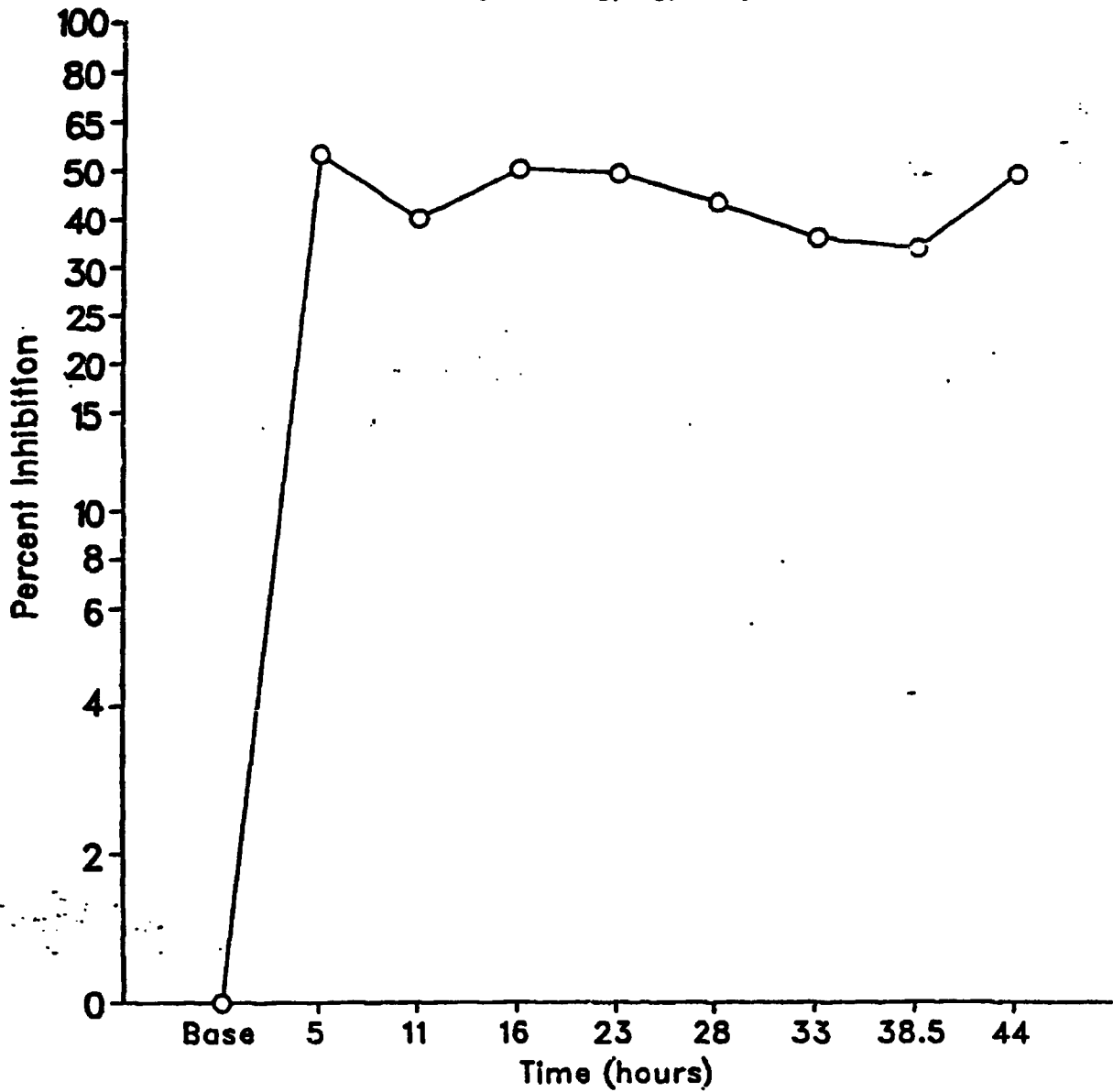


**Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Dose of Brevibloc (Log Scale) -**

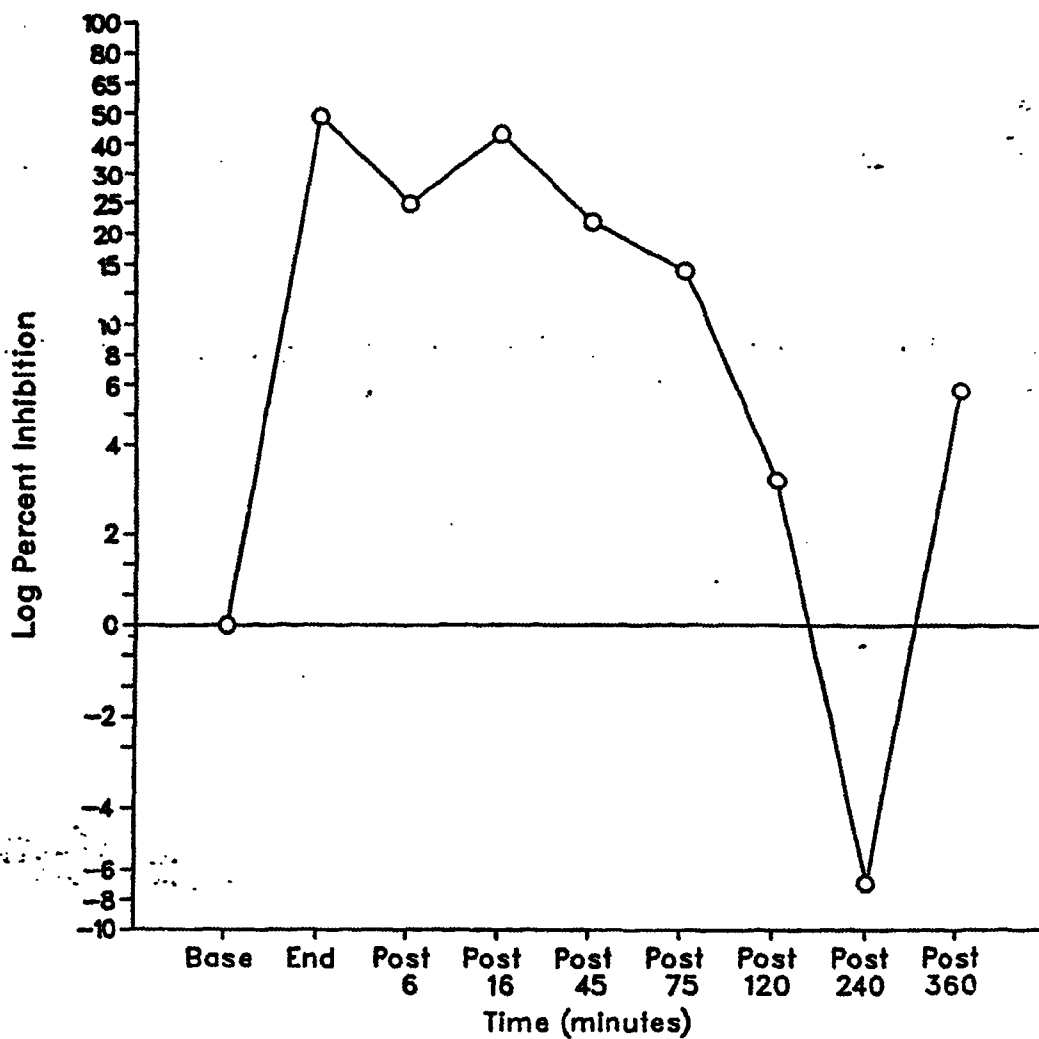
**Pooled Data
Williams 8052-84-58
Schnelle 8052-81-02**



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time (During Infusion) -
Schnelle 8052-81-03
(150 mcg/kg/min)

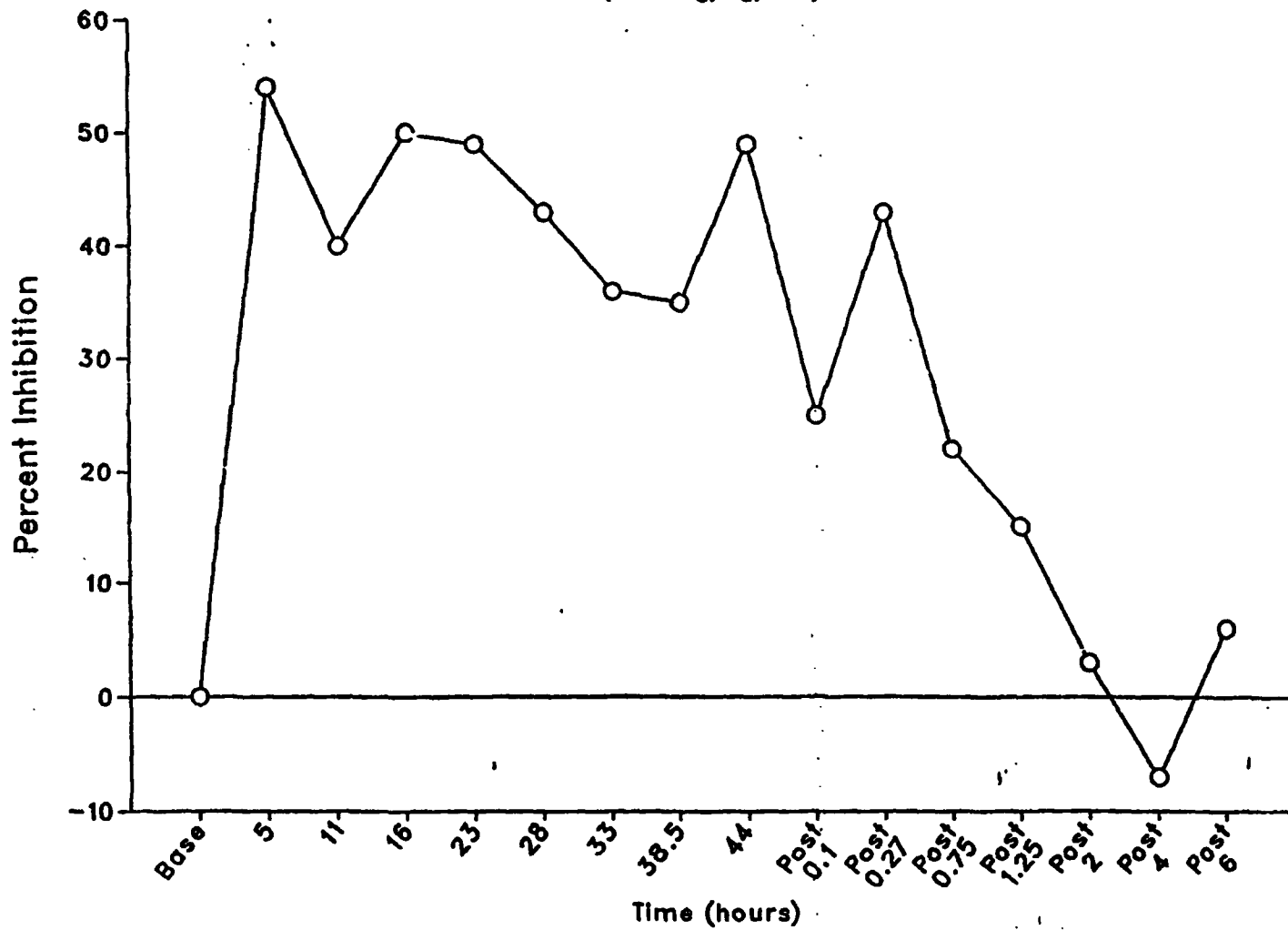


Relationship Between Percent Inhibition (Log Scale)
and Time (Follow-Up)
Schnelle 8052-81-03
(150 mcg/kg/min)



