(0.04 mg'/mL, 0.08 mg/mL, or 0.12 mg/mL) and started as a bolus of 0.03, 0.06 or 0.10 mg/kg, then an infusion of 0.5, 1.0 or 1.5 mcg/kg/min.

The primary assessment was a categorical six step scale (0 Agitated, 1 Awake, 2 Asleep (eyes open to noise), 3 Asleep (eyes open to name), 4 Asleep (eyes open to touch), 5 Asleep (moves to touch), 6 Asleep (Unresponsive). Physicians were advised to titrate the patients to a target score of 3-5 (Asleep but responsive), reduce dosage for a score of 6 (Unresponsive), and increase dosage for a score of 0-2 (Agitated, Awake or responding to the environment). All dose increases were ordered by volume to protect the blind.

For most patients the infusion period was to be six hours, with a 48 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

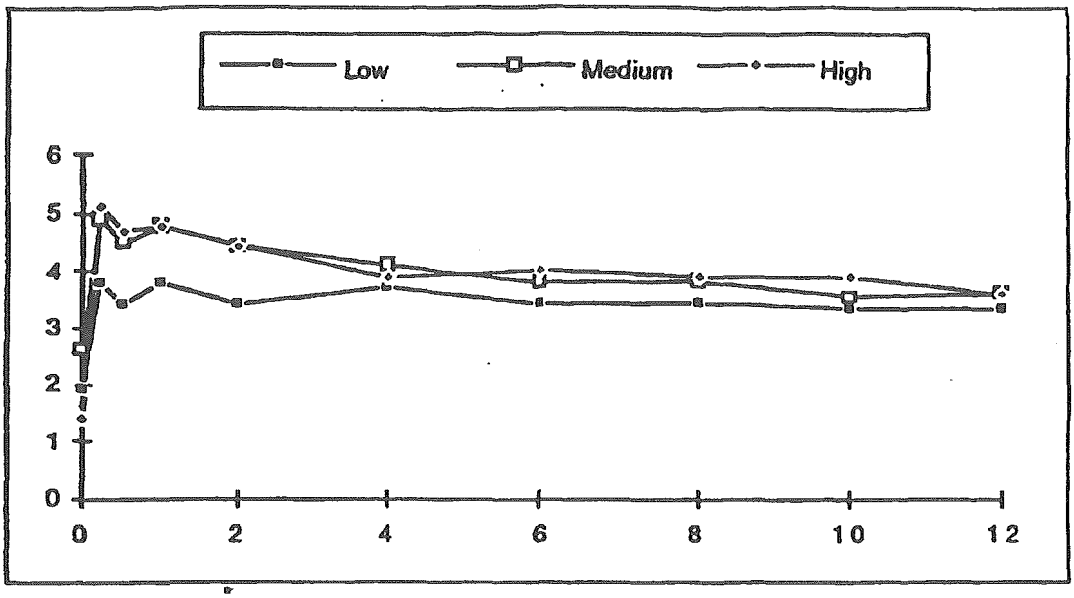
Enrollment, Randomization, and Evaluabilty

Thirty patients were enrolled, six had minor weight problems (to heavy, too thin), but all were evaluated and none excluded. The groups were similar in most ways:

Item (MEAN &'SD)	Low Dose	Medium Dose	High Dose
AGE	64 (8.4)	68 (7.4)	70 (5.6)
WEIGHT	69 (7.8)	77 (10.3)	74 (13.6)
HEIGHT	170 (8.8)	172 (9.5)	173 (13.1)
DURATION OF SURGERY	2.6 (0.6)	2.8 (0.7)	2.4 (0.3)
MALE	5	9	7
FEMALE	5	1	3
ASA III	9	10	10
ASA IV	1	0	0
CAUCASIAN	10	10	10
Occlusive Disease	4	3	4
Aneurysm	6	7	6

