Dose Proportionality and Absolute Bioavailability of Dolasetron after Three IV Infusion Doses and One oral Dose in Normals

Study: MCPR0080

Objectives:

1. To determine the dose proportionality of iv administered DM,
2. To determine the absolute oral bioavailability of DM,
3. To determine pharmacokinetics of DM, total DMA and R(+) and S(-) enantiomers of DMA.
4. To investigate the effect of DM on ECG measurement after IV and oral administration.

Formulation: A 10 mg/ml injectable solution of dolasetron mesylate was used in this study for both iv and oral treatment.

Batch No.	C-49127
Site of Manufacturing	
Date of Manufacturing	10-15-91
Dosage Form	Injectable Solution
Strength	10 mg/ml
Batch Size	

Study Design and Sampling: The study was an open-label, randomized, complete, four-way cross-over design with 24 healthy, male subjects between the ages of years. Each subject received one of the following treatments for each period:

Treatment A: 200 mg DM given by 10 minute iv infusion.
Treatment B: 100 mg DM given by 10 minute iv infusion.
Treatment C: 50 mg DM given by 10 minute iv infusion.
Treatment D: 200 mg DM in solution given orally.

Blood samples for iv treatments (A, B and C) were collected immediately before the start of infusion, and at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after the end of infusion. Blood samples for the oral treatment (D) were collected immediately before the dose, and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after the dose. Urine samples for both iv and oral treatments were collected immediately before oral dosing or the start of iv infusion, and at intervals of 0-4, 4-8, 8-12, 12-24 and 24-48 hours after oral dosing or the end of iv infusion.

Pharmacodynamic analysis was performed using NONMEM to investigate the relationship between changes in PR interval or QRS duration and plasma concentrations of the major, active metabolite of DM, DMA.

Results: Figure 1 and 2 show mean plasma concentration versus time plots for DM and total DMA, respectively. Following tables present mean pharmacokinetic parameters of DM and total DMA, respectively.

Mean PK parameters for DM

Variable	TRT	Mean	% CV
AUC_{0-} (ng*h/ml)	A	285.5	19
	B	137.6	22
	C	75.0	19
t1/2 (h)	A	0.14	15
	B	0.14	45
	C	0.14	21
CL (ml/min/kg)	A	114.9	31
	B	120.9	34
	C	110.0	33
V(L/kg)	A	1.40	27
	B	1.48	45
	C	1.35	41

Mean PK parameters for DMA

Variable	TRT	DMA (Mean, % CV)	R (+) DMA	S(-) DMA
AUC_{0-} (ng*h/ml)	A	3637.5 (33)	2801.0 (23)	764.5 (16)
	B	1796.6 (28)	1309.5 (28)	391.7 (24)
	C	909.9 (31)	645.0 (20)	209.4 (24)
	D	2680.3 (30)	2100.5 (29)	526.2 (21)
Cmax (ng/ml)	A	646.9 (29)	554.4 (29)	88.3 (21)
	B	320.4 (25)	272.5 (32)	46.4 (20)
	C	160.9 (29)	150.3 (34)	29.0 (37)
	D	601.2 (35)	522.7 (41)	105.0 (26)
tmax (h)	A	0.67 (37)	0.56 (23)	1.60 (38)

	B	0.62 (64)	0.48 (24)	1.27 (46)
	C	0.62 (61)	0.60 (31)	1.31 (51)
	D	0.74 (44)	0.71 (25)	0.48 (27)
t1/2 (h)	A	7.66 (22)	6.09 (17)	6.27 (19)
	B	7.32 (24)	5.39 (19)	5.06 (17)
	C	6.57 (33)	5.24 (18)	4.68 (15)
	D	8.84 (23)	6.96 (39)	6.89 (17)
CLapp (ml/min/kg)	A	9.48 (34)		
	B	9.39 (28)		
	C	9.31 (28)		
CLapp,po (ml/min/kg)	D	12.9 (34)		
CL_R (ml/min/kg)	A	2.91 (25)	3.46 (14)	1.52 (20)
	B	2.58 (32)	3.26 (27)	1.41 (29)
	C	2.65 (27)	3.06 (11)	1.26 (12)
	D	2.61 (28)	2.82 (26)	1.81 (21)
Vapp (l/kg)	A	6.08 (30)		
	B	5.77 (25)		
	C	5.00 (27)		
F(%)	D	76.0 (28)		

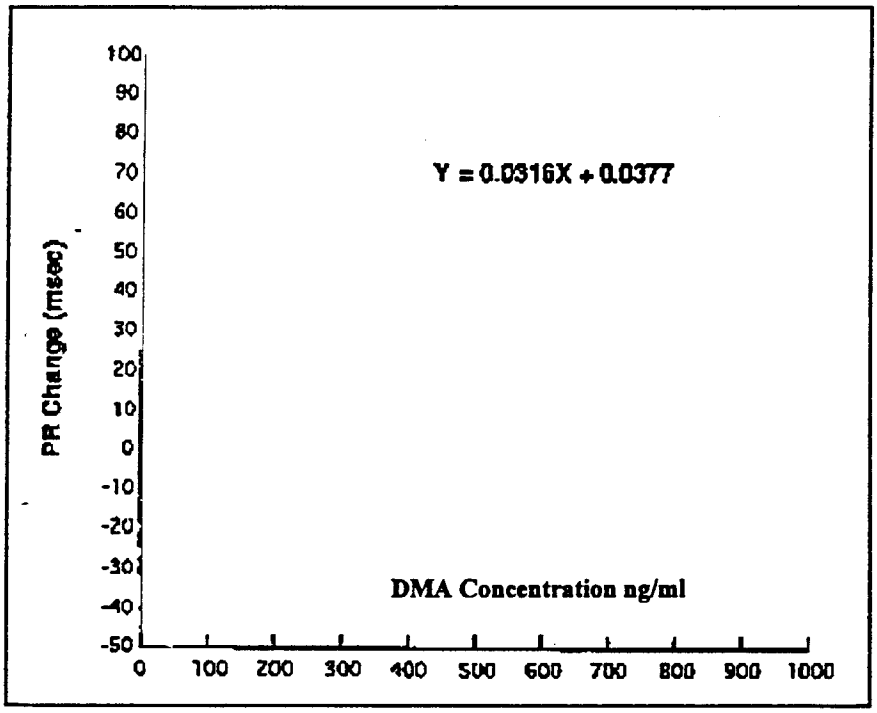
The reduction of DM to the major metabolite, DMA is a stereoselective process. The R(+) DMA represented the majority of DMA in plasma as the plasma $AUC_{0-\infty}$ and Cmax of R(+) DMA were approximately 3 to 4 times higher than those of S(-) DMA, respectively. The plasma $AUC_{0-\infty}$ of both R(+) and S(-) DMA increased proportionally with dose over the iv dose range of 50 to 200 mg DM. The increase in Cmax for R(+) DMA after administration of 50 to 200 mg DM appears to be proportional to dose, however a less proportional increase in Cmax was observed for S(-) DMA. For R(+) DMA, two fold increase in dose from 50 to 100 mg and from 100 to 200 mg resulted in 1.8 and 2.0 fold increase in Cmax, respectively. For S(-) DMA, two fold increases in dose from 50 to 100 mg and from 100 to 200 mg resulted in 1.6 and 1.9 fold increase in Cmax, respectively.

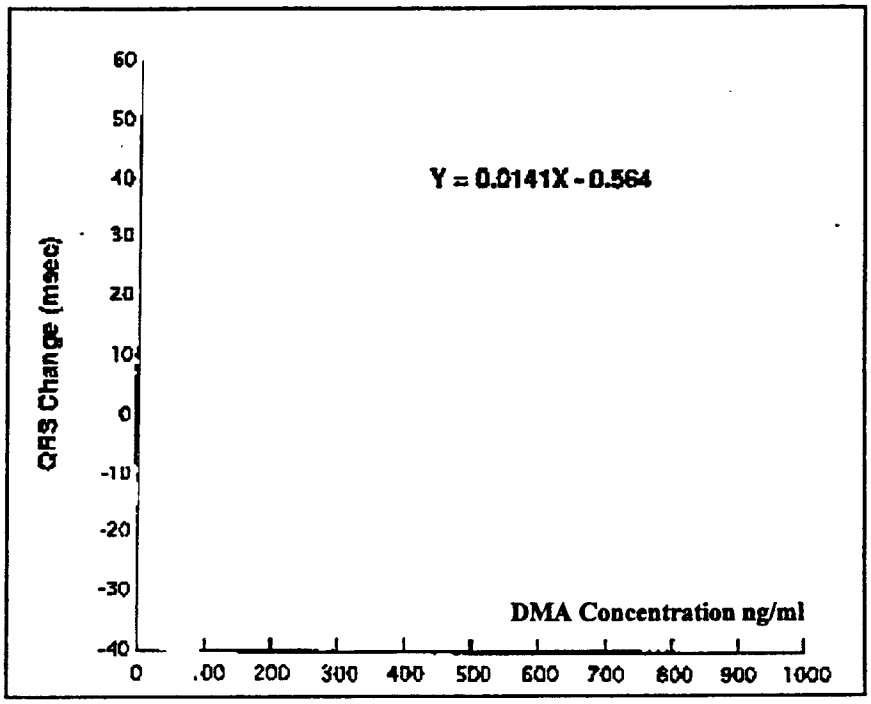
PK-PD

Approximately 30 % and 22 % of the dose were excreted in urine as DMA following iv and oral administration of DM, respectively. The majority (>86 %) of DMA was excreted in urine as R(+) DMA. Urinary excretion of total, R(+) and S(-) DMA was similar over the iv dose range

studied.

Acute and reversible changes in PR interval and QRS duration observed after 50 to 200 mg IV and 200 mg oral doses of DM were linearly related to plasma concentrations of DMA (Table 1 and 2 summarize the NONMEM model building procedure). The estimated slope for the PR change with plasma DMA concentrations for individual subjects ranged from msec/ng/ml with mean population mean of 0.0316 msec/ng/ml. Those for QRS change ranged from with a population mean of 0.0141 msec/ng/ml.The slope for both PR and QRS changes were positive in most subjects (23 out of 24), indicating PR and QRS changes increase with an increase in plasma concentration of DMA. The range of slopes for PR and QRS changes were small, indicating that small changes in PR interval and QRS duration are predicted with large changes in the plasma DMA concentration. The population predicted changes in PR interval and QRS duration over the plasma DMA concentrations observed following 50 to 200 mg IV and 200 mg oral administration of DM were less than 26 and 11 msec, respectively. The route of administration (iv and oral) had no effect on the magnitude of PR or QRS changes with plasma concentrations of DMA.





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Conclusion:

1. The plasma AUC_{0-} of DM increased proportionally with dose following iv administration of 50 to 200 mg DM.

2. The plasma AUC_{0-} and Cmax of DMA increased proportionally with dose after iv administration of 50 to 200 mg DM. The plasma AUC_{0-} of DMA was approximately 12 times higher than of DM.

3. The R(+) DMA accounted for the majority of DMA present in plasma (> 75 %) and urine (>86 %). The plasma AUC_{0-} of both R(+) and S(-) DMA increased proportionally with dose after iv administration of 50 to 200 mg DM.

4. Reversible changes in PR interval and QRS duration observed following 50 to 200 mg IV and 200 mg oral administration of DM were linearly related to plasma concentrations of DMA. The predicted increase in PR interval and QRS duration for normal subjects over the IV dose range of 50 to 200 mg DM was less than 26 msec and 11 msec, respectively.