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Time

Schnelle 8052-81-03
(150 mcg/kg/min)



Appendix 1E - Methanol Blood Levels as a Function of Esmolol Dose

Appendix F.2

Methanol (ug/ml) Data Listings, by Famolol Dosage

----- Dosage=50 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	1							
2	3							
3	4							
4	1							
5	3							
6	2							
7	4							
8	2							

----- Dosage=100 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	2							
2	1							
3	1							
4	2							
5	1							
6	1							
7	1							
8	1							

Appendix F.2

Methanol (ug/ml) Data Listings, by Esmolol Dosage

Dosage=150

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	36 HR	42 HR	INF MAX
1	5									
2	5									
3	5									
4	5									
5	5									
6	5									
7	5									
8	5									

Appendix F.2

Methanol (ug/ml) Data Listings, by Esmolol Dosage

----- Dosage=200 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	3							
2	2							
3	2							
4	3							
5	2							
6	3							
7	2							
8	3							

----- Dosage=300 -----

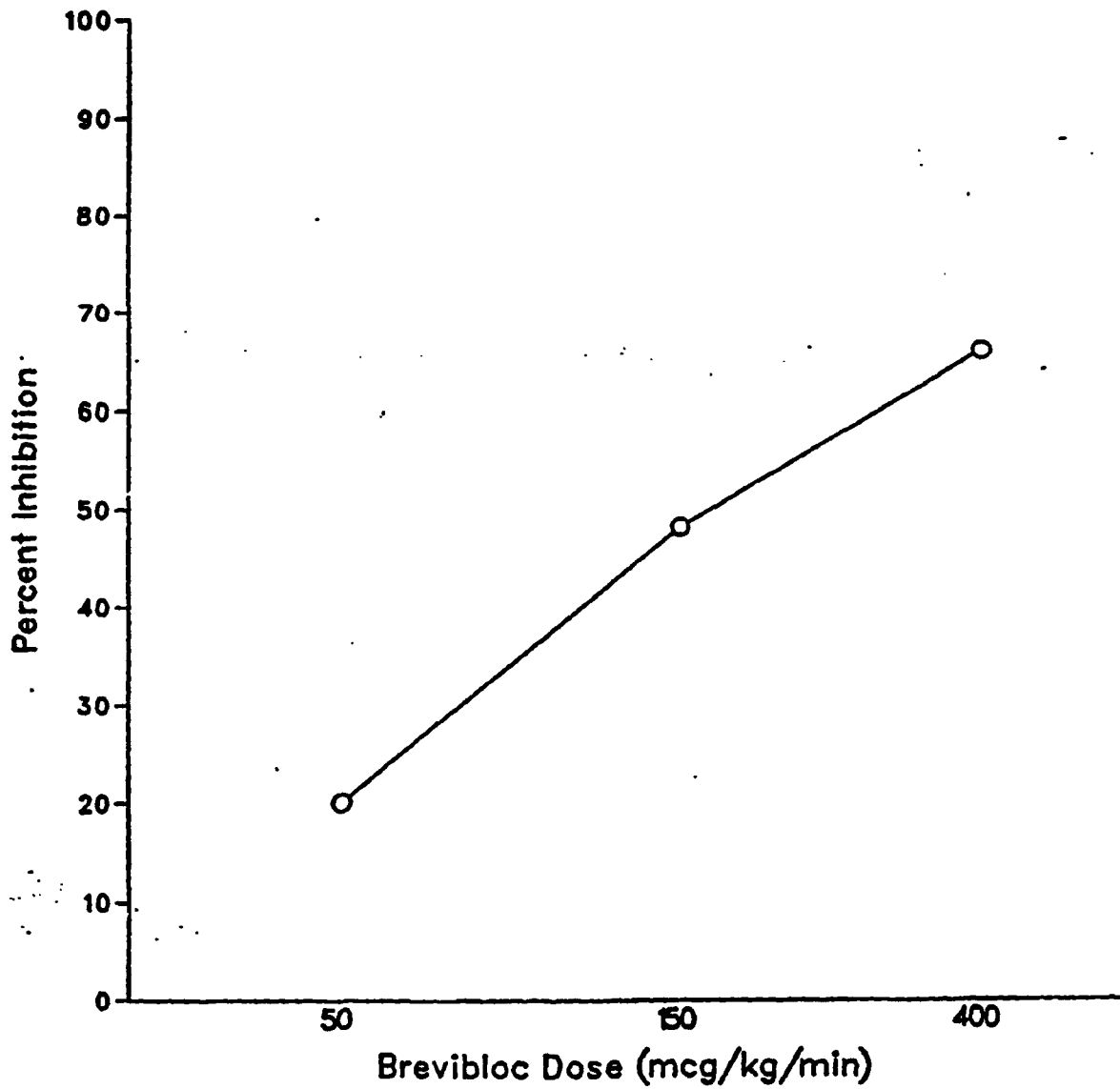
SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
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2	4							
3	3							
4	4							
5	4							
6	4							
7	3							
8	4							

8 Pages

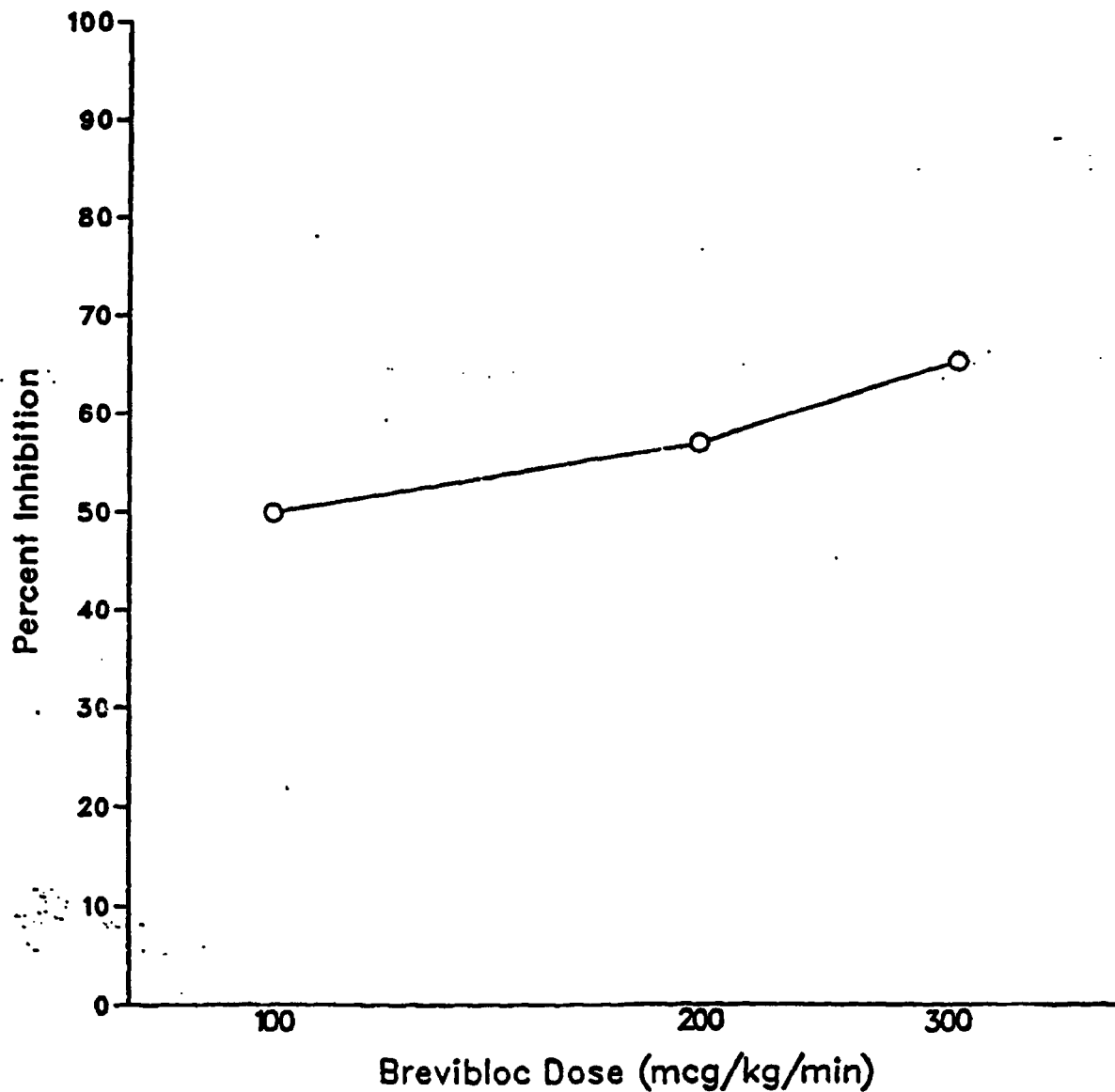
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**Appendix 10 - Dose Response Relationship Between Percent of Beta Blockade and
Dose of Esmolol**