Results

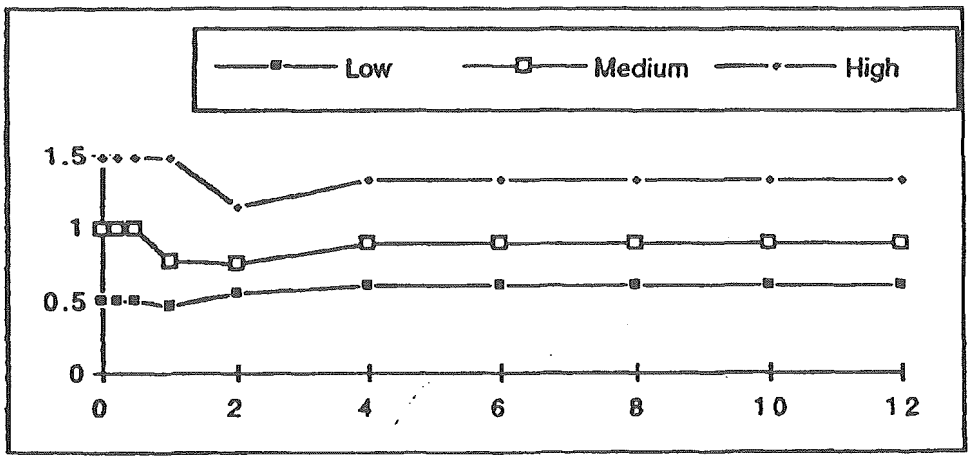
All three groups showed a marked change in sedation scores:



Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	1.9	3.8	3.4	3.8	3.4	3.7	3.4	3.4	3.3	3.3
Medium	2.6	4.9	4.5	4.8	4.4	4.1	3.8	3.8	3.5	3.6
High	1.4	5.1	4.7	4.8	4.4	3.9	4	3.9	3.9	3.6

Dose of Midazolam by group

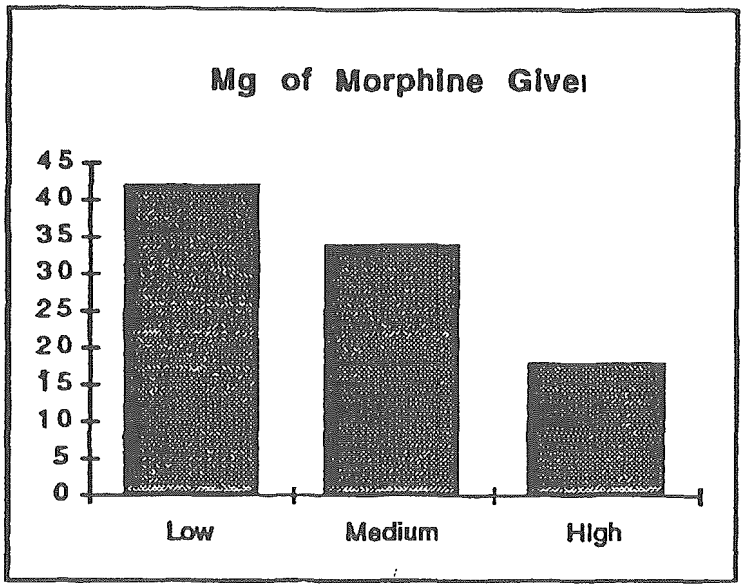
Since this was a titration design, the next step seemed to be to look at the actual doses of drug given (infusion rates in mcg/kg/min).



Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	0.5	0.5	0.5	0.47	0.55	0.6	0.6	0.6	0.6	0.6
Medium	1	1	1	0.78	0.75	0.9	0.9	0.9	0.9	0.9
High	1.49	1.49	1.49	1.49	1.15	1.34	1.34	1.34	1.34	1.34

Effect on Concurrent Medication

At first glance, this suggests that all three doses have roughly equal sedating effects, despite a three fold increase in the infusion rate. What actually happened is seen in the next plot which is the total dose of narcotics given to the patients in each group (converted to mg of morphine as some received meperidine or fentanyl).



Efficacy Conclusion

The midazolam infusions caused a marked reduction in the amount of narcotic needed by the patients to remain comfortable on the ventilator. There is a hint that the highest dose resulted in oversedation seen in the immediate reduction in dosage @ 1 hour, and the lower dosage carried through the study. The efficacy conclusion is that the physicians in the study preferred to adjust the opiate dose, rather than titrate the infusion. Interestingly, the fall in opiate dosage (42->15) is of the same magnitude as the rise in midazolam dose (0.5->1.3).