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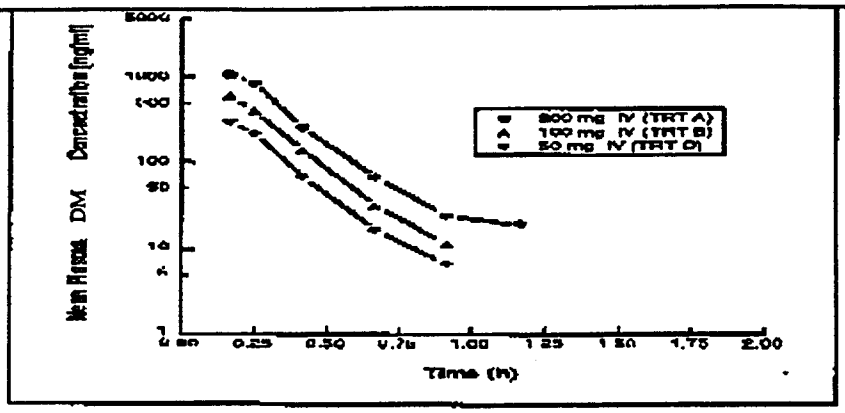


Figure 1. Mean Plasma Concentration versus Time Plots for DM (N=23)

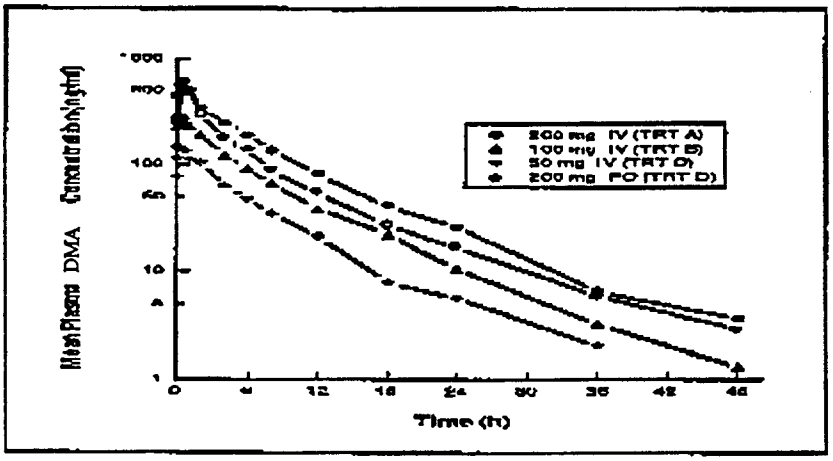


Figure 2. Mean Plasma Concentration versus Time Plots for Total DMA (N=24)

Dose Proportionality of Dolasetron after Single and Multiple Administration to Normal Volunteers

Study: MCPR0081

Objectives: To determine the dose proportionality and extent of accumulation of DM and DMA

Formulation: A 10 mg/ml injectable solution of DM was administered orally for all treatments.

Batch No.	C-49127
Site of Manufacturing	
Date of Manufacturing	10-15-91
Dosage Form	Injectable Solution
Strength	10 mg/ml
Batch Size	
Comments	Pilot lot

Study Design and Sampling: The study was an open-label, randomized, three-way cross-over design with 18 healthy, male subjects between the ages of years. Each subject received one of the following treatments in each period:

Treatment A: 200 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.
Treatment B: 100 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.
Treatment C: 50 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.

Serial blood and urine samples were collected for 48 hours after the single dose on day 1 and after the last multiple dose on day 7.

Results: Figures 1 and 2 show mean plasma concentration versus time plots for DMA observed after single (day 1) and multiple (day 7) oral administration of 50 to 200 mg DM, respectively. The following tables show the mean pharmacokinetic parameters of DMA obtained after single dose and at steady state.

The parent drug DM, was not detected in urine following single and multiple oral doses of 50 to 200 mg DM. After single dose of DM, approximately , of the dose was excreted in urine as DMA. The majority (> 87 %) of DMA was excreted in urine as R(+) DMA. Approximately 2 % of the dose was excreted in urine as 5'OH-DMA, and as 6'OH-DMA. The urinary excretion of R(+) and total DMA was slightly igher after 200 mg dose than after 100 mg and 50 mg doses.

Subject #5 in this study showed very low urinary excretion of 5'OH and 6'OH DMA after both single and multiple oral doses of DM compared to other subjects in the group. Based on genotyping information, this subject was identified as a poor metabolizer (PM) for cytochrome P450 IID6 substrates. After single oral dose of DM, the plasma $AUC_{0-\infty}$ of DMA for this subject was about 2 times higher than the mean of other normal subjects in the group. At steady state, the plasma AUCss of DMA for this subject was within the range observed in other normal subjects in the group. The Cmax of DMA for this subject was not different from that observed in other normal subjects in the group after both single and multiple oral doses of DM. The increase in $AUC_{0-\infty}$ without proportional change in Cmax could be due to multiple elimination routes (i.e. renal excretion, hydroxylation, glucuronide conjugation etc.)

involved in elimination of DMA.

Table 1. Mean pharmacokinetic parameters of treatments A, B and C for DMA.

Variable	TRT	Mean	% CV
AUC_{0-} (ng.h/ml)	A	2735.1	38
	B	1181.4	39
	C	613.3	42
Cmax (ng/ml)	A	520.4	26
	B	224.6	24
	C	106.9	20
tmax (h)	A	0.81	14
	B	0.70	30
	C	0.72	24
$t_{1/2}$ (h)	A	8.86	19
	B	7.47	21
	C	7.74	36
CLapp,po (ml/min/kg)	A	13.3	36
	B	15.5	35
	C	15.2	38
CL_R (ml/min/kg)	A	2.69	31
	B	2.45	24
	C	2.16	20

Variable	TRT	Mean	% CV
AUCss (ng.h/ml)	A	3097.0	36
	B	1339.2	33
	C	672.9	42
$Cmax_{ss}$ (ng/ml)	A	579.3	34
	B	235.5	21
	C	108.1	25
$tmax_{ss}$ (h)	A	0.90	36
	B	0.91	49
	C	0.77	27
$t_{1/2}$ (h)	A	8.35	23
	B	9.00	29
	C	7.17	23
CLapp,po (ml/min/kg)	A	11.5	30
	B	13.4	34
	C	13.7	37
CL_R (ml/min/kg)	A	2.90	35
	B	2.31	22
	C	2.17	30

Conclusions:

1. DMA exhibited dose proportionality with respect to AUC and Cmax over a DM dose range of 50 to 200 mg, at single and multiple doses.
2. The accumulation index for DMA for orally administered DM (QD) over a dose range of 50 to 200 mg ranged from

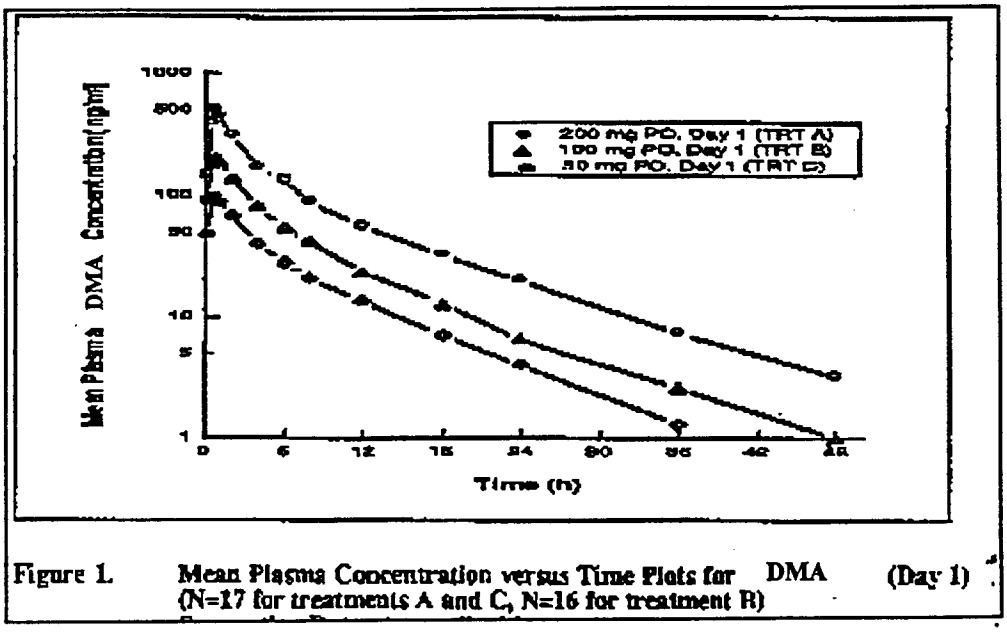


Figure 1. Mean Plasma Concentration versus Time Plots for DMA (Day 1)
(N=17 for treatments A and C, N=16 for treatment B)

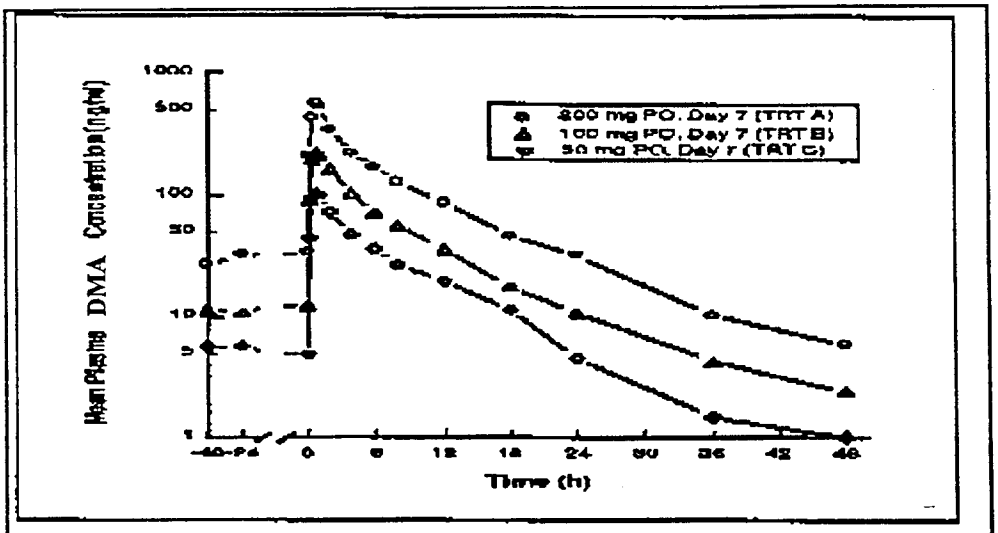
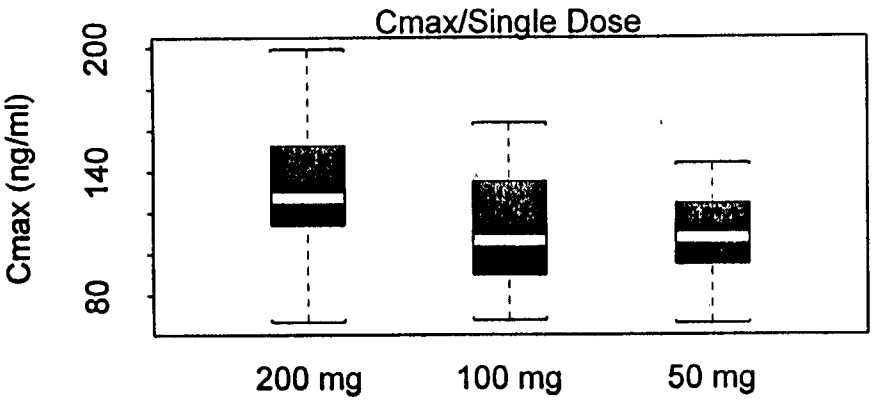
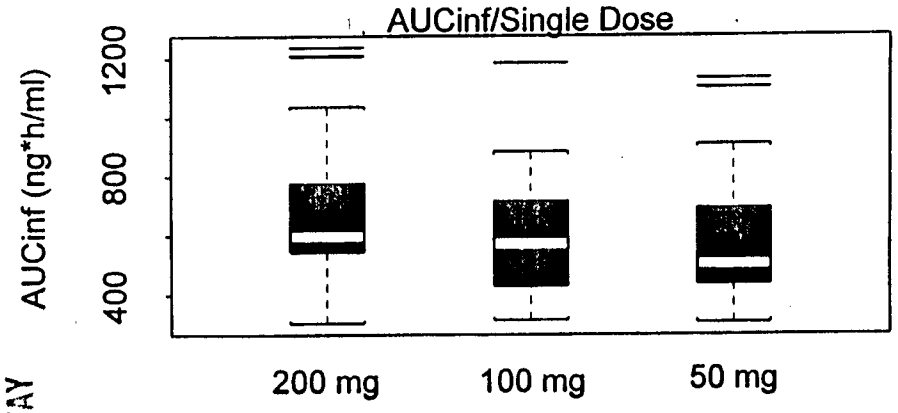
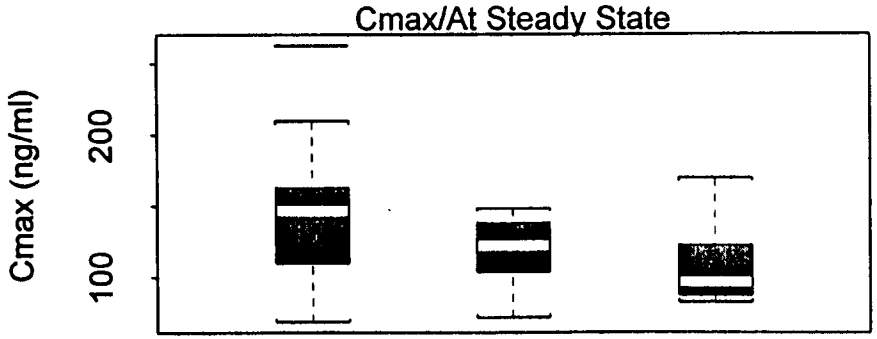