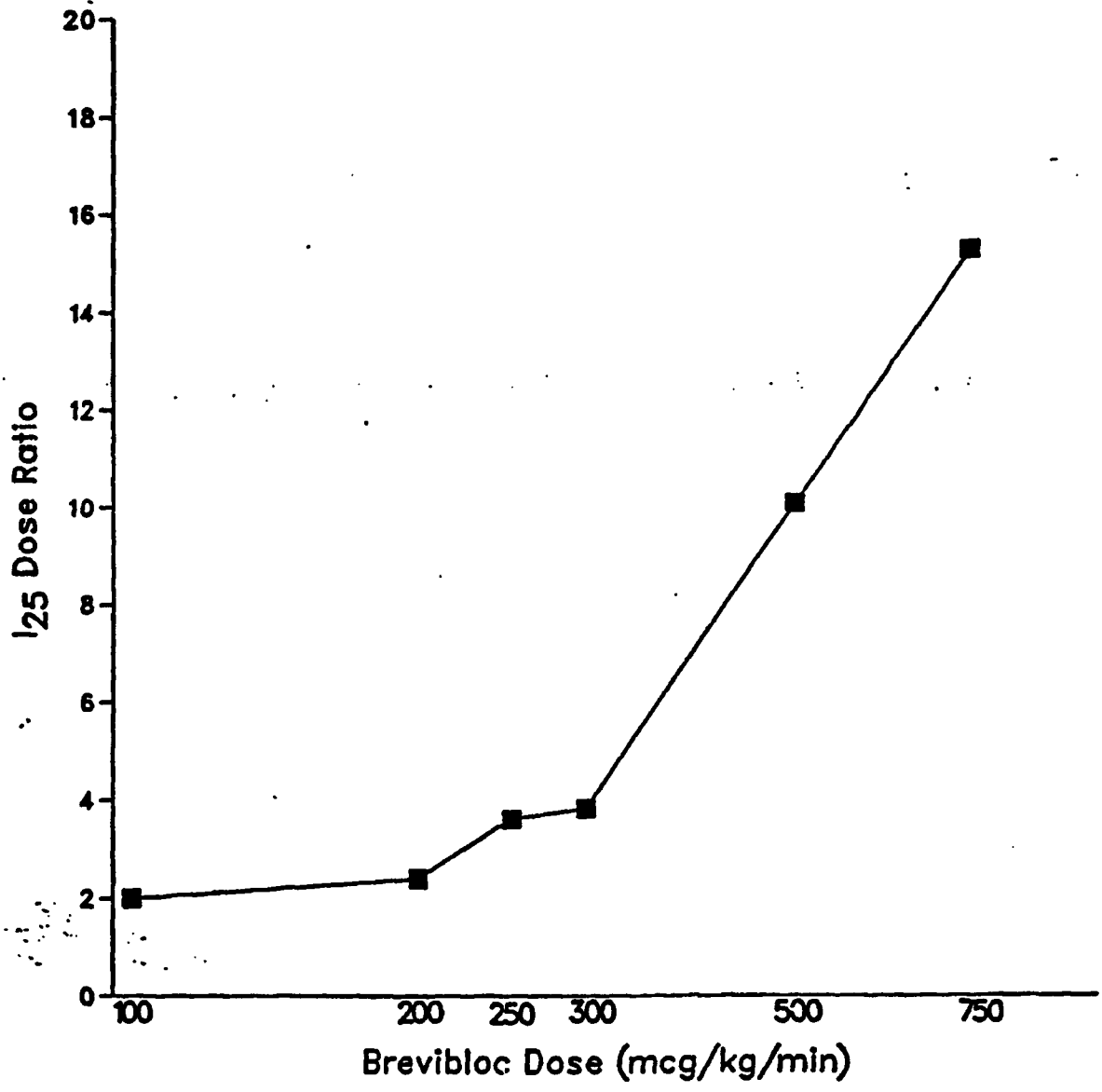
Relationship Between Percent Inhibition
and Dose of Brevibloc (Log Scale)
Schnelle 8052-81-02



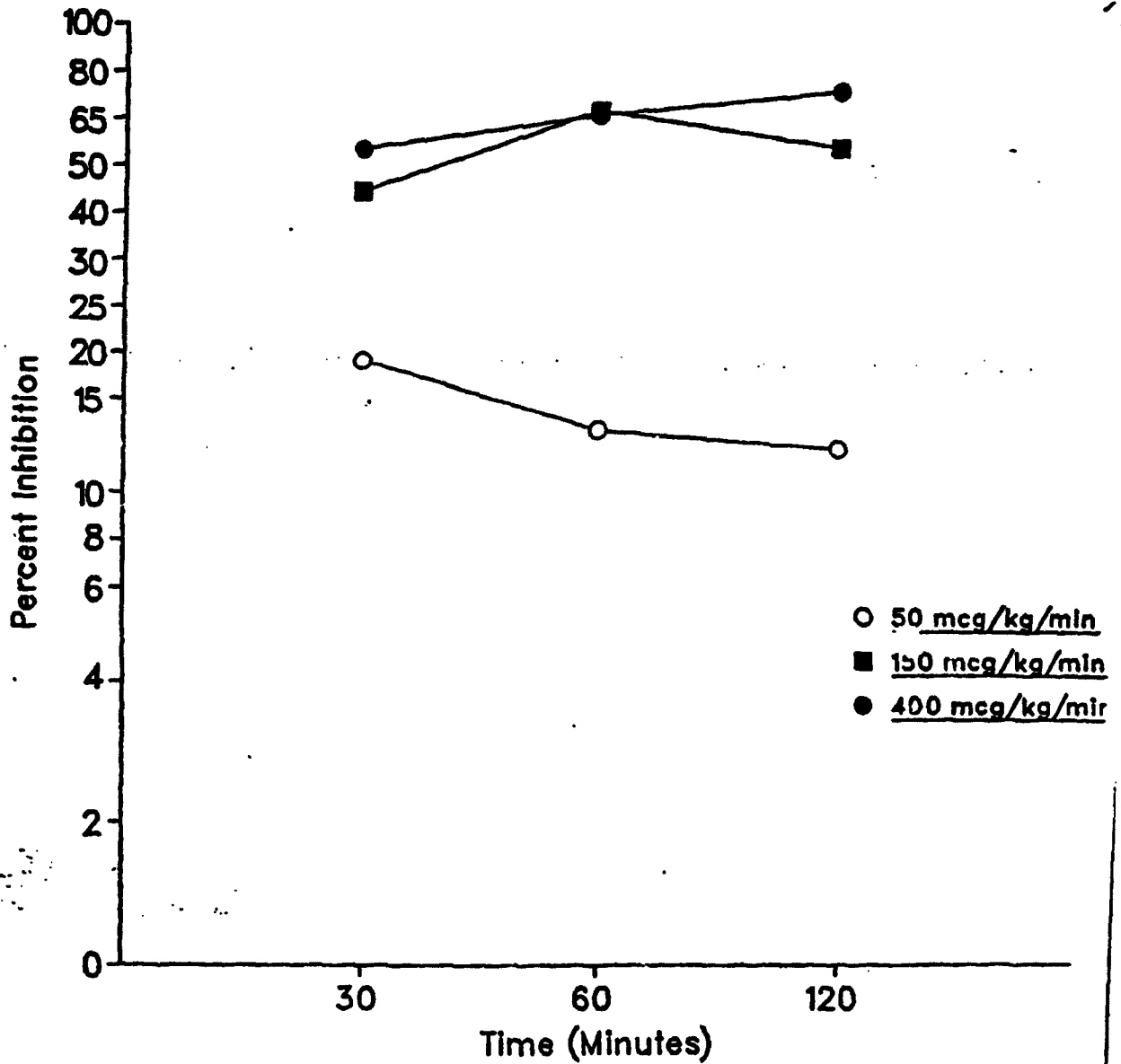
**Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Dose of Brevibloc (Log Scale)**
Williams 8052-84-58



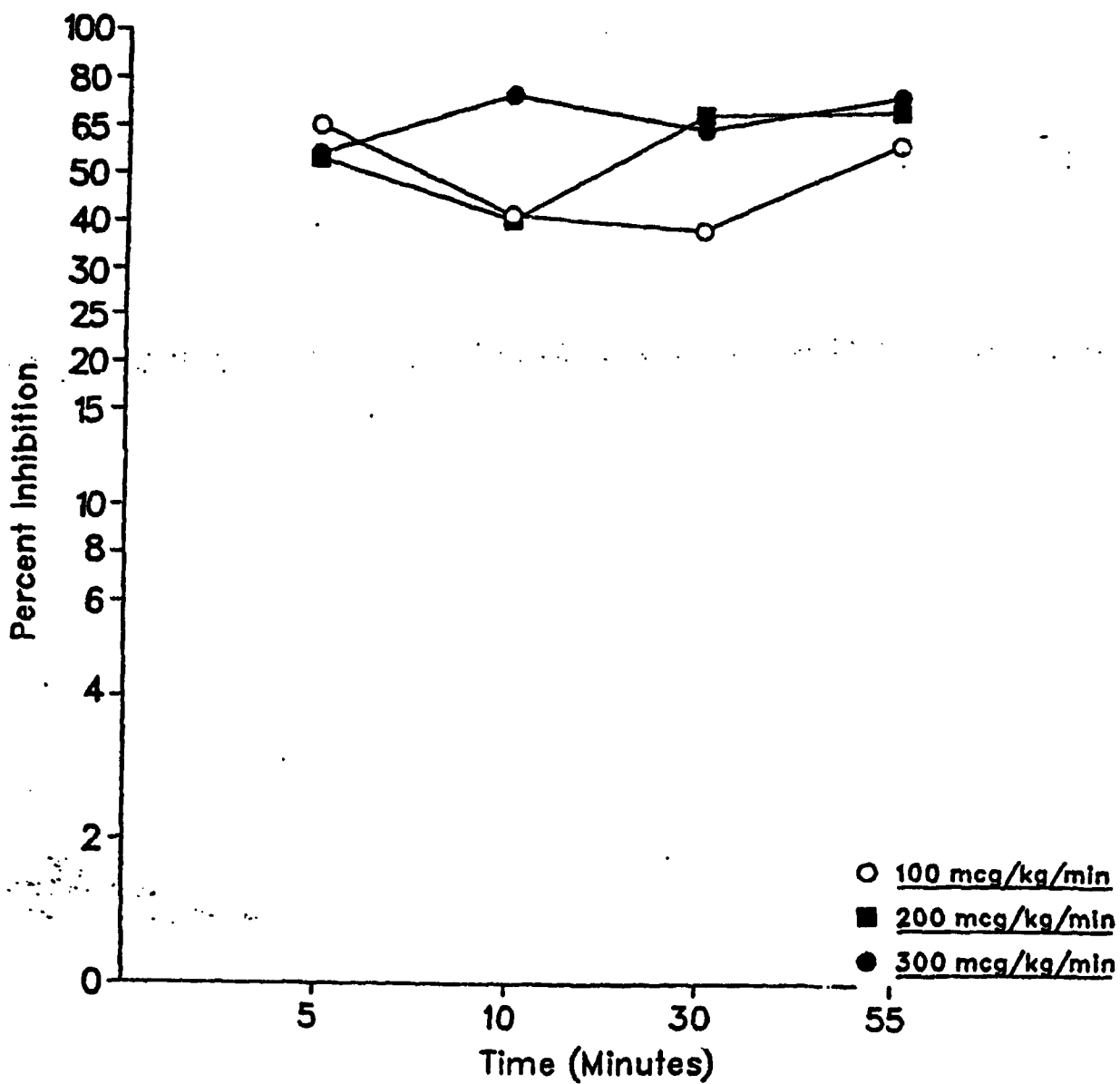
Relationship Between I₂₅ Dose Ratio
and Dose of Brevibloc (Log Scale)
Wood 8052-83-43