The data provide some suggestion that the bolus dose for the medium and high dose group are perhaps too high, since at the time of peak effect the average patient's score was 5 (Asleep, responsive to painful stimuli), suggesting that at least some of the patients were unresponsive.

Safety

One patient ([redacted] low dose group) had a serious AE. He experienced postoperative hemorrhage, hypovolemia, shock lung from crystalloid, and an intercurrent MI. He recovered and was discharged to home. The relationship to drug was listed as remote, and the reviewer agreed.

Five patients experienced hallucinations, confusion, or agitation, with no dose-relatedness.

There were no treatment related alterations in vital signs or laboratory tests, despite careful examination for acute withdrawal phenomena.

One marked finding in the survey results was the question, "Do you remember being on the breathing machine". Zero of 10 low dose, 6 of 10 medium dose, and 4 of 9 high dose patients were amnesic for the respirator. Patients appear to have an amnesic response to these doses of midazolam.

Conclusion

This was an adequate and well-controlled study that showed a marked opiate sparing effect from midazolam infusion. It does not support midazolam ALONE in the postoperative patient with post-surgical pain, but does suggest that doses of about 0.5 mcg/kg/min were tolerated and effective for the short term ICU stay. The higher bolus doses and infusion rates may be too high for some patients, as evidenced by some patients being unresponsive and needing downward titration in the medium and high dose groups.

It does not adress the risk of either acute withdrawal or precipitated withdrawal following longer infusions.

Curtis Wright

Laurence Landow

CC:

NDA	18-654
HFD-170	Division File
CSO	Morgan
Team Leader	Landow
Reviewer	C Wright

Medical Officer Review
Roche NDA 18-654
Supplement for Midazolam Infusion

Protocol 912 Teasdale (Toronto)

NDA- 18-654 Midazolam
Sponsor- Hoffmann La Roche INC.
Primary Reviewer- Curtis Wright
Secondary Reviewer- Larry Landow
Date of Review- 8/7/96
Material Reviewed- Jacket 7

Summary

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 30 patients (3 groups of 10 each), who received a bolus dose of midazolam then either low dose (0.5 mcg/kg/min), medium dose (1.0 mcg/kg/min) or high dose (1.5 mcg/kg/min) infusions that remained constant in volume but varied in concentration. The hypothesis was that each group would titrate to a common dose (mcg/kg/hr.). All patients were initially excessively sedated from the bolus dose, but were titrated to a common dose of 0.2-0.3 mcg/kg/min to good effect.

The study showed good dose finding for the infusion, but the need to titrate the bolus dose.

Background

Midazolam is a benzodiazepine sedative used in anesthesia that is most frequently dosed to effect in bolus doses. The sponsor wishes to provide instructions for use by infusion, and has conducted clinical studies to establish the dose. This is one such study. There is no question that midazolam is a sedative, no question that we know the blood level range where the drug is active (these were established in the original NDA and in the evaluation of the cases of drug toxicity associated with improper use of the drug during endoscopy).

The pivotal questions for this application are the suitability of the dose, the effect on use of other medication, and course of recovery from sedation for the patients.

Protocol

Patients scheduled to undergo elective coronary artery bypass surgery who had uncomplicated surgery were eligible for the protocol. Excluded were women at risk of pregnancy, pregnant women, patients with severe congestive heart failure, patients with severe lung disease, and patients with severe hepatic or renal disease, history of drug abuse, glaucoma, or recovering from shock or multiple trauma.

All patients had standard premeds (morphine & perphenazine), high dose fentanyl induction (30 mcg/kg IV) with pancuronium, and fentanyl and halothane or fentanyl & isoflurane maintenance (I suspect nitrous oxide was used as part of standard technique).

Patients were then taken to the ICU where they were given morphine 2 -4 mg IV prn for pain, agitation, "fighting the respirator, or tachycardia.

The dose of midazolam was amended during the protocol. It started at the 0.03-0.10 mg/kg bolus such as was in the other site in the study. This was lowered due to signs of excessive sedation in the first 7 patients. In the revised protocol, after the bolus (starting) dose of 0.015, 0.03, or 0.05 mg/kg, the infusions were started at 0.5, 1.0 & 1.5 mcg/kg/min, and could be titrated as before.