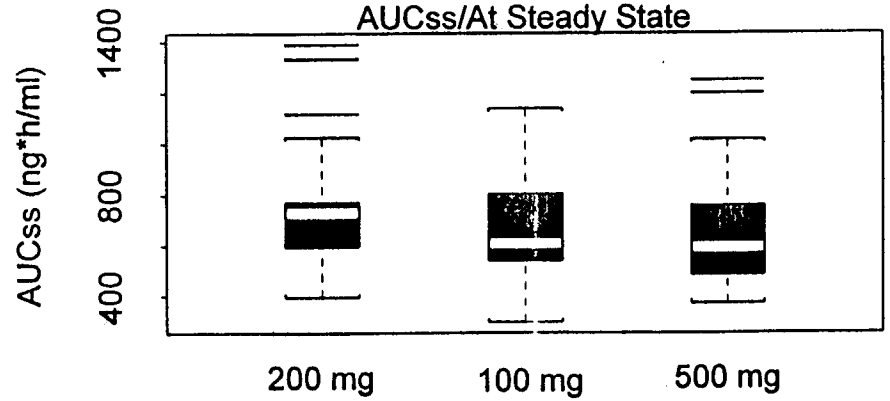
Figure 2. Mean Plasma Concentration versus Time Plots for DMA (Day 7)
(N=17 for treatments A and C, N=16 for treatment B)

Dose Proportionality/PK Parameters Normalized to 50 mg









A Randomized Double-Blind Placebo-Controlled Study of the Effects of Increasing Infusion Rates on Tolerance to and Pharmacokinetics of Intravenous Dolasetron Mesylate in Healthy Males

Study: MCPR0082

Objectives: To evaluate the safety and tolerance of healthy males to intravenous DM infused at increasing rates; assess the effects of infusion rate on the pharmacokinetics and pharmacodynamics of IV DM.

Study Design and Sampling: The study was conducted as a double blind, placebo-controlled trial in which a fixed dose of 100 mg IV DM or placebo controlled trial in which a fixed dose of 100 mg IV DM or placebo was infused into 3 parallel groups of healthy male volunteers (12 active/4 placebo for treatments A and C; 13 active /4 placebo for treatment B). The rate of infusion of DM was increased for each successive group of subjects as:

Treatment A: 100 mg dose administered over 2 minutes (50 mg/min)
Treatment B: 100 mg dose administered over 1 minutes (100 mg/min)
Treatment C: 100 mg dose administered over 0.5 minutes (200 mg/min)

Ten (10) ml of blood samples were taken just prior to and at 5 min, 15 min, 30 min, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr after the end of infusion. Twelve-lead ECGs were obtained on study day 1 at predose and at 5 min, 15 min and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after beginning of DM infusion.

Results: Table 1 shows the mean pharmacokinetic parameters of DM and Figure 1 shows the mean plasma DM concentration versus time plots following three treatments. Table 2 shows the mean pharmacokinetic parameters of DMA and Figure 2 shows the mean plasma DMA concentration versus time plots following three treatments.

For pharmacodynamic analysis, data form all infusion rate groups were combined since no consistent differences among the three infusion rates were observed. Figures 3 and 4 show the changes in PR and QRS intervals are linearly related to DMA concentrations observed after administration of 100 mg dose of DM in this study.

Conclusion: Pharmacokinetics of DM and DMA were not significantly altered with increase in infusion rate form 50 to 200 mg/min of dolasetron mesylate. The changes in PR and QRS intervals were best described by the changes in plasma DMA concentrations.

Table 1. Mean Pharmacokinetics of Dolasetron			
Parameter	*Treatment A*	*Treatment B*	*Treatment C*
t1/2 (min)	8.91 (5.40)@	9.91 (47.96)	9.16 (10.46)
AUC(0-∞) (ng.hr/ml)	153.13 (20.53)	190.04 (23.26)	139.79 (25.17)
CL (ml/min)	8393.23 (21.85)	6811.86 (22.74)	9413.71 (28.33)
CL (ml/min/kg)	113.71 (22.45)	95.32 (20.78)	130.04 (28.61)
Vd (L/kg)	1.47 (26.47)	1.34 (39.25)	1.75 (38.36)

@ Values in parentheses are CV, %.

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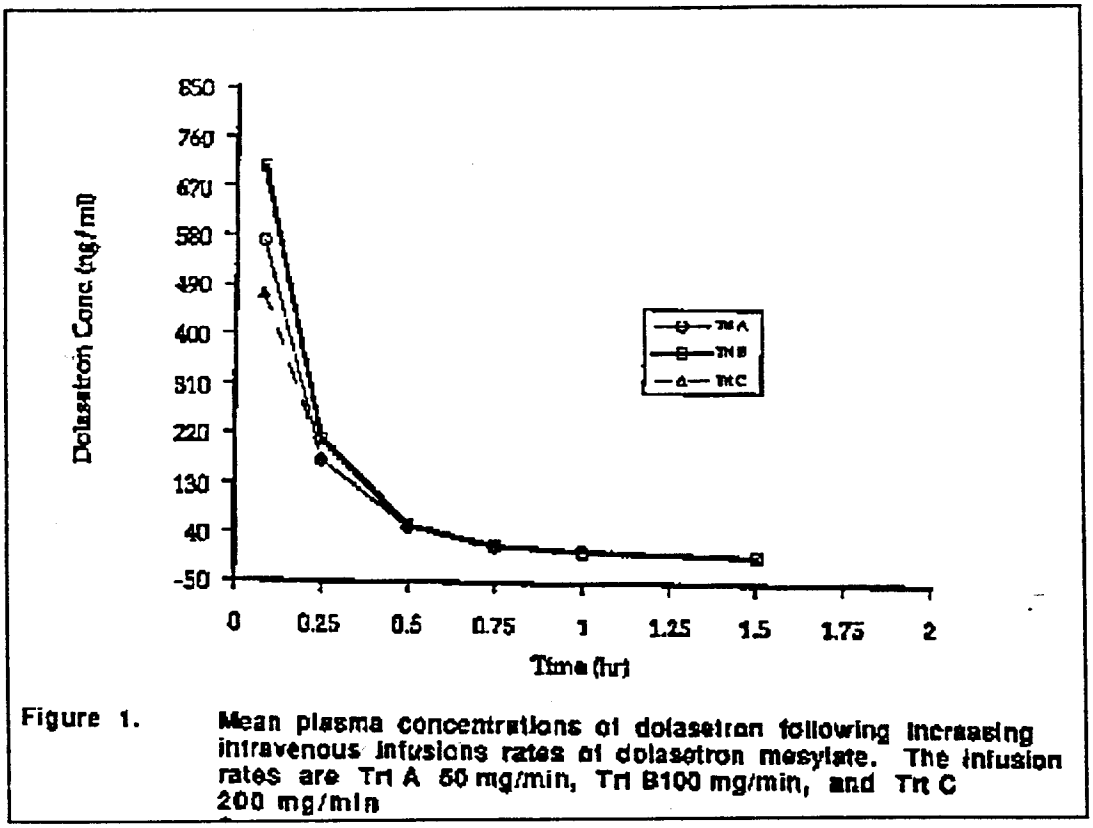

Figure 1. Mean plasma concentrations of dolasetron following increasing intravenous infusions rates of dolasetron mesylate. The infusion rates are Trt A 50 mg/min, Trt B100 mg/min, and Trt C 200 mg/min

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Table 2. Mean Pharmacokinetics of MDL 74,156 after IV Administration of Dolasetron Mesylate

Parameter	*Treatment A*	*Treatment B*	*Treatment C*
t1/2	7.59	9.02	7.18
(hr)	(19.70)@	(21.03)	(20.54)
Cmax	273.8	319.85	290.9
(ng/ml)	(22.75)	(21.86)	(21.82)
tmax	0.40	0.52	0.50
(hr)	(32.52)	(30.84)	(42.64)
AUC(0'∞)	1679.1	1917.40	1601.2
(ng.hr/ml)	(38.04)	(46.62)	(18.97)
CLapp	823.42	733.84	806.68
(ml/min)	(30.06)	(28.73)	(23.53)
CLapp	11.15	10.20	11.13
(ml/min/kg)	(25.65)	(27.20)	(22.43)
Vdapp	7.12	7.92	7.00
(L/kg)	(21.04)	(34.74)	(40.02)

@ Values in parentheses are CV,%.