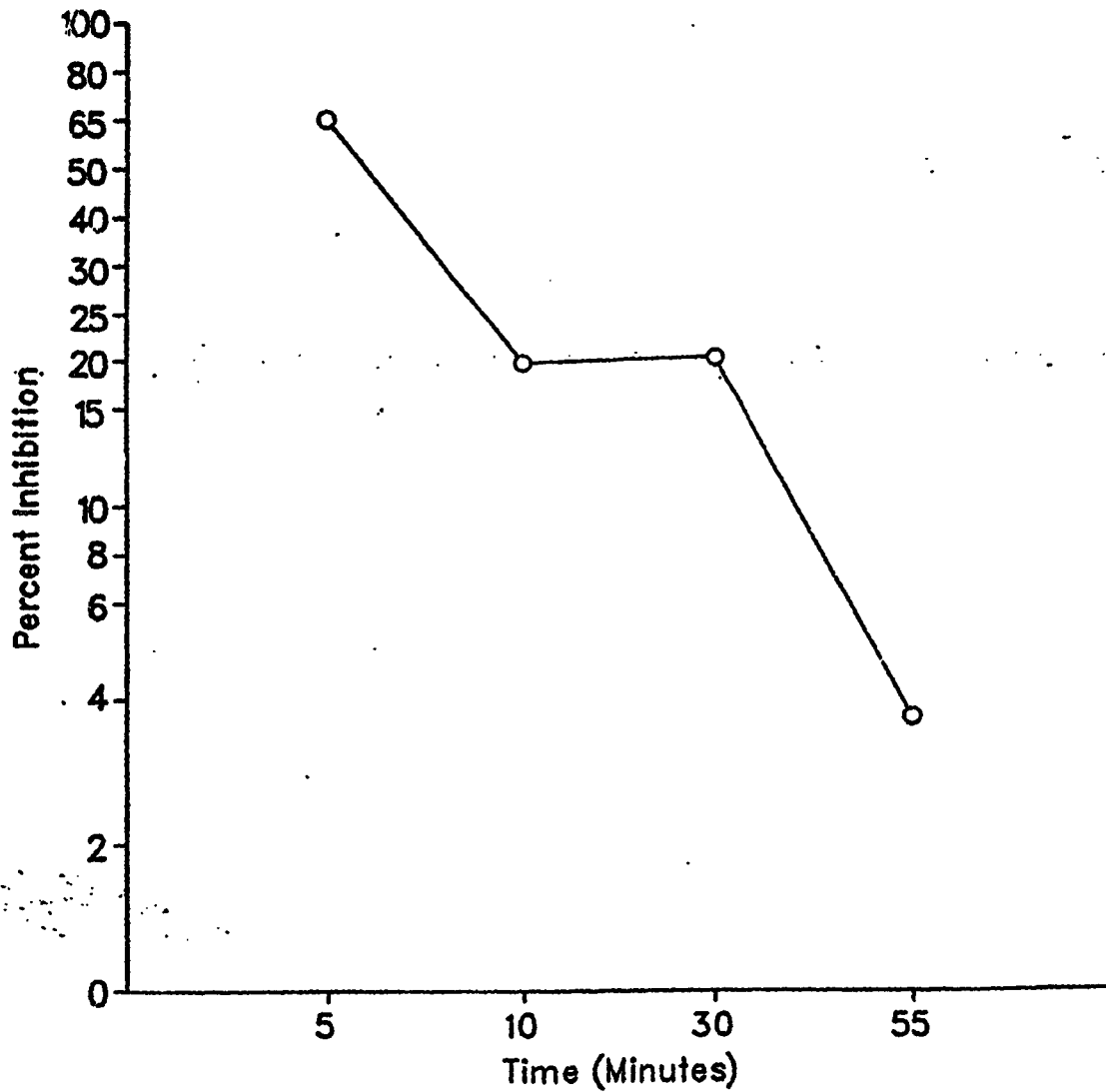
Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time At Various Dose Levels
Schnelle 8052-81-02



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time at Various Dose Levels
Williams 8052-84-58



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time During Follow-Up Period
Williams 8052-84-58



Wood 8052-83-43

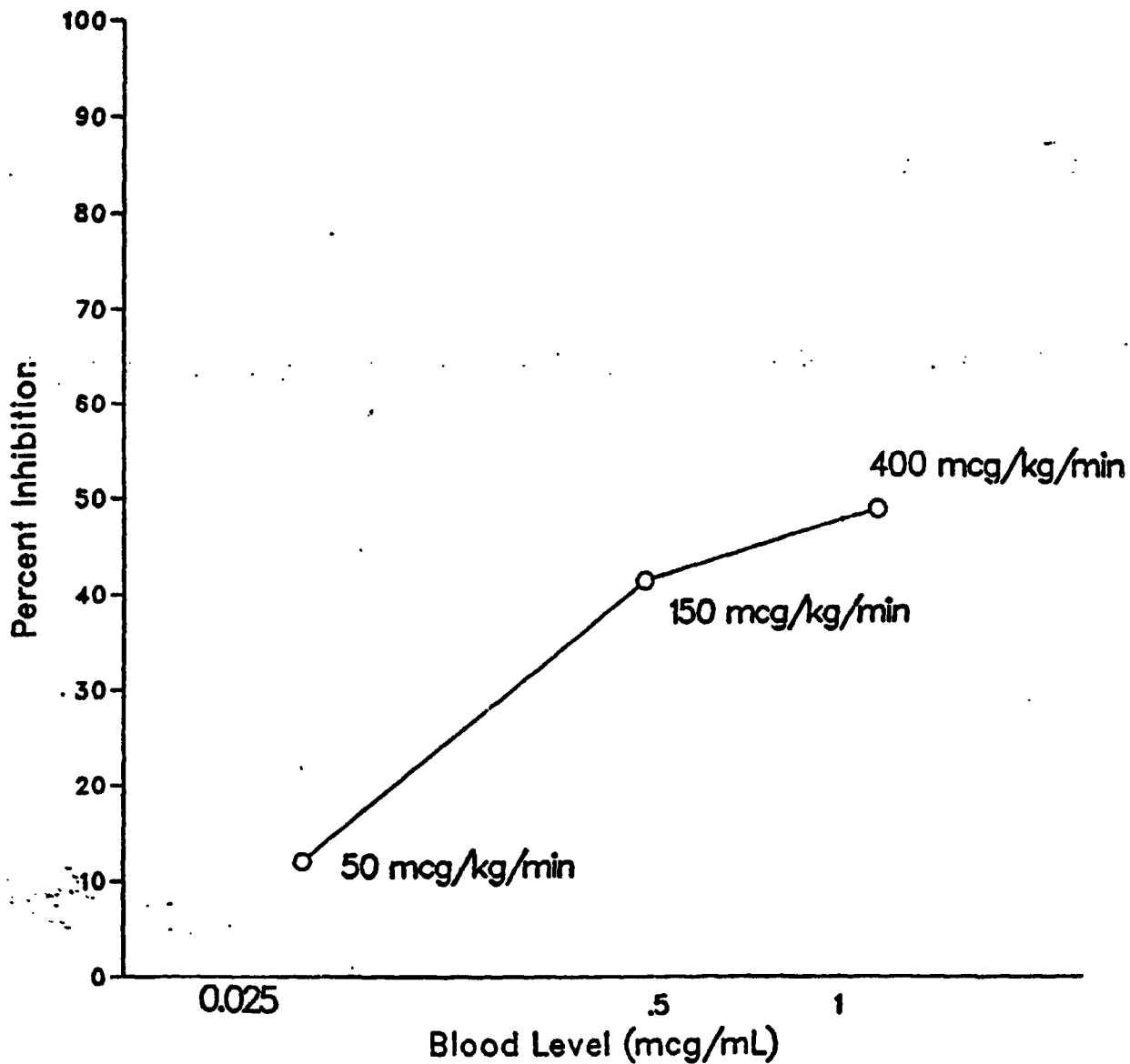
COMPARISON OF HEART RATE RESPONSE
TO ISOPROTERENOL AT 5 AND 25 MINUTES
DURING EACH ESMOLOL INFUSION RATE¹

Dose Esmolol mcg/Kg/min	N	Mean (s.e.) Dose of Isoproterenol ²	Time of Infusion	
			5 Minutes	25 Minutes
			Mean (s.e.) HR Increase	Mean (s.e.) HR Increase
100	12	1.18 (0.07)	16.17 (0.89)	17.67 (0.57)
200	7	2.16 (0.16)	18.43 (0.61)	19.86 (0.70)
250	4	1.28 (0.17)	8.25 (2.21)	11.00 (3.81)
300	7	3.09 (0.29)	18.14 (0.74)	19.00 (0.93)
500	4	4.73 (0.24)	11.25 (1.03)	13.25 (3.75)
750	3	9.83 (1.59)	13.67 (4.48)	14.67 (2.40)

¹ There were no significant differences (at $\alpha = 0.05$ level) between the means at 5 and 25 minutes at each dosing level.