The primary assessment was a categorical six step scale (0 Agitated, 1 Awake, 2 Asleep (eyes open to noise), 3 Asleep (eyes open to name), 4 Asleep (eyes open to touch), 5 Asleep (moves to touch), 6 Asleep (Unresponsive). Physicians were advised to titrate the patients to a target score of 3-5 (Asleep but responsive), reduce dosage for a score of 6 (Unresponsive), and increase dosage for a score of 0-2 (Agitated, Awake or responding to the environment). All dose increases were ordered by volume to protect the blind.

For most patients the infusion period was to be six hours, with a 48 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

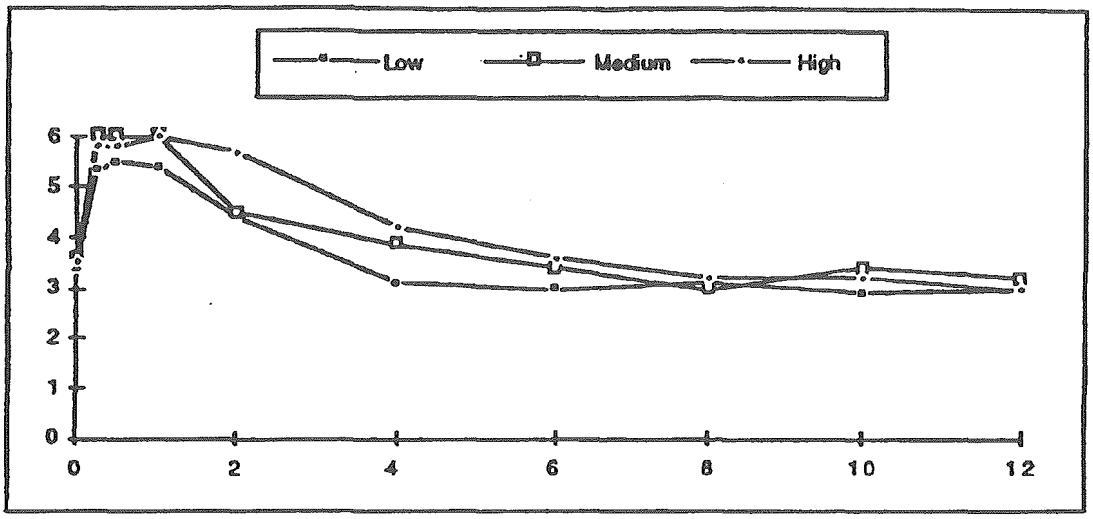
Enrollment, Randomization, and Evaluability

The first 7 patients enrolled were evaluated only for safety, an additional thirty patients were enrolled, five had minor protocol violation problems (the protocol was unwisely restrictive in matters that were unrelated to the study), but all were evaluated and none excluded. The groups were similar in most ways:

Item (MEAN & SD)	Low Dose	Medium Dose	High Dose
AGE	57 (6)	61 (9)	61 (7)
WEIGHT	79 (10)	75 (8)	68 (12)
HEIGHT	170 (8)	172 (9)	165 (12)
DURATION OF SURGERY	2.8 (0.4)	2.8 (0.6)	2.8 (0.5)
MALE	9	9	6
FEMALE	1	1	4
ASA III	10	10	10
ASA IV	0	0	0
CAUCASIAN	8	8	9
BLACK	0	0	1
INDIAN	2	2	0

Results

All three groups showed a marked change in sedation scores:

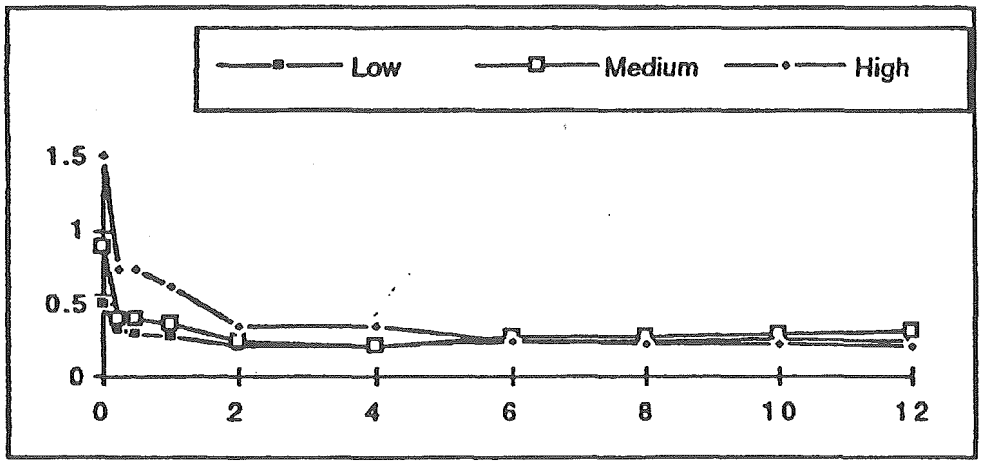


Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	3.4	5.3	5.5	5.4	4.4	3.1	3	3.1	2.9	3
Medium	3.6	6	6	6	4.5	3.9	3.4	3	3.4	3.2
High	3.5	5.8	5.8	6	5.7	4.2	3.6	3.2	3.2	3

What we see here is that the patients in the medium and high dose groups, even at the reduced dosage, are unresponsive to pain within 15 minutes after the bolus, while in the low dose group things are a bit better, and only half to 2/3 of the patients are anesthetized. The patients have started to recover by 2 hours, and are in good shape by 4.

Dose of Midazolam by group

Since this was a titration design, the next step seemed to be to look at the actual doses of drug given (infusion rates in mcg/kg/min).

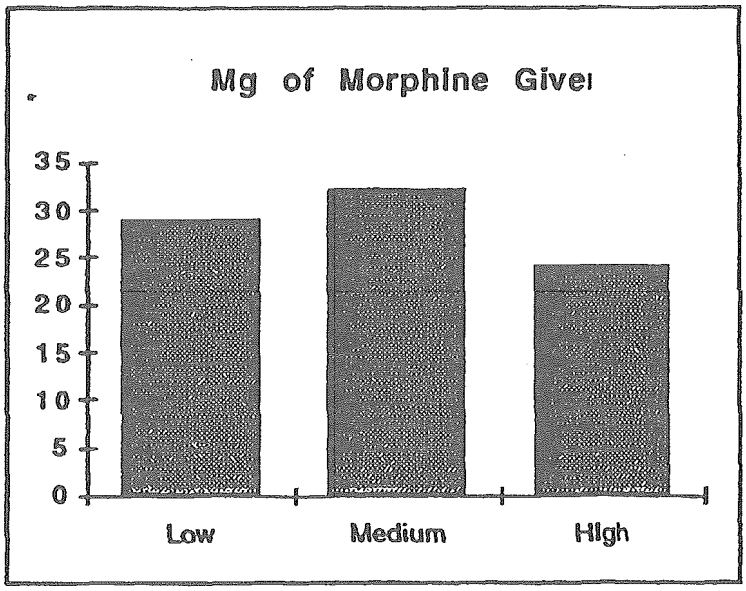


Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	0.5	0.33	0.3	0.28	0.21	0.21	0.24	0.24	0.27	0.25
Medium	0.9	0.4	0.4	0.37	0.25	0.21	0.28	0.28	0.29	0.31
High	1.5	0.74	0.74	0.62	0.35	0.34	0.25	0.23	0.23	0.21

What we see here is that the physicians quickly detected that the bolus dose was too high, and reduced the dosage in all groups down to a common dose of about 0.2-0.3 mcg/kg/min which seemed to keep the patients in the desired range after the bolus wore off.

Effect on Concurrent Medication

Since the patients all got about the same amount of midazolam, it is nit unexpected that they all required about the same amount of narcotic (converted to mg of morphine as some received meperidine or fentanyl).



Efficacy Conclusion

The bolus doses in these patients were too high, perhaps far too high, and these patients might have done better with half or a third as much midazolam in the bolus (say 5-15 mcg/kg). The carry away message seems to be that the bolus dose in these studies seems to vary according to the anesthetic technique, and the degree of sedation that is desired for the immediate postoperative setting.

In contrast to the bolus dose, the infusion doses rapidly converged, and do appear to be what is called for.