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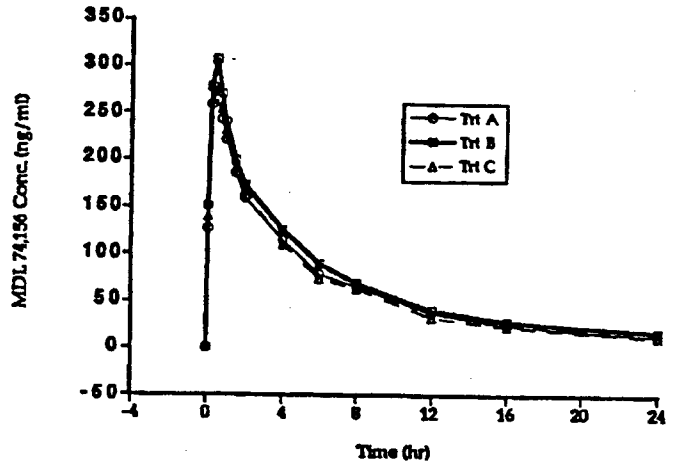


Figure 2. Mean plasma concentrations of MDL 74,156 following increasing intravenous infusion rates of dolasetron mesylate. The infusions rates are Trt A 50 mg/min, Trt B 100 mg/min, and Trt C 200 mg/min

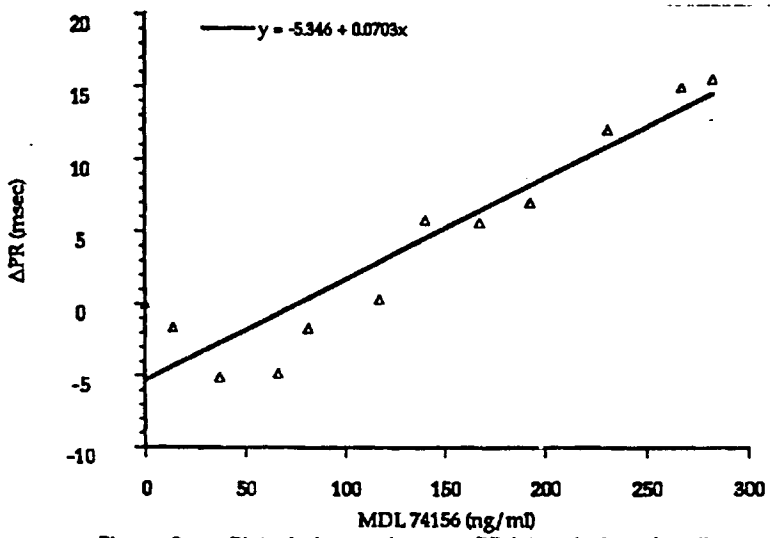


Figure 3. Plot of changes in mean PR intervals from baseline vs MDL 74,156 plasma mean concentrations. The solid line is a linear least square fit to the data.

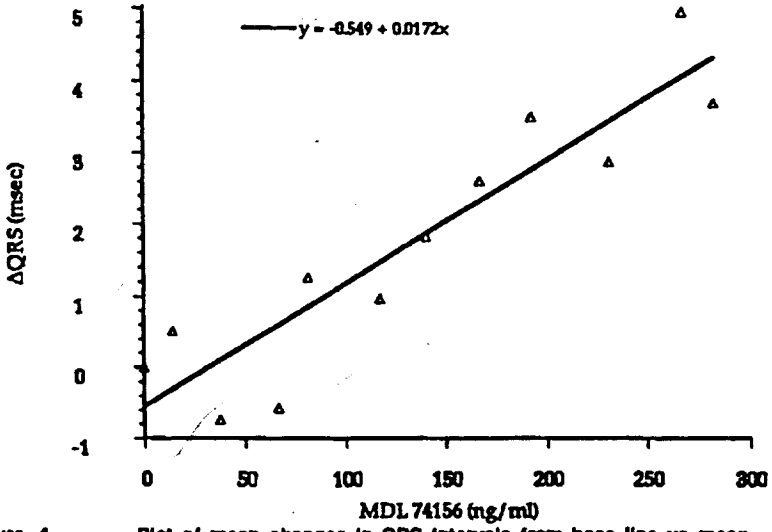


Figure 4. Plot of mean changes in QRS intervals from base line vs mean MDL 74,156 plasma concentrations. The solid line is a linear least square fit to the data.

Pharmacokinetic Evaluation of Single Oral Doses of DM for the Prevention of Acute (24 hour) Nausea and Vomiting in Pediatric Cancer Patients Receiving Moderately to Highly Emetogenic Chemotherapy

Study #: AN-PD-0292

Objectives: To evaluate the pharmacokinetics (PK) of oral DM to support the selection of the appropriate single oral dose in pediatric cancer patients.

Study Design: Doses of 0.3, 0.6, 1.2, 1.8 or 2.4 mg/kg were to be evaluated for the prevention of acute emesis in pediatric patients receiving moderately to highly emetogenic chemotherapy.

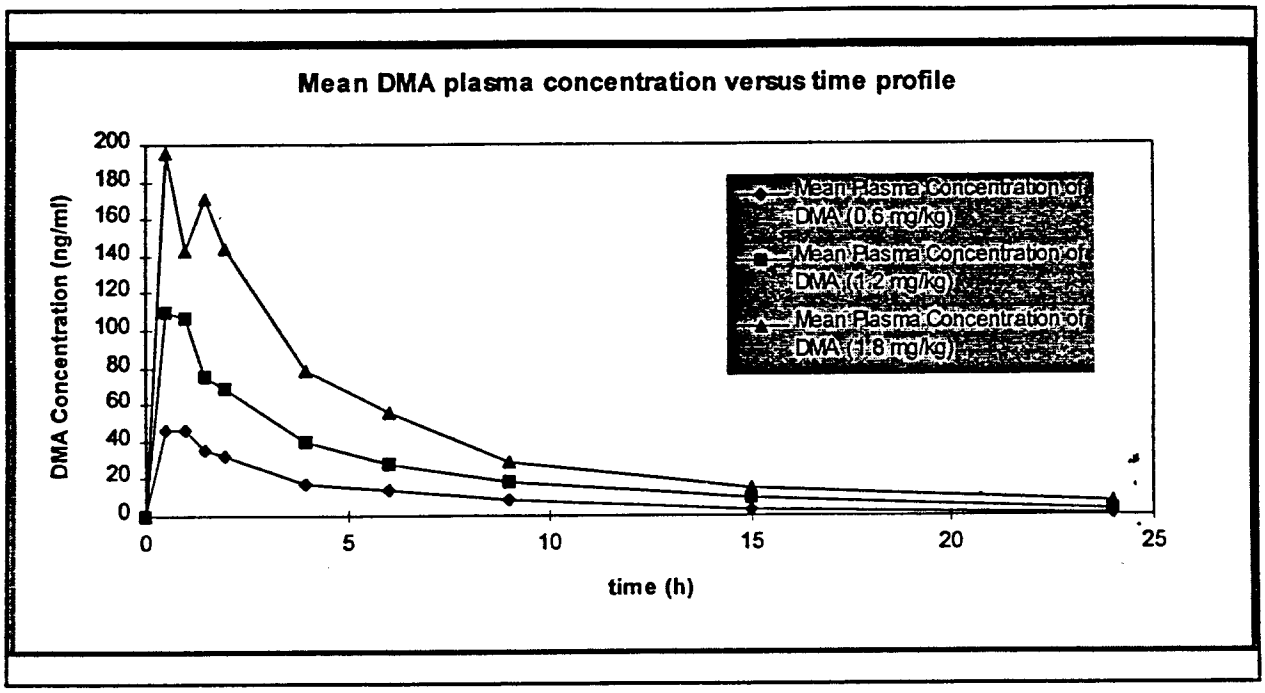
Protocol Changes: Sub-optimal efficacy results were obtained at the 0.6 mg/kg dose, so the 0.3 mg/kg dose level was not evaluated and the protocol was amended to remove this dose. Due to slow recruitment, a decision was made by the sponsor to finish the study without 2.4 mg/kg dose group as no patient had been recruited for this dose.

A total of 32 pediatric cancer patients received oral doses of 0.6 (N=9), 1.2 (N=13), or 1.8 (N=10) mg/kg of DM with apple or apple-grape juice 30 minutes prior to receiving emetogenic chemotherapy. Most of the pediatric patients (30/32) were caucasian. Serial blood samples were taken just prior to dosing, and at 0.5 (30 min), 1, 1.5, 2, 4, 6, 9, 15 and 24 hours after the end of DM oral administration.

Formulation: DM was supplied to each clinic in ampules containing 10 ml of a 20 mg/ml solution of the drug. Each dose was administered either undiluted, or diluted in a sufficient quantity of apple or apple-grape juice to make 20 ml of oral dosing solution. If the dose was administered undiluted, it was followed by apple or apple-grape juice without restriction on the quantity of juice.

Results: The mean DMA plasma concentration-time profiles for the oral doses administered in

this study are shown in the following Figure.



The following table summarizes mean (%cv) PK parameters for DMA.

Parameter	Pediatric Patients Dose (Oral)			Healthy Adult Volunteer Dose (Oral) (from study MCRP0081)		
	0.6 mg/kg N=9	1.2 mg/kg N=13	1.8 mg/kg N=10	0.65 mg/kg N=17	1.3 mg/kg N=16	2.6 mg/kg N=17
Cmax (ng/ml)	54.7 (38)	135.4 (52)	264.0 (58)	106.9 (20)	224.6 (24)	520.4 (26)
tmax (h)	1.0 (50)	0.9 (56)	0.9 (55)	0.72 (24)	0.70 (30)	0.81 (14)
AUC_{0-} (ng.h/ml)	252.8 (46)	578.0 (72)	1085.3 (79)	613.3 (42)	1181.4 (39)	2735.1 (38)
$t_{1/2}$ (h)	5.21 (30)	6.07 (39)	6.19 (34)	7.74 (360	7.47 (21)	8.86 (19)
$CL_{app,po}$ (ml/min/kg)	37.4 958)	40.4 (61)	32.4 (58)	15.2 (38)	15.5 (35)	13.3 (36)

The following table shows mean apparent oral clearances, half-lives and Tmax by age.

Parameter	Age Group		
	Pediatric Patients 3-11 years (N=19)	Pediatric Patients 12-17 years (N=13)	Healthy Adults 20-43 years (N=18)
$CL_{app,po}$ (ml/min/kg)	44.24 (49)	26.52 (67)	14.7 (36)
$t_{1/2}$ (h)	5.50 (39)	6.39 (30)	8.04 (27)
tmax (h)	0.93 (54)	0.97 (52)	0.75 (23)

Conclusion: For comparable doses, the mean apparent oral clearance values for the pediatric cancer patients ages 3-11 years and 12-17 years were 3 and 1.8 times greater than those observed in normal healthy adult volunteers. Maximum plasma concentration (Cmax) in pediatric cancer patients were approximately lower than those observed in healthy adults.

Pharmacokinetic Evaluation of a Single Oral Dose (1.2 mg/kg) of Dolasetron Mesylate in Children Undergoing Elective and Uncomplicated Surgery Under General Anesthesia

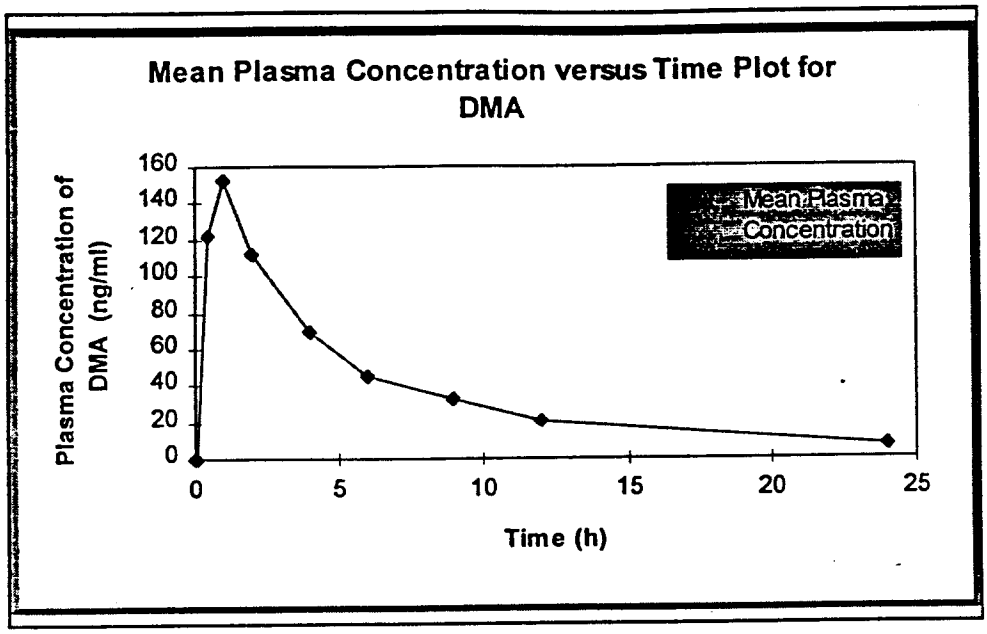
Study: AN-PD--0993

Formulation: The manufacturing history of the 20 mg/ml injectable solution (used orally) in the study is as follows:

Batch No.	92A014
Site of Manufacturing	
Date of Manufacturing	March 1992
Dosage Form	Injectable Solution
Strength	20 mg/ml
Batch Size	

Study Design and Sampling: This was an open-label, single center study. Twelve subjects (2-12 yr) received a single oral dose (1.2 mg/kg) as a solution, administered 1 to 2 hours preoperatively. Serial plasma samples were collected for 24 hours (0.5, 1, 2, 4, 6, 9, 12 and 24 hr) after dosing.