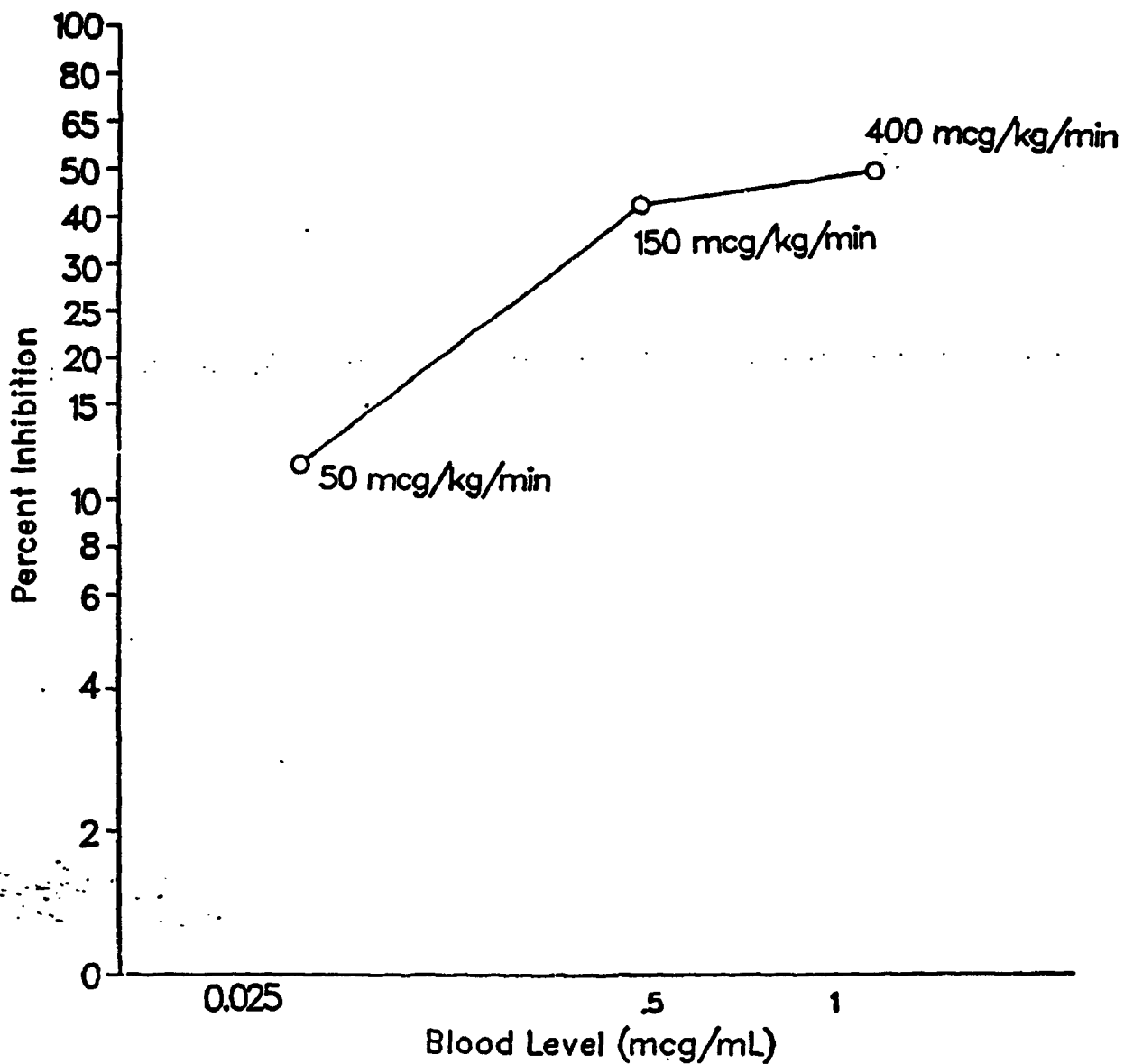
² In each subject the dose of isoproterenol administered was the I_{25e} determined during the previous (lower) esmolol infusion (or in the absence of esmolol infusion for the 100 mcg/Kg/min dose). The I_{25e} was defined as the estimated dose of isoproterenol, determined from the isoproterenol heart rate dose response curve, that would increase heart rate by 25 beats/minute.

Relationship Between the Mean Percent Inhibition
of Isoproterenol Heart Rate Response
and Mean Blood Level of Esmolol (Log Scale)
at Each Dose
Schnelle 8052-8102

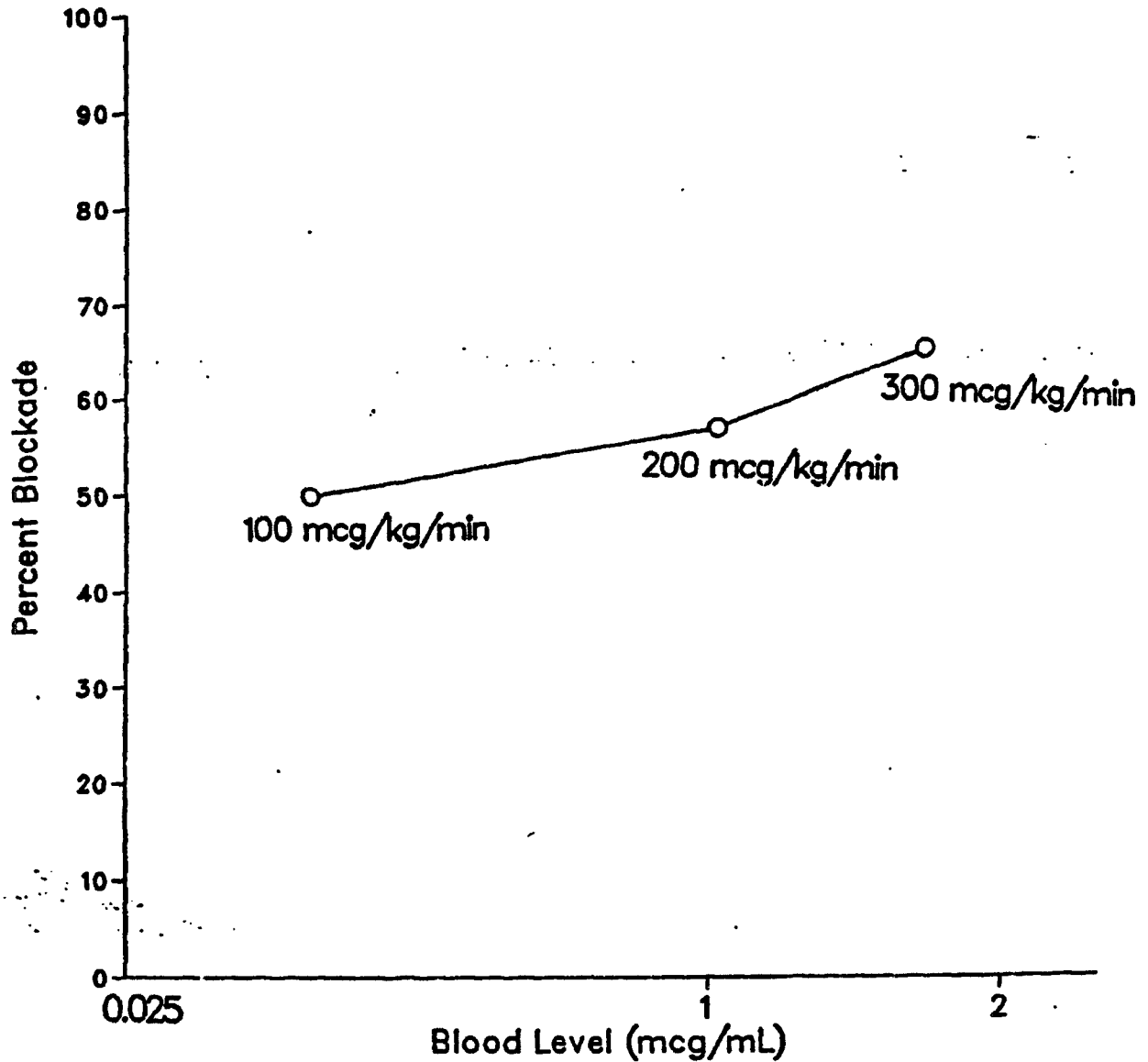


Relationship Between Mean Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Mean Blood Level of Esmolol (Log Scale)
at Each Dose

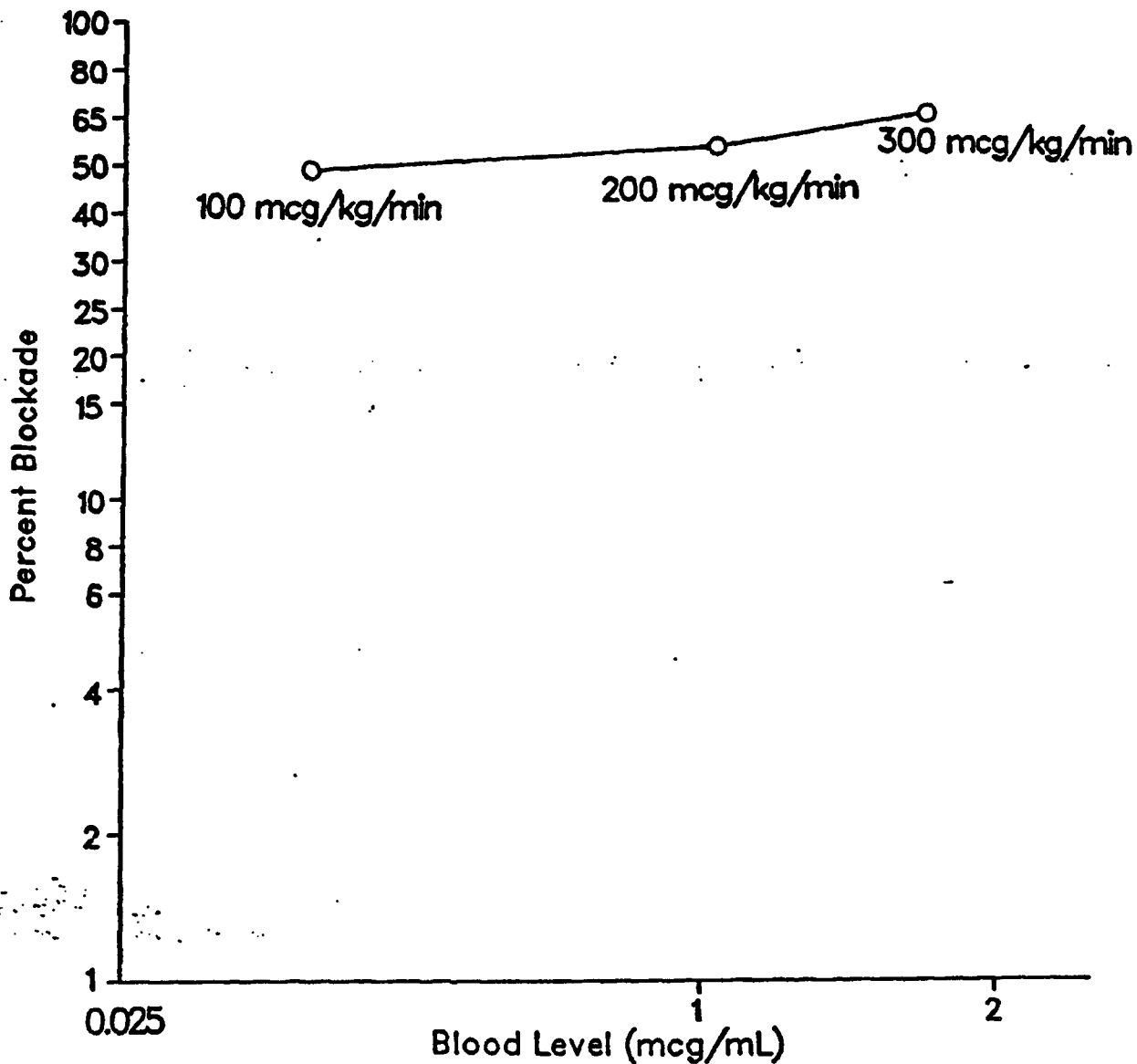
Schnelle 8052-81-02



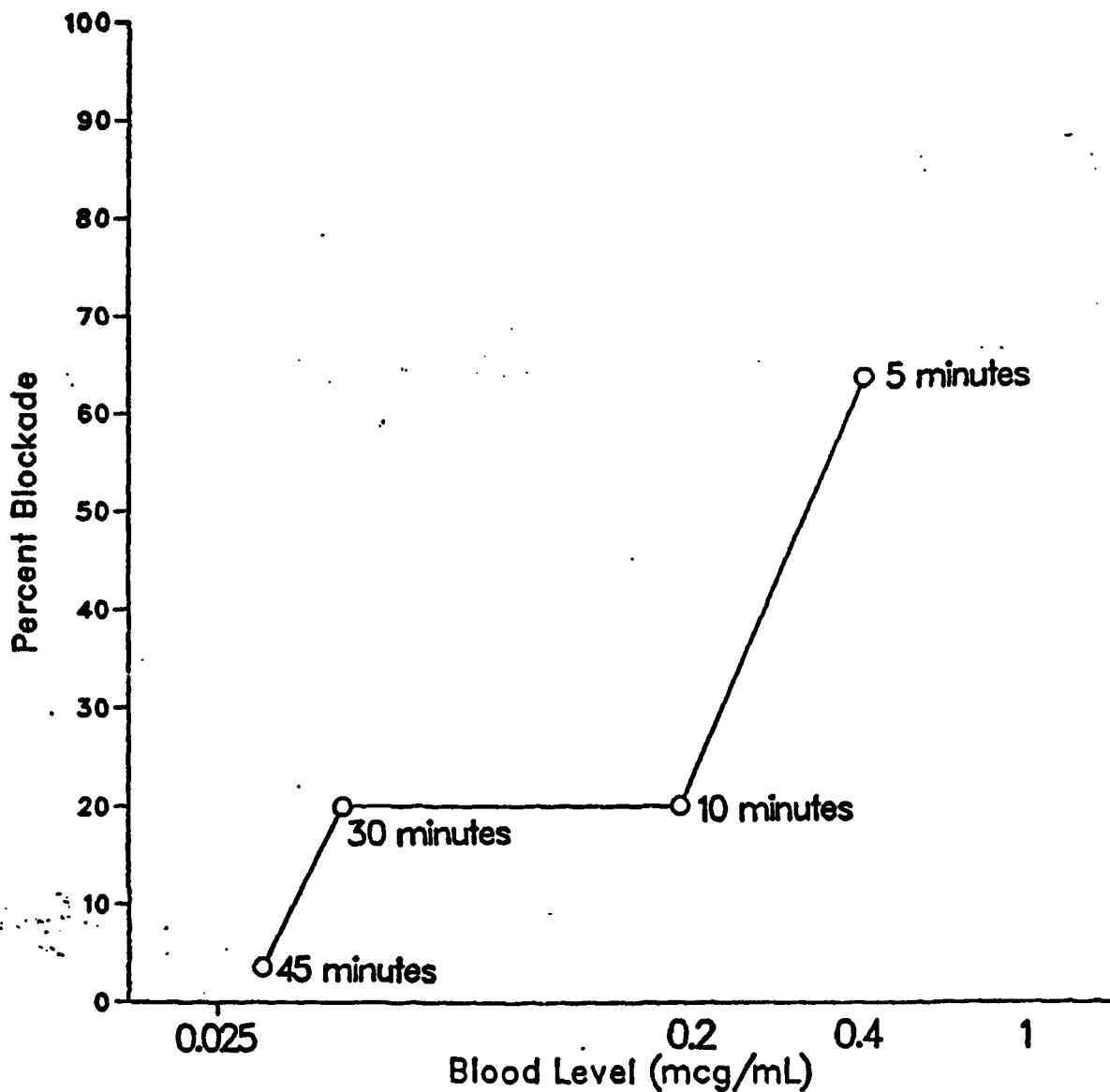
**Relationship Between Mean Percent Inhibition
of the Isoproterenol Heart Rate Response and
Mean Blood Level of Esmolol (Log Scale) at Each Dose**
Williams 8052--84-58



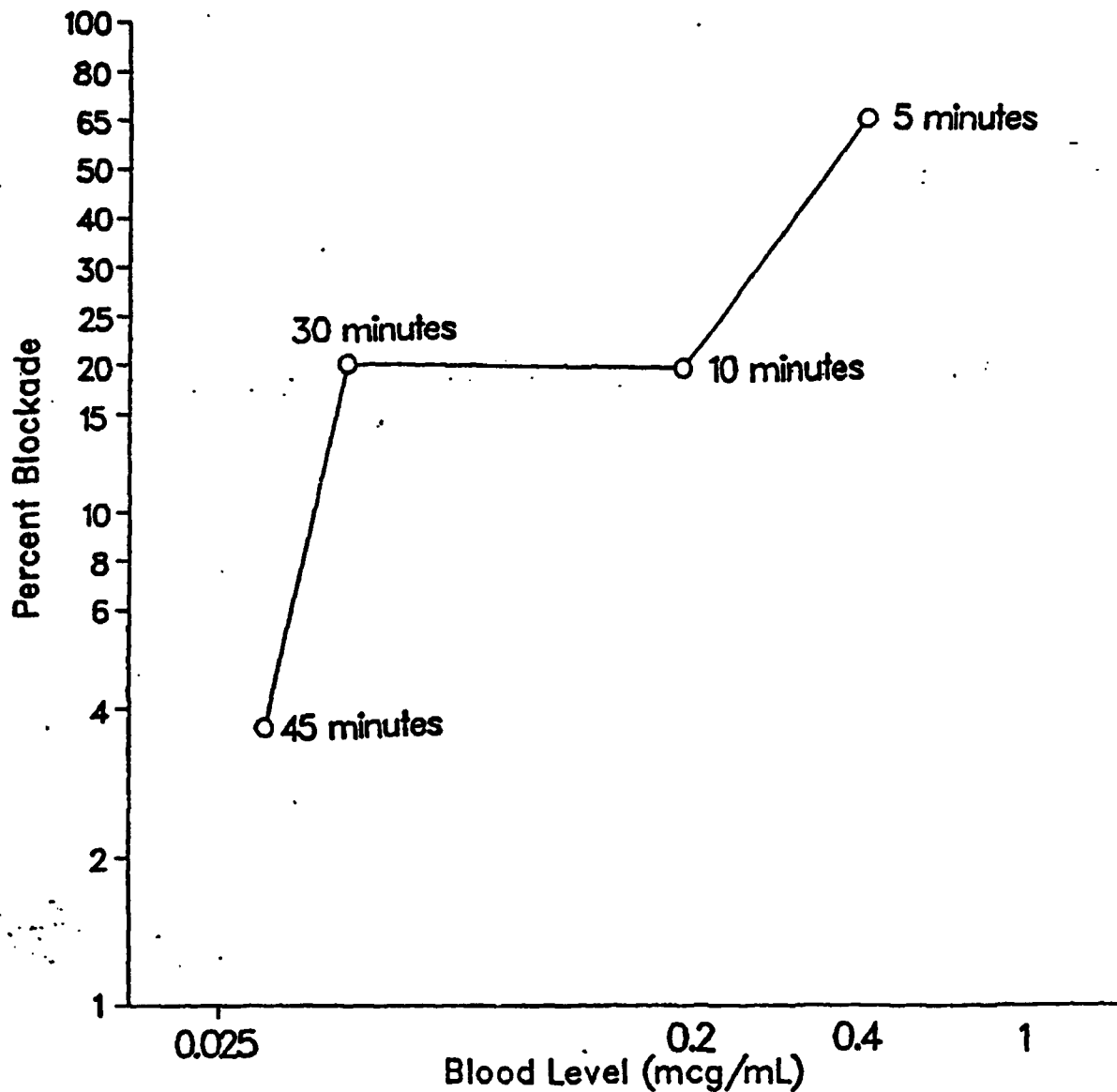
Relationship Between Mean Percent of
Beta Blockade (Log Scale)
and Mean Blood Level of
Esmolol (Log Scale) at Each Dose
Williams 8052-84-58



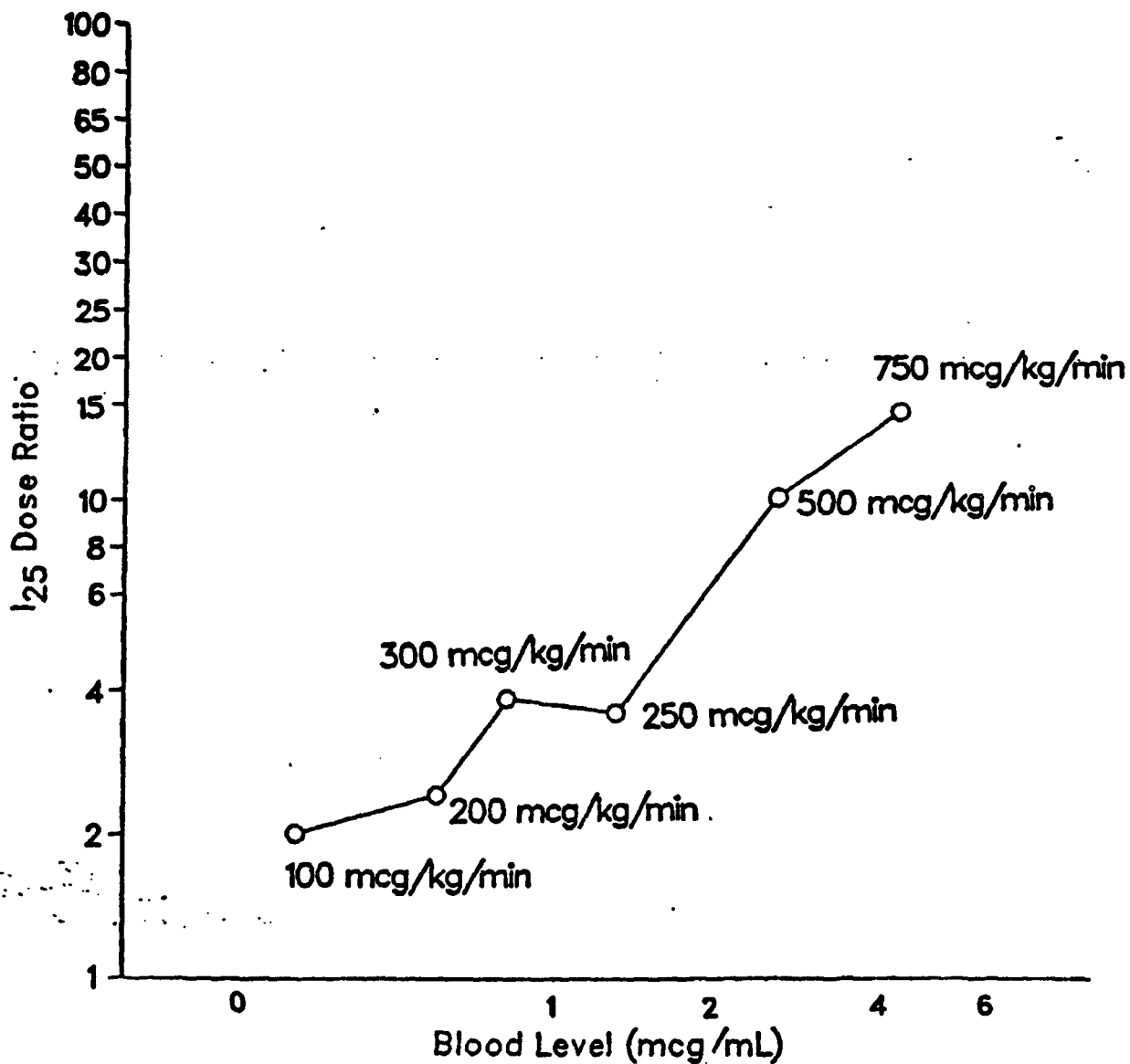
Relationship Between Percent Inhibition
of the Isoproterenol Heart Rate Response
and Blood Level of Esmolol (Log Scale) at Follow-Up
Williams 8052-84-58