Results: The following figure presents mean plasma concentration-time plot for DMA.



The following table summarize the mean (%cv) PK parameters for DMA following oral Administration of 1.2 mg/kg DM in children undergoing general anesthesia for surgery.

Parameters	Mean (%CV)
AUC_{0-} (ng.h/ml)	933 (61)
Cmax (ng/ml)	159 (32)
tmax (h)	1.39 (70)
CLapp,po (ml/min/kg)	20.77 (49)
t1/2 (h)	5.89 (24)

Conclusions: Mean apparent clearance was 34 % greater and half-life was 21 % shorter in pediatric surgical patients than in healthy adult volunteers.

Pharmacokinetic Evaluation of Single IV Doses of DM for the Prevention of Acute (24 hour) Nausea and Vomiting in Pediatric Cancer Patients Receiving Moderately to Highly Emetogenic Chemotherapy

Study: AN-PD-0192

Objectives: To determine the appropriate single IV doses of DM for children by conducting pharmacokinetic (PK) assessments.

Formulation: DM was supplied to each clinic in ampules containing 10 ml of a 20 mg/ml

Study Design: The study was conducted as an open-label dose escalation study in pediatric patients between the ages of years old receiving moderately to highly emetogenic chemotherapy. A total of 46 pediatric cancer patients received IV infusion doses of 0.6 (n=10), 1.2 (n=12), 1.8 (n=12) or 2.4 (n=12) mg/kg of DM in Normal Saline USP. Most of (42/46) of pediatric patients were caucasian.

Serial blood samples were taken just prior to the beginning of infusion, and at 0.08 (5 min), 0.5, 1, 2, 4, 6, 9, 15 and 24 hours after the end of DM infusion.

Results: Figure 1 shows the mean DMA plasma concentrations after a single IV infusion dose of DM in pediatric cancer patients. Table 1 summarize the PK parameters of DMA. The following table shows the mean apparent clearance, half-life and Tmax by age (3 to 11 years, 12 to 17 years and adults). Apparent clearance values are highest and half-lives are lowest in the youngest age group. For the 3-11 year and the 12-17 year age groups, mean apparent oral

clearances are 2 and 1.3 times greater, respectively, compared to healthy adults.

Parameter	Age Group		
	3 - 11 yr (n = 25)	12 - 17 yr (n = 21)	Healthy Adults (n = 24)
CLapp (ml/min/kg)	19.18 (30)	12.48 (37)	9.39 (30)
t1/2 (h)	4.36 (24)	5.50 (31)	7.18 (27)
tmax (h)	0.48 (42)	0.53 (39)	0.64 (54)

Conclusion:

1. Mean apparent clearance of DMA was between : in pediatric cancer patients than in normal healthy adult subjects for the iv dose range of DM.
2. The sponsor wants to propose that no dose adjustment is necessary in pediatric group, however, no justification is provided by the sponsor.

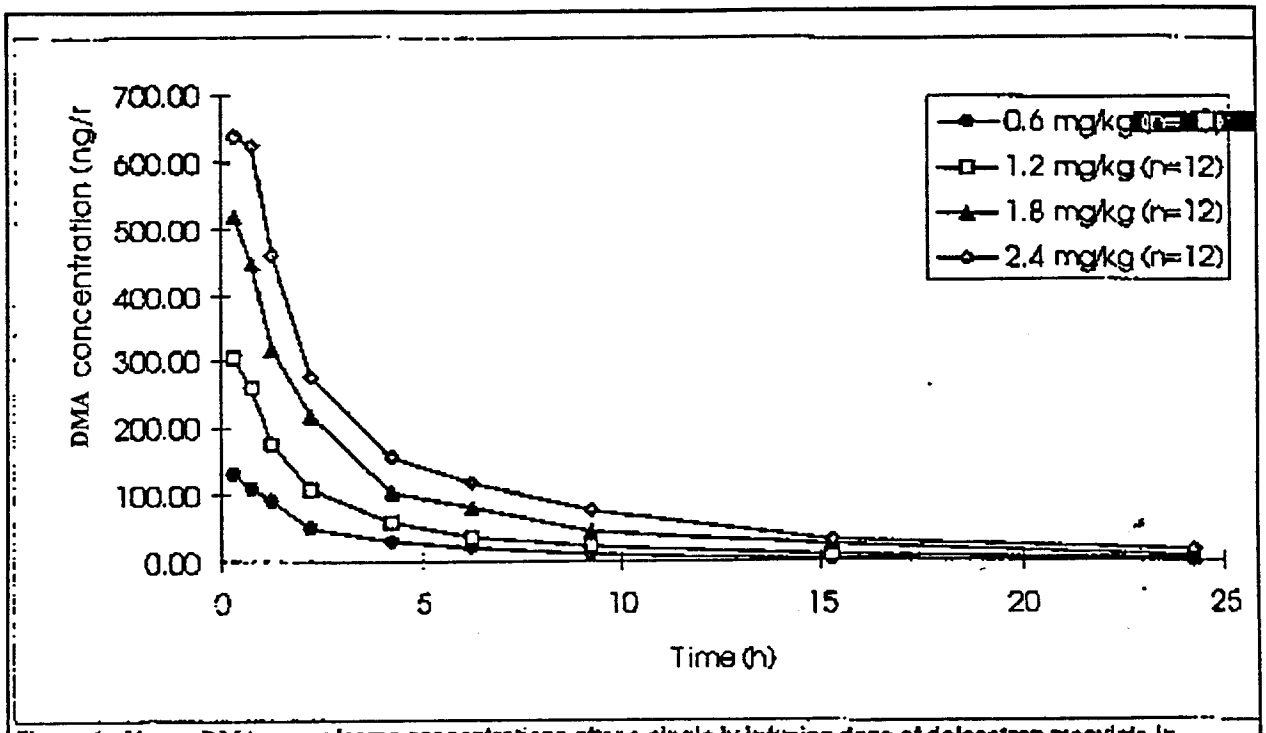


Figure 1. Mean DMA plasma concentrations after a single iv infusion dose of dolasetron mesylate in pediatric cancer patients (Source of Data: Appendix A)

Table 1. Mean* Pharmacokinetic Parameters of DMA After a Single iv Infusion Dose of Dolasetron Mesylate In Pediatric Cancer Patients and Healthy Male Volunteers

Parameter	Pediatric Patient Dose (iv)				Healthy Male Volunteer Dose (iv)** (Protocol MCPR0080)		
	0.6 mg/kg N=10	1.2 mg/kg N=12	1.8 mg/kg N=12	2.4 mg/kg N=12	~0.64 mg/kg N=24	~1.27 mg/kg N=24	~2.54 mg/kg N=24
C_{max} (ng/ml)	135.5 (24)	316.0 (34)	538.2 (45)	738.7 (53)	160.9 (29)	320.4 (25)	646.9 (29)
t_{max} (h)	0.41 (43)	0.52 (37)	0.47 (44)	0.61 (34)	0.62 (61)	0.62 (64)	0.67 (37)
AUC(0-∞) (h*ng/ml)	450.6 (37)	949.4 (36)	1881.7 (53)	2730.9 (73)	909.9 (31)	1796.6 (28)	3637.5 (33)
$t_{1/2}$ (h)	4.80 (25)	4.60 (35)	4.98 (19)	5.13 (40)	6.57 (33)	7.32 (24)	7.66 (22)
V_{app} (liters/kg)	7.43 (29)	6.80 (54)	5.89 (33)	5.91 (41)	5.00 (27)	5.77 (25)	6.08 (30)
CL_{app} (ml/min/kg)	18.83 (41)	17.17 (29)	14.29 (38)	14.65 (43)	9.31 (28)	9.39 (28)	9.48 (34)

*Percent coefficient of variation shown in parentheses
**Dose normalized by individual subject body weight (Doses 50, 100, and 200 mg, respectively
N: Number of observations

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.

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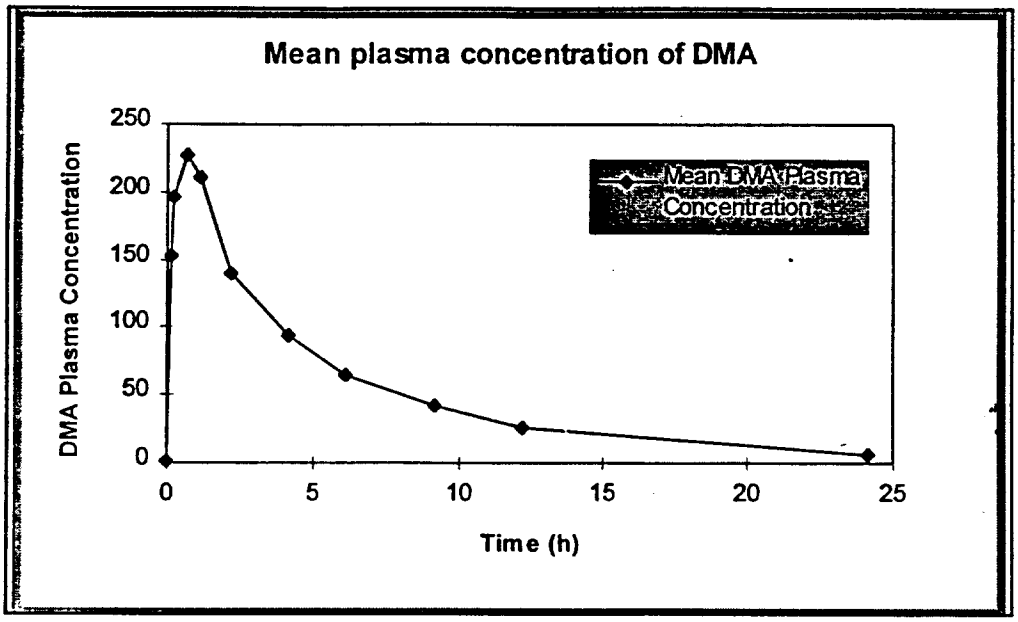

Parameters	Mean (%CV)
Cmax (ng/ml)	254.6 (22)
tmax (h)	0.63 (57)
$AUC_{0-\infty}$ (ng.h/ml)	1356.0 (42)
t1/2 (h)	4.77 (23)
CLapp (ml/min/kg)	13.13 (47)
Vapp (L/kg)	5.17 (43)

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.