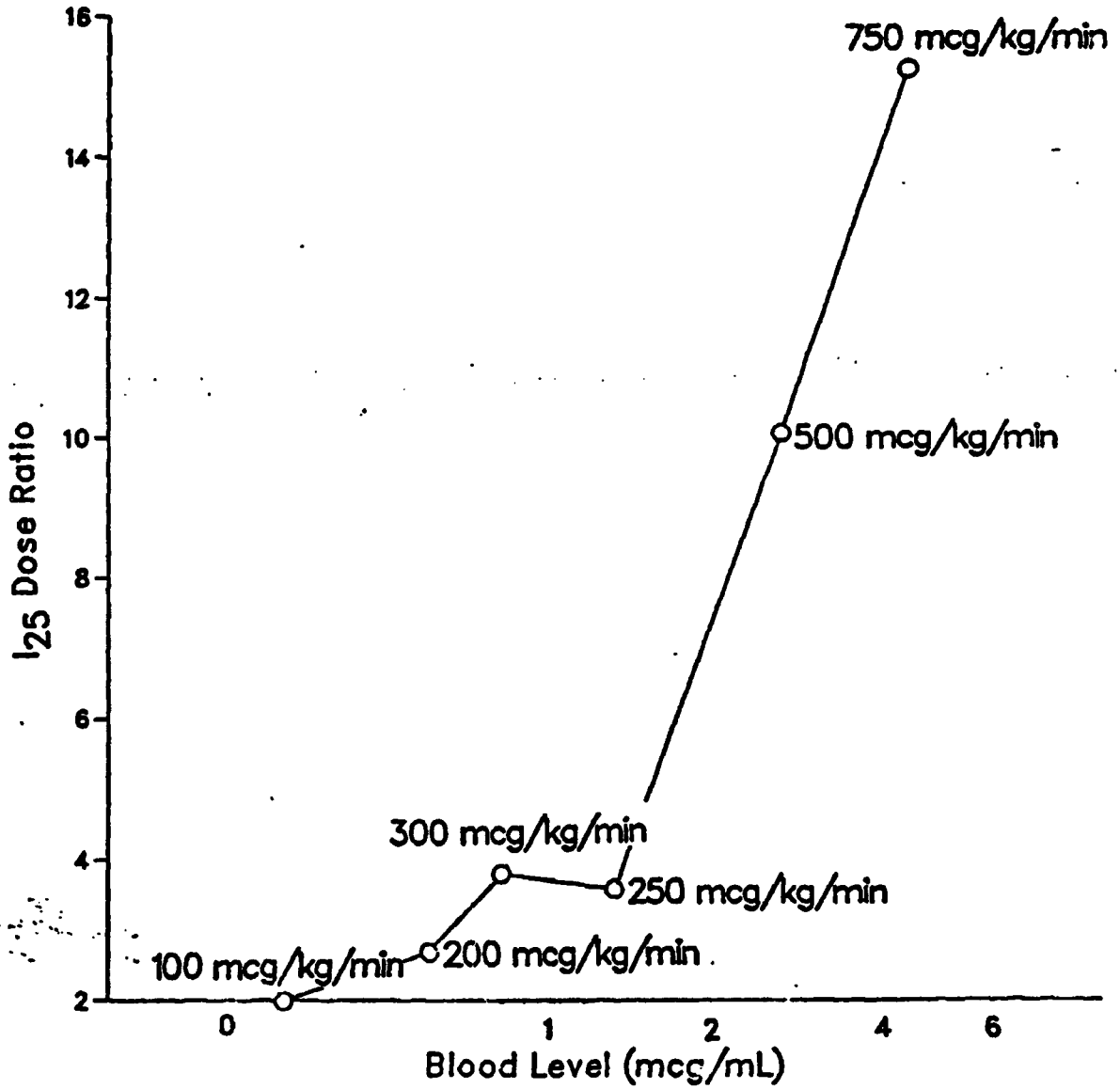
Relationship Between Percent of Beta Blockade (Log Scale)
and Blood Level of Esmolol (Log Scale) at Follow-Up
Williams 8052-84-58



Relationship Between I₂₅ Dose Ratio (Log Scale)
and Blood Level of Esmolol (Log Scale)
Wood 8052-83-43



Relationship Between I₂₅ Dose Ratio
and Blood Level of Esmolol (Log Scale)
Wood 8052-83-43