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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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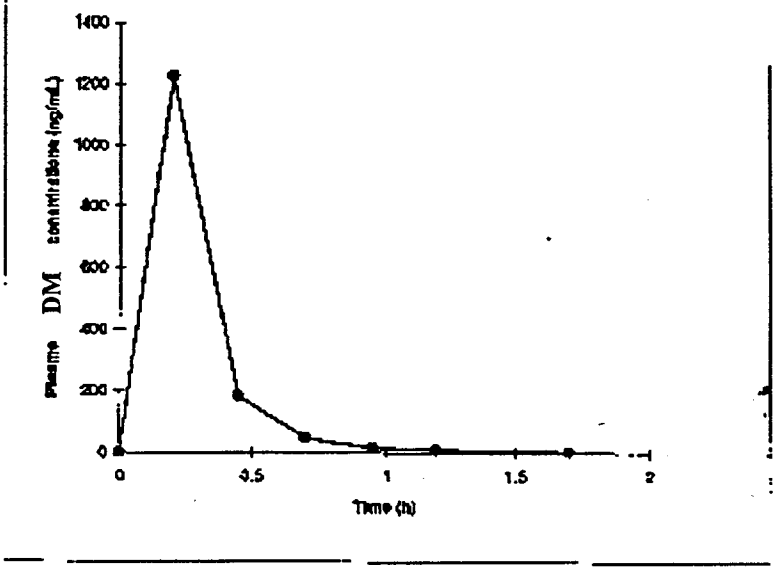

Figure 1. Mean Plasma Concentration vs. Time Plots for DM Following IV Administration (N=22).

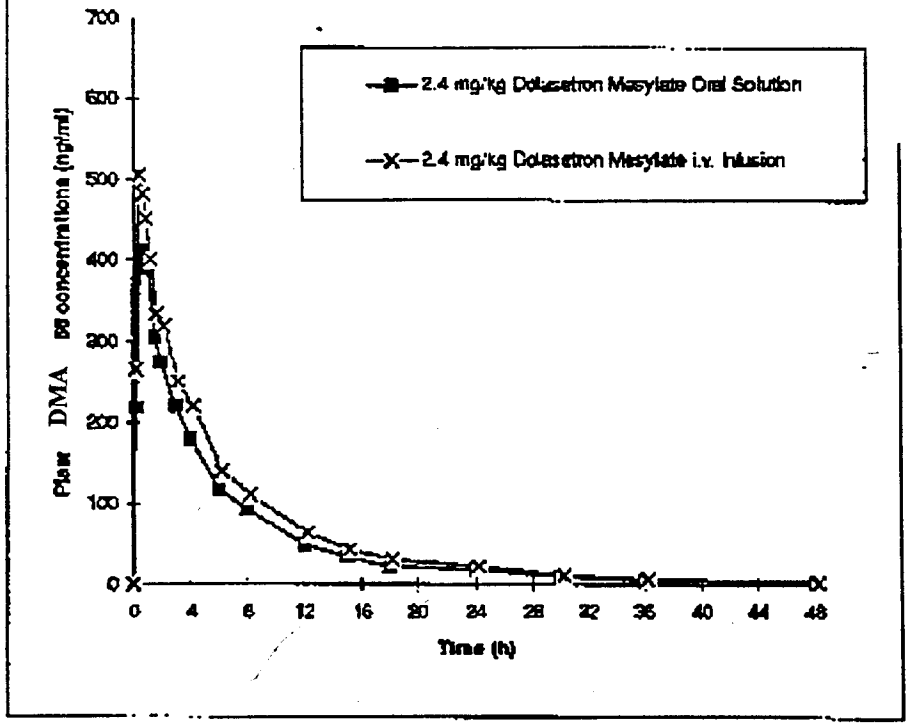

Figure 2. Mean Plasma Concentration vs. Time Plots for MDL 74,156 Following IV and Oral Administration (N=24) DMA

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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.

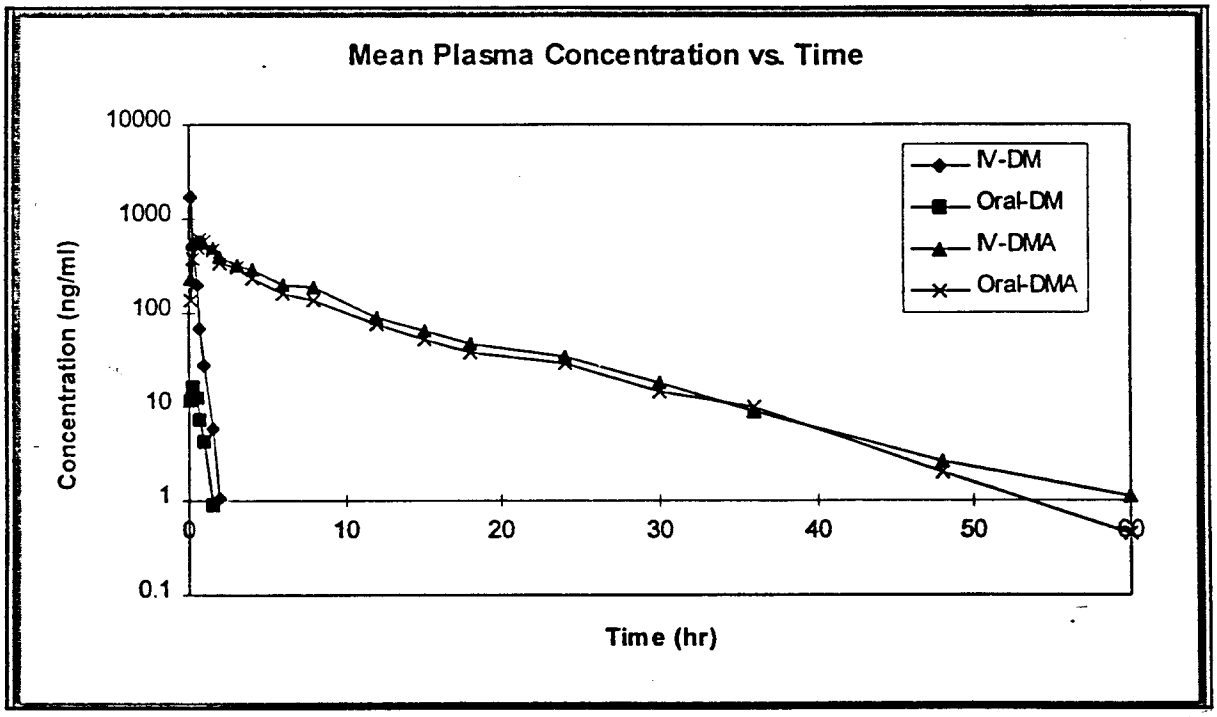


Table 1. Mean PK parameters of DM following single IV and P.O. doses of 2.4 mg/kg of DM

Parameters	IV	Oral
$AUC_{0\text{-last}}$ (ng.h/ml)	395.27 ± 177.33	11.17 ± 5.81
AUC_{0-} (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.

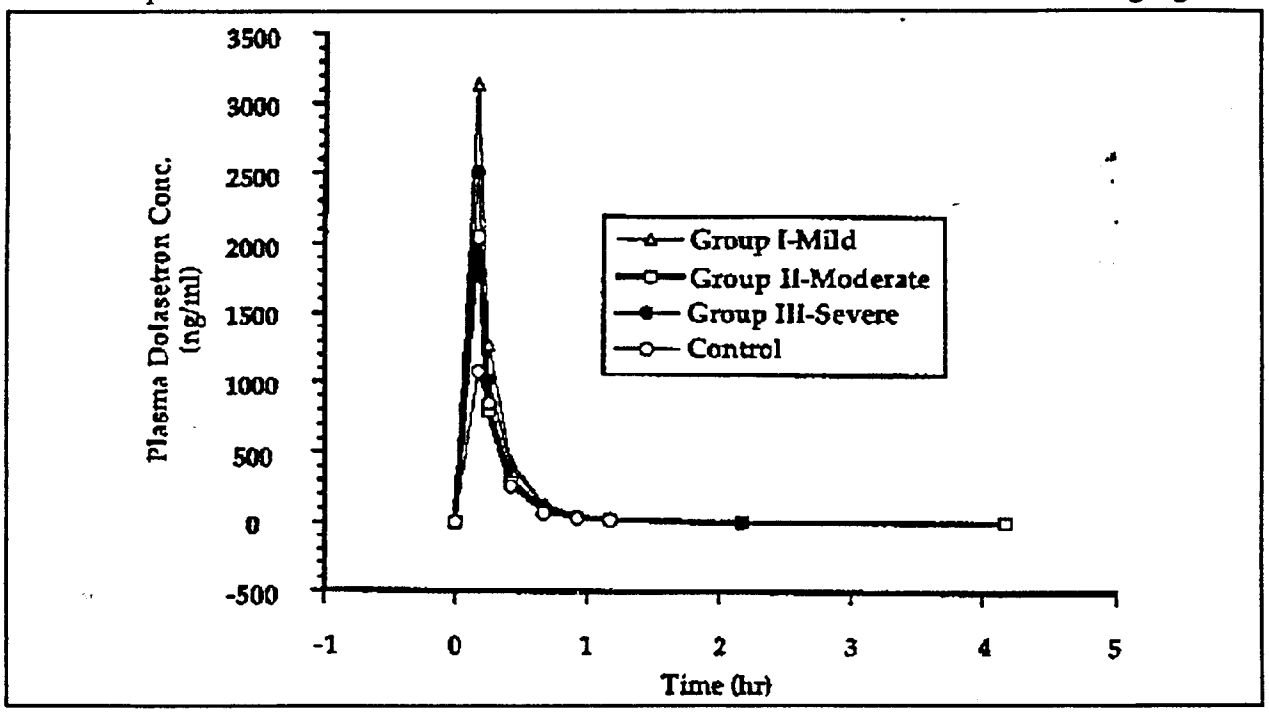
Study Design and Sampling: The study was conducted as an open-label, randomized, stratified, two-way complete cross over design. The two treatments were administered to 36 subjects assigned to one of three renal function groups. Renal function was assessed from each subject's 24 hour creatinine clearance.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

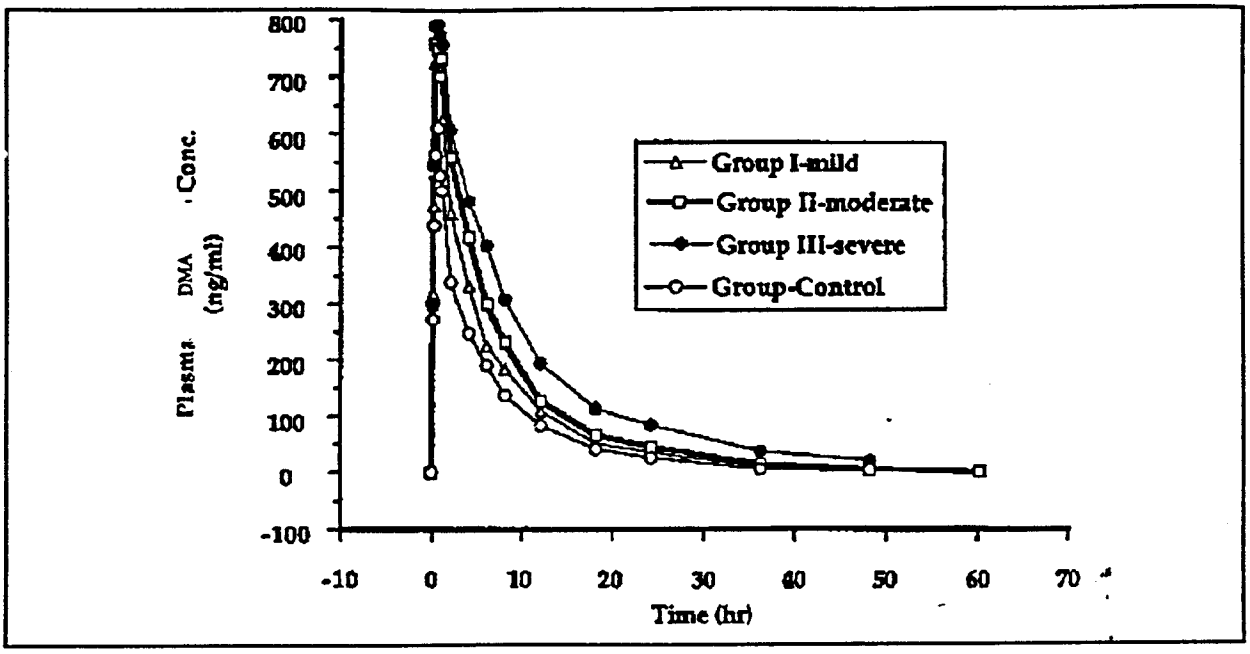
Results: Mean plasma DM concentrations after IV administration are shown in the following figure.



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

Group	Control	Mild	Moderate	Severe
AUC_{0-} (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.

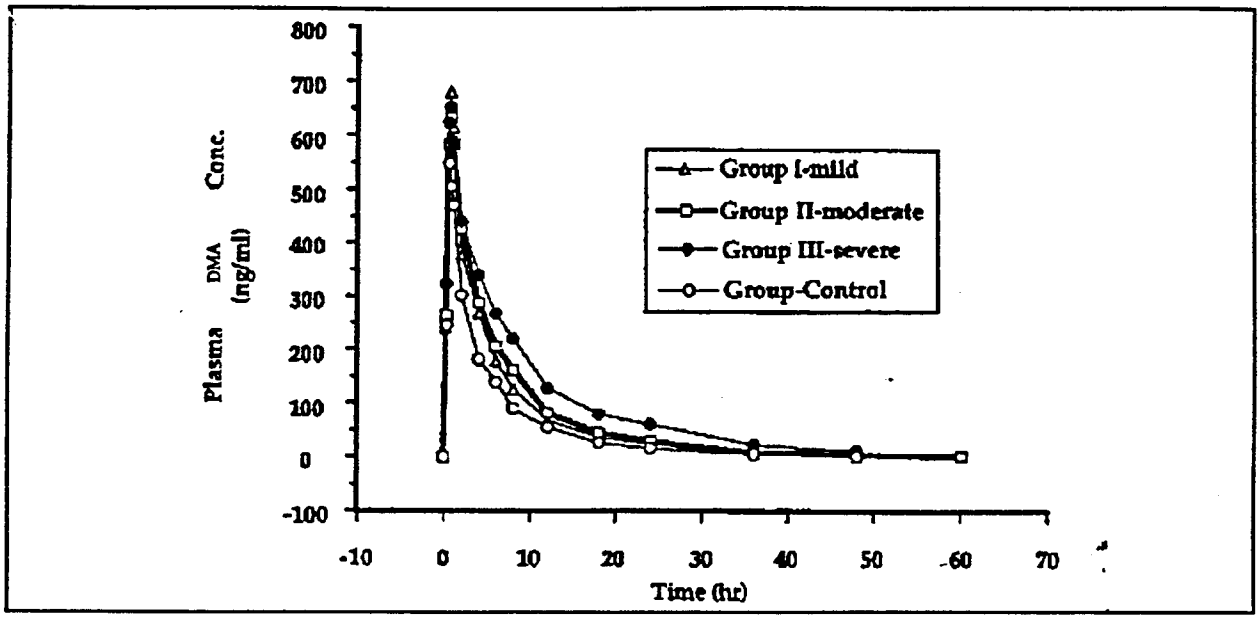


The pharmacokinetic parameters for DMA after IV administration of DM are summarized in the following table.

Group	Control	Mild	Moderate	Severe
AUC_{0-} (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-} 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)

$\frac{12.88-7.2}{12.88} \times 100 = 44\%$

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, $AUC_{0-\infty}$ 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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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	

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*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.

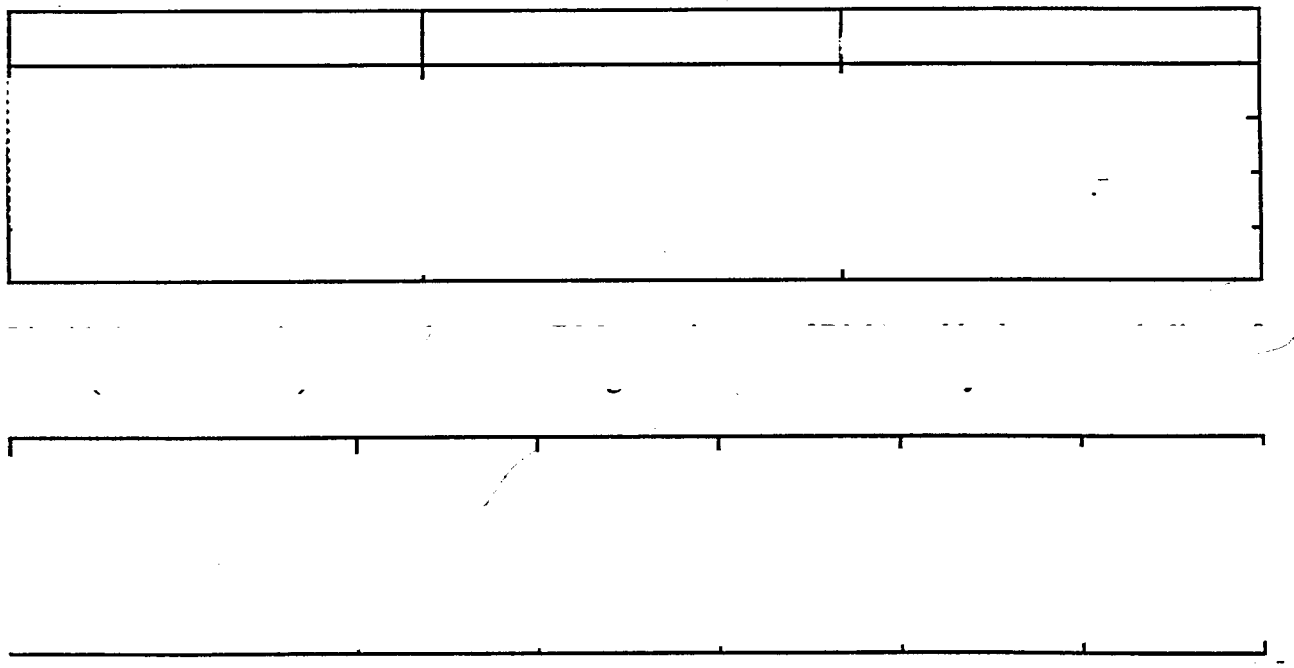
Study Design and Sampling: This was an open-label, randomized, three-way cross-over design with 18 healthy, male subjects between the Seventeen subjects completed all study procedures and one subject was dropped after two periods for a non drug-related illness.

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

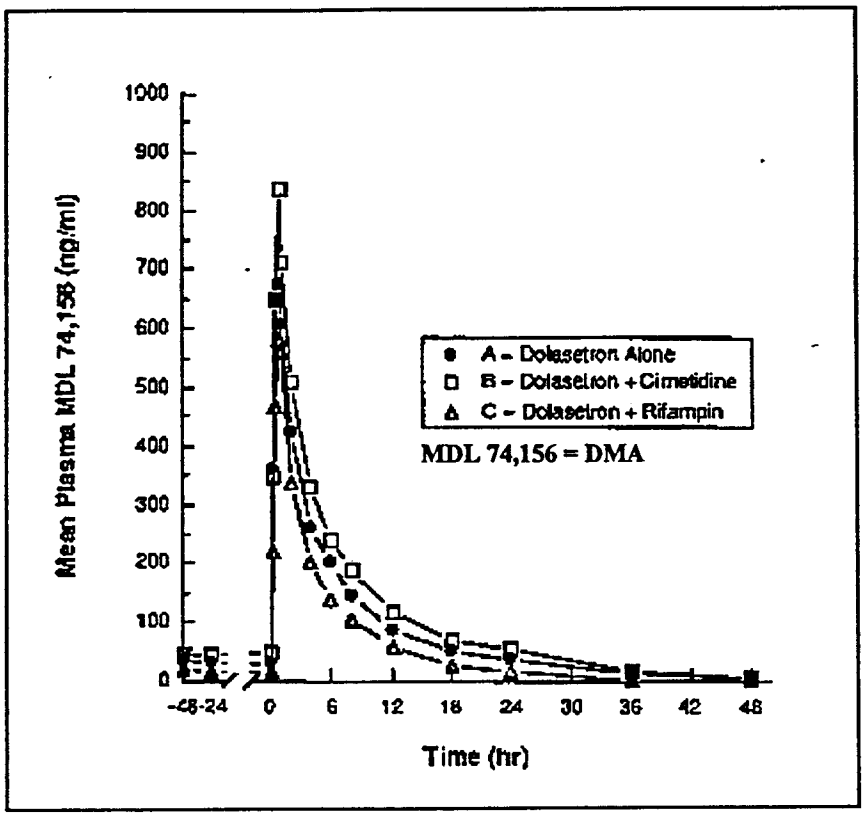
Treatment B: 200 mg DM oral solution given at 8 AM on days 1 through 7 and one 300 mg cimetidine tablet given at 2 AM, 8 AM, 2 PM and 8 PM starting at 8 AM on day 1 through 2 AM on day 8.

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 η_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 ω^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 ε_{ij} are independent, identically distributed errors with a mean of 0 and a variance of σ^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
$\theta 1$	L/hr/kg	0.607	7.68	0.514	0.700
$\theta 2$	Coefficient for Race	0.303	31.85	0.110	0.496
$\theta 3$	Coefficient for Atenolol	-0.184	43.64	-0.345	-0.0234
$\theta 4$	$L^2/\mu mol/hr$	-0.090	34.11	-0.151	-0.0286
$\theta 5$	V (L/kg)	1.56	8.14	1.306	1.814
$\theta 6$	Q (L/hr)	39.0	5.59	34.64	43.36
$\theta 7$	Vs (L/kg)	4.10	4.56	3.726	4.474
ω^2_{CL}	interindividual variability	0.209	11.34	0.162	0.256
ω^2_V	interindividual variability	0.327	24.13	0.169	0.485
σ^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 η_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 ω^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, ΔPR_{ij} is the predicted value, and ε_{ij} are independent, identically distributed errors with a mean of 0 and a variance of σ^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
θ_1	Slope (msec/(ng/ml))	0.0353	9.41	0.0287	0.0419
θ_2	Coefficient of BPR	-0.159	25.09	-0.239	-0.0792
θ_3	Intercept (msec)	29.0	20.90	16.88	41.12
ω^2 slope	Interindividual Variability $(msec)^2$	98.0	16.02	66.6	129.4
σ^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 η_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 ω^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, ΔQRS_{ij} is the predicted value, and ε_{ij} are independent, identically distributed errors with a mean of 0 and a variance of σ^2.