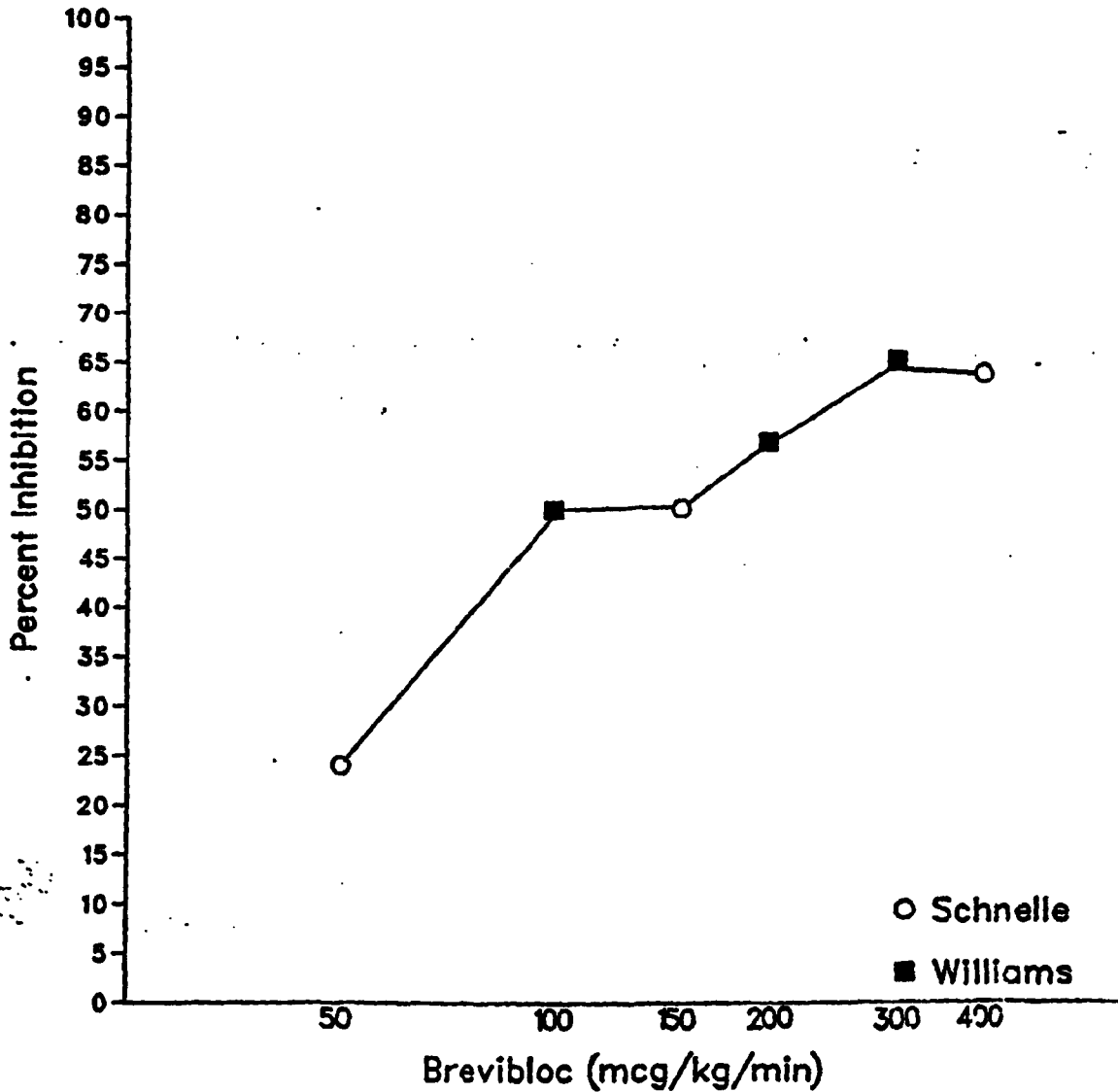


**Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Dose of Brevibloc (Log Scale)**

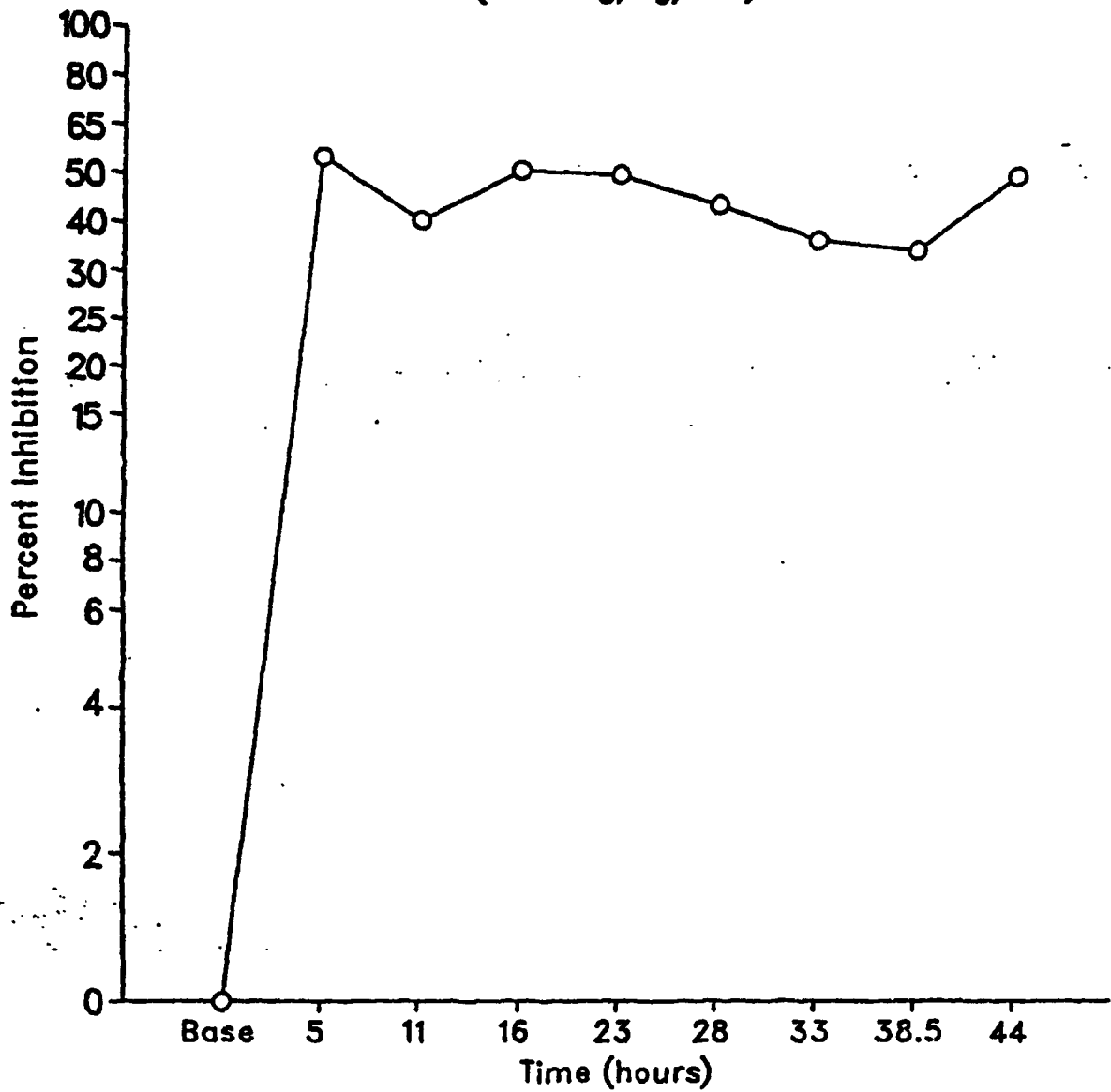
Pooled Data

Williams 8052-84-58

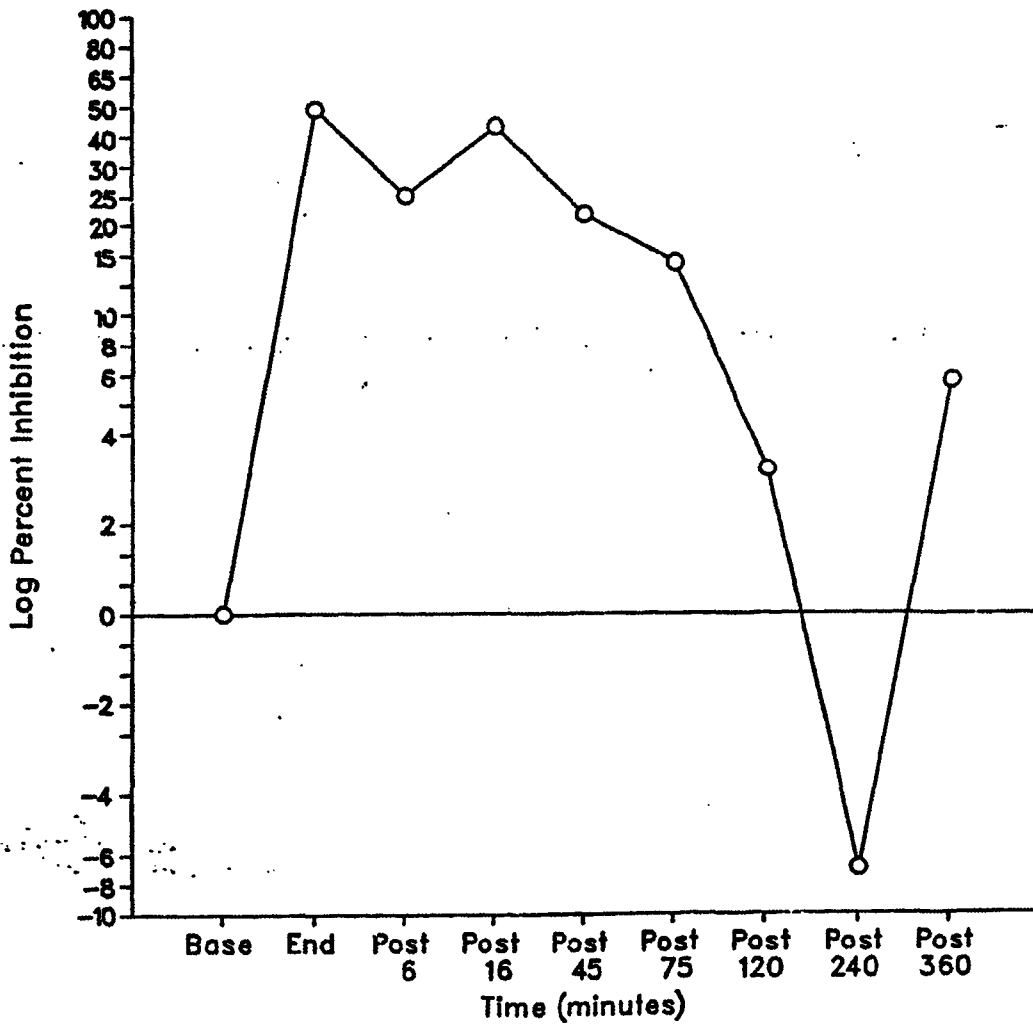
Schnelle 8052-84-02



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response (Log Scale)
and Time (During Infusion)
Schnelle 8052-81-03
(150 mcg/kg/min)

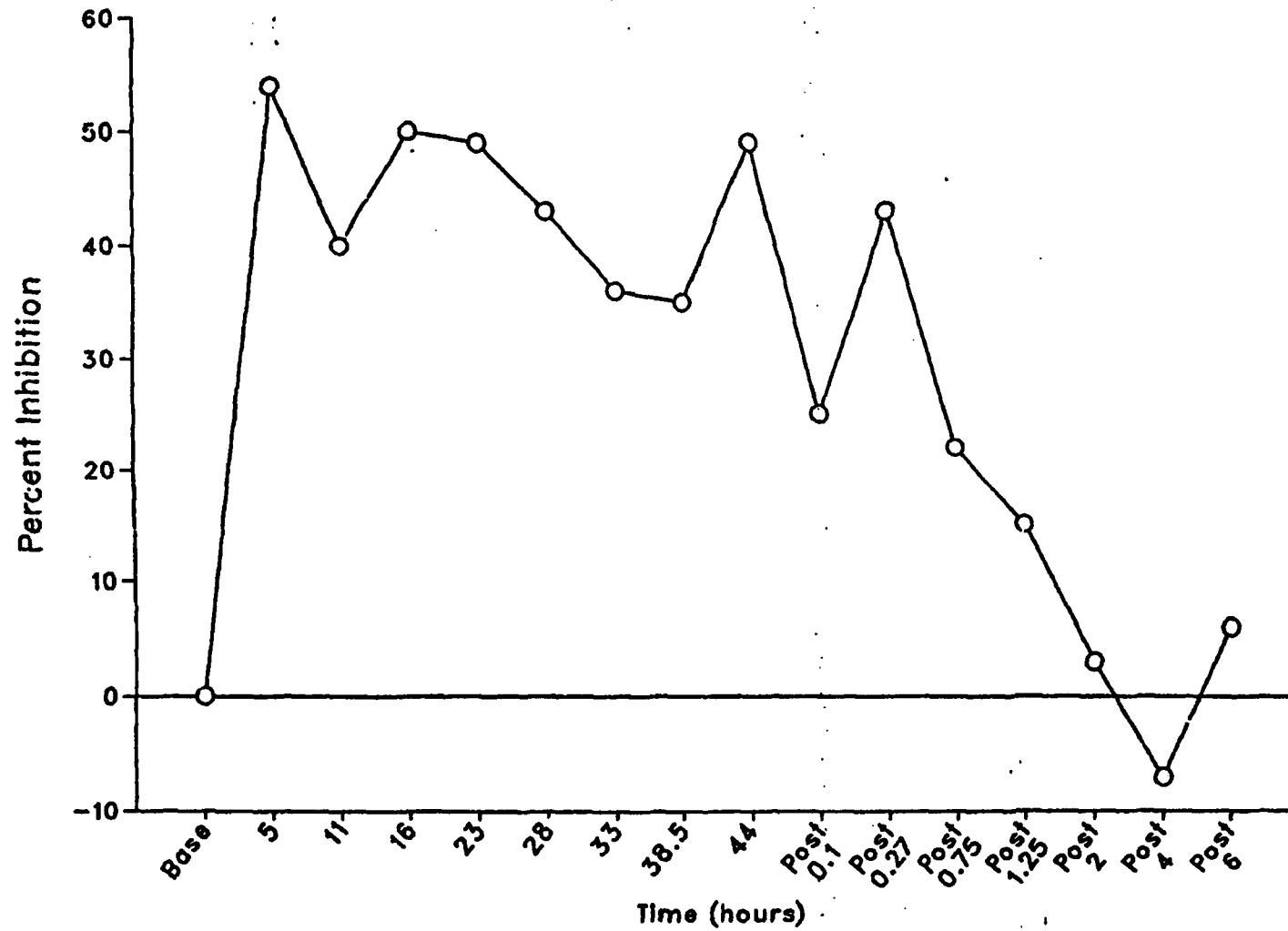


Relationship Between Percent Inhibition (Log Scale)
and Time (Follow-Up)
Schnelle 8052-81-03
(150 mcg/kg/min)



Relationship Between Percent Inhibition
of Isoproterenol Heart Rate Response
and Time

Schnelle 8052-81-03
(150 mcg/kg/min)



Appendix 1E - Methanol Blood Levels as a Function of Esmolol Dose:

Appendix F.2

Methanol (ug/ml) Data Listings, by Esmolol Dosage

----- Dosage=50 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	1							
2	3							
3	4							
4	1							
5	3							
6	2							
7	4							
8	2							

----- Dosage=100 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	2							
2	1							
3	1							
4	2							
5	1							
6	1							
7	1							
8	1							

Appendix F.2

Methanol (ug/ml) Data Listings, by Esmolol Dosage

----- Dosage=150 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	36 HR	42 HR	INF MAX
1	5									
2	5									
3	5									
4	5									
5	5									
6	5									
7	5									
8	5									

Appendix F.2

Methanol (ug/ml) Data Listings, by Esmolol Dosage

----- Dosage=200 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	3							
2	2							
3	2							
4	3							
5	2							
6	3							
7	2							
8	3							

----- Dosage=300 -----

SUBJ	PHASE	PRE INF	1 HR	3 HR	6 HR	12 HR	24 HR	INF MAX
1	4							
2	4							
3	3							
4	4							
5	4							
6	4							
7	3							
8	4							

8 Pages

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