Parameter	Description	Estimate	% CV	Lower 95% CI	Upper 95 % CI
θ_1	Slope (msec/(ng/ml))	0.0139	16.98	0.00918	0.01862
θ_2	Intercept (msec)	1.05	34.10	0.334	1.766
ω^2 slope	Interindividual Variability $(msec)^2$	15.3	24.38	7.84	22.76
σ^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 ΔQTc 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 ($=\sqrt{\omega^2}; =\sqrt{\sigma^2}$)
θI-PD	Covariate intercept for anthracycline chemotherapy (msec)	140	19.0	102.7 - 177.2	-
θI-S	Covariate intercept for healthy normal subjects (msec)	108	16.9	74.9 - 141.1	-
θI-PN	Covariate intercept for patients not receiving doxorubicin (msec)	131	18.8	94.2 - 167.8	-
θEM-P	Emax - Patients (msec)	36.4	8.07	20.6 - 52.2	-
θEM-S	Emax - Subjects (msec)	23.1	5.22	16.8 - 29.4	-
θEC-P	EC_{50} - Patients (ng/mL)	411	145	127 - 695	-
θEC-S	EC_{50} - Subjects (ng/mL)	100	31.5	38 - 161	-
θBQ	Covariate slope for baseline QTc	-0.315	0.0453	(-0.404) - (-0.226)	-
ω^2EM	Intersubject variability for Emax (ω^2) $(msec)^2$	218	75.1	70.8 - 365.2	14.8
ω^2EC	Intersubject variability for EC_{50} (ω^2) $(ng/mL)^2$	24800	15500	0* - 55180	157
ω^2BQ	Intersubject variability for the slope associated with BQTC (ω^2)	0.00112	0.000146	0.00083 - 0.00141	0.033
σ^2	Residual error - σ^2 $(msec^2)$	239	16.7	206 - 272	15.5

θ* Negative intervals of the variability estimates were set at zero due to inability to interpret negative results
ω^2, σ^2 Variance
SD: Standard Deviation

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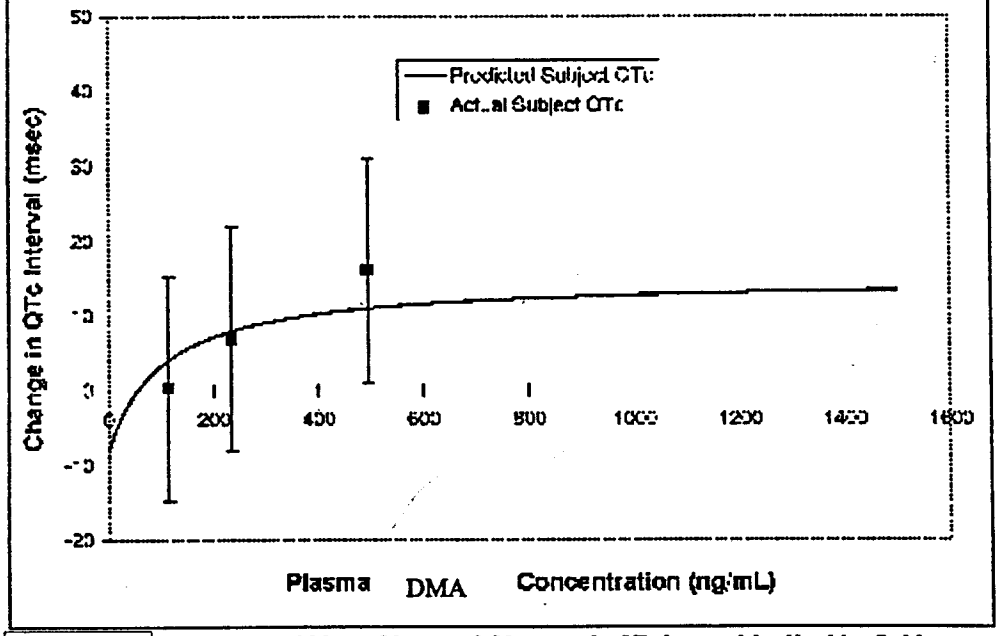

Predicted and Mean Observed Changes in QTc Interval for Healthy Subjects As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 50, 100 and 200 mg IV and Oral Doses

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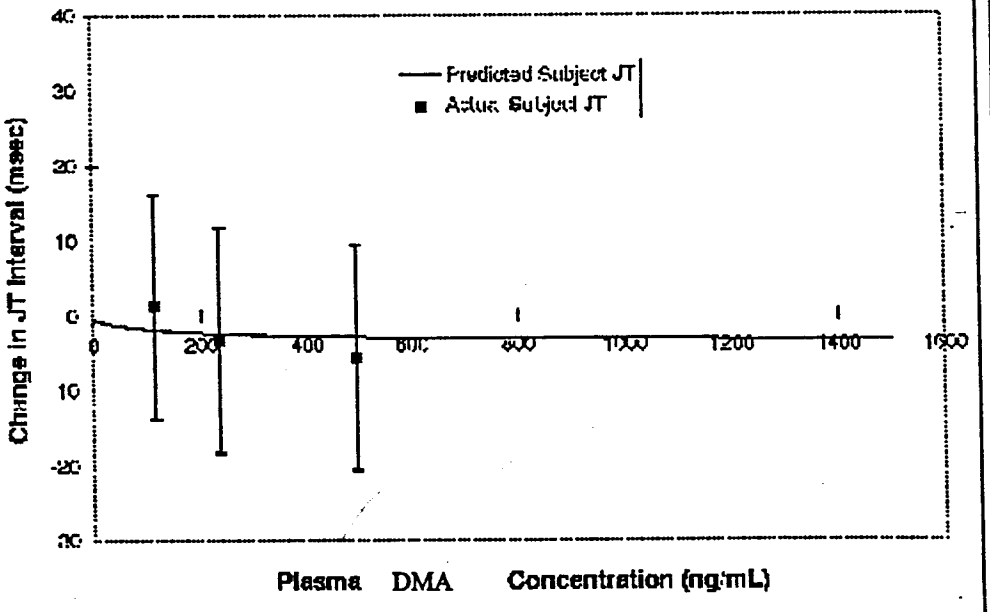
The following table shows population PD parameters for ΔJT(combined data)

PD Parameter	Description	Parameter Estimate	Standard Error of Parameter Estimate	95% Confidence Interval on the Estimate	SD (=√ω2; =√σ2)
θ1	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	-
ω^2_1	Inters ubject variability for the intercept (ω^2: ms ec^2)	20.0	127	0* - 269	4.47
ω^2BS	Inters ubject variability for the slope parameter (ω^2)	0.000605	0.000475	0* - 0.00154	0.025
ω^2EM-S	Inters ubject variability for the Emax parameter (ω^2: ms ec^2)	47.4	95.1	0* - 234	6.88
ω^2EC-S	Inters ubject variability for the EC50 parameter (ω^2: [ng/mL]2)	5190000	10200000	1.5 + 107 - 2.5 + 107	2278
ω^2C-P	Inters ubject variability for concentration parameter (ω^2: [ms ec/ng/mL]2)	0.00331	0.00174	0* - 0.0067	0.058
σ^2	Residual error - σ^2 (msec^2)	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
ω^2,σ^2 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

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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.

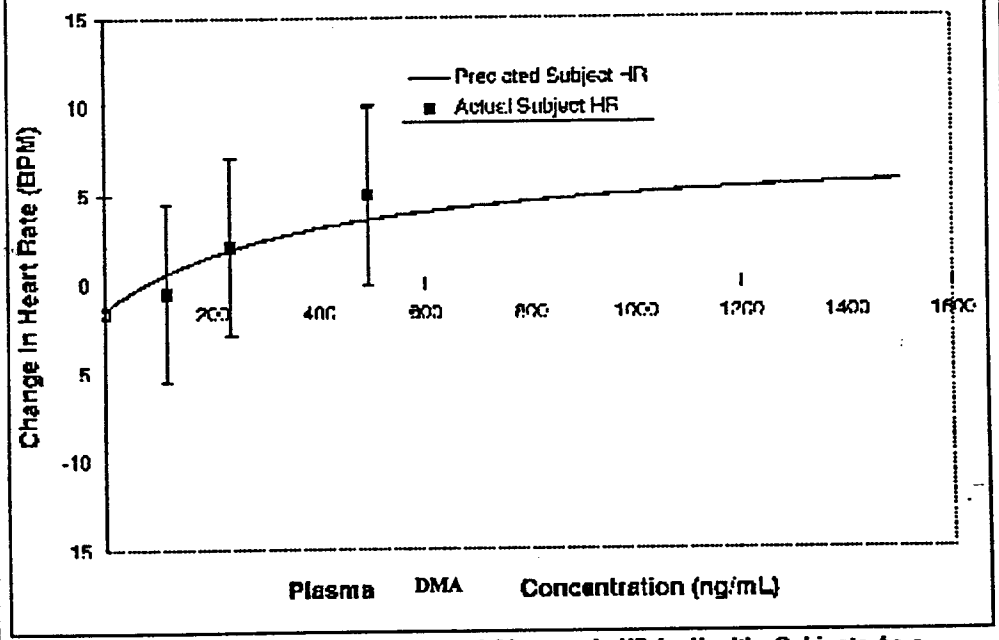
Summary: Increases in JT interval were not meaningfully related to plasma concentrations of DMA. The relationship was fitted to an Emax model and a linear model in healthy subjects and cancer patients, respectively. Overall, any change in JT interval which may be correlated to plasma levels of DMA would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

C Heart Rate

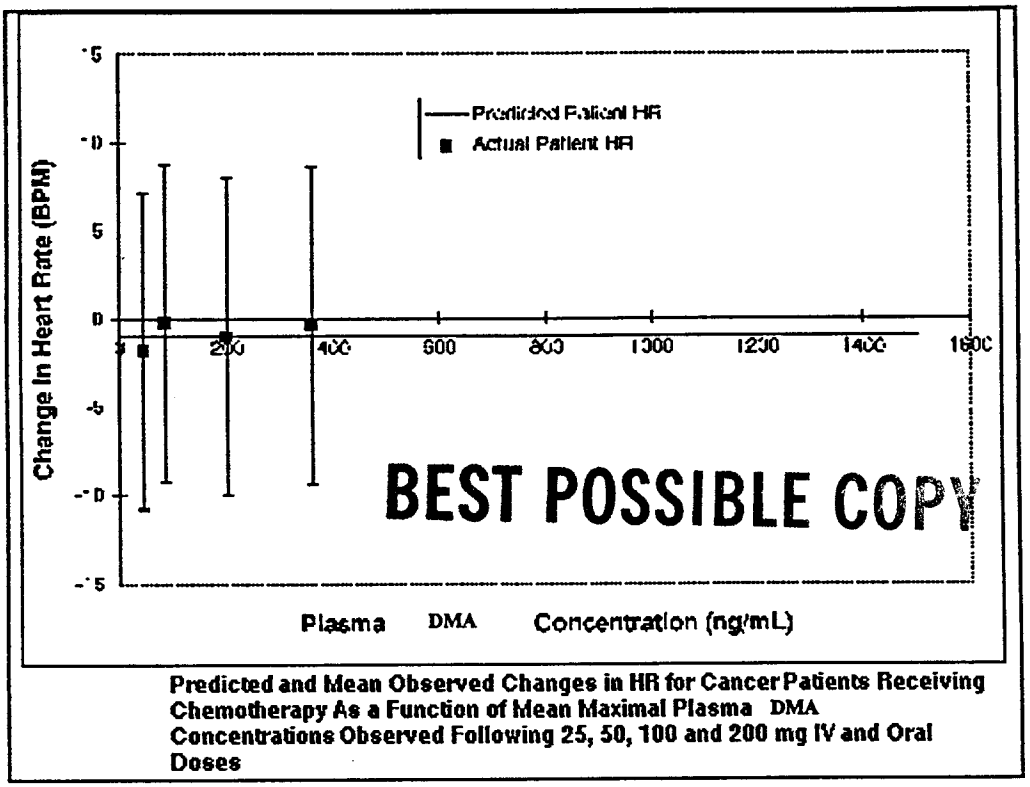
The sponsor carried out the PD analysis of HR as changes in HR could influence QTc interval changes. The analysis used HR recorded on ECG tracings. The relationship between plasma concentrations of DMA and changes in HR differed between healthy subjects and cancer patients. NONMEM analysis indicated 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)	20.6	2.03	16.2 - 24.6	-
$\theta_{I\text{-}S}$	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	-
θ_{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 (ω^2: $(ng/mL)^2$)	393000	284000	0^a - 949640	627
ω^2_{BH}	Intersubject variability for the slope associated with BHR (ω^2)	0.00659	0.000839	0.0049 - 0.0082	0.081
σ^2	Residual error - σ^2 (BPM^2)	40.9	2.18	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.