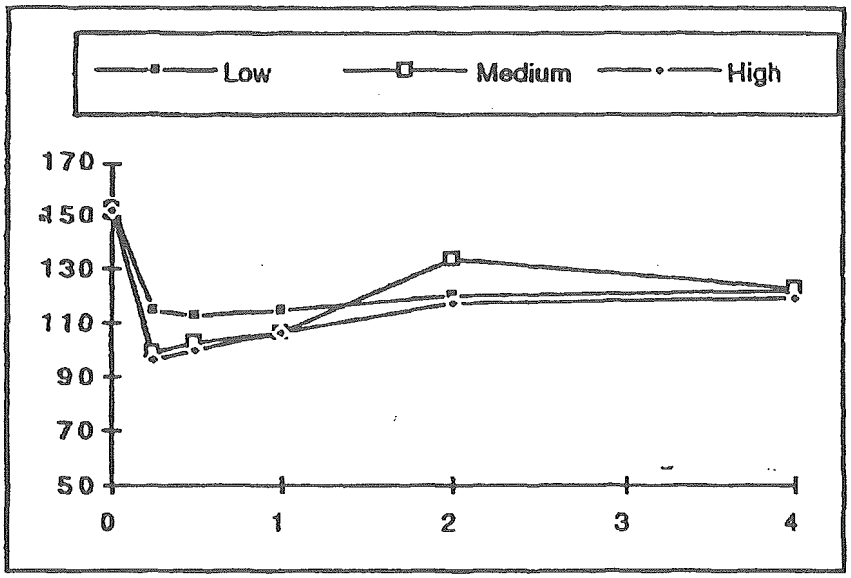
In this study, most of the patients were not amnestic for most of their stay (8-10 in each group remembered the respirator, visitors, etc.).

Safety

There were no deaths or serious side effects attributable to study drug, though patients in all three treatment groups had transient episodes of either hypotension or hypertension, which responded to therapy. Hypoventilation was not seen (the patients were on ventilators) though it might occur if imprudent minimums were set on the ventilators.

Transient arrhythmias, one episode of elevated cardiac enzymes, and a pneumothorax were seen, again not unexpected.

One unacceptable result of the excessively high bolus doses were 40 & 50 point drops in the systolic blood pressure from the bolus.



Hours	0	0.25	0.5	1	2	4
Low	154	115	113	115	120	122
Medium	152	99	103	107	134	123
High	152	97	100	107	118	119

Conclusion

This was an adequate and well-controlled study that clearly showed that midazolam bolus and infusion were effective in the ICU. It also showed that the proposed bolus doses were too high for this patient population post-op. It is likely that the size of the bolus dose needed will vary depending on the anesthetic technique, the patient's condition, and the degree of sedation required.

I strongly recommend an integrated review of all the dosing data, and a recommended bolus technique that avoids the kind of excessive sedation seen in this study.

Curtis Wright

Larry Landow

CC:

NDA	18-654
HFD-170	Division File
CSO	Morgan
Team Leader	Landow
Reviewer	C Wright

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
NDA No; 18-654 S#29

Midazolam HCl
1, 5ml vials containing 5mg midazolam/ml
2, 10ml vials containing 1mg midazolam/ml

Hoffmann La Roche Inc
340 Kingsland Street
Nutley
New Jersey 07110 1199

Tradename; Versed
Reviewer: Peter Lockwood MS
Review Start: Thursday, August 1 Submission Date; Sept. 28 1995

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1. BACKGROUND

Versed (midazolam HCl) is a water soluble short-acting benzodiazepine central nervous system depressant. It is 95% plasma protein bound over the concentration range encountered in clinical usage and is subject to approximately 55% first pass metabolism. The main metabolite is 1-hydroxy midazolam which is pharmacologically active but much less than the parent has a half-life og about 0.8 hrs. Midazolam is currently approved under the above mentioned NDA for three indications in adults, namely (1) for preoperative sedation following intramuscular administration, (2) for conscious sedation prior to short diagnostic, therapeutic or endoscopic procedures following intravenous administration and (3) for induction or adjunct to general or regional anesthesia.

All these approved indications pertain to short term use of injectable midazolam in adults. A supplemental application No. 029 to this NDA was submitted September 13, 1995 providing data for the following new indication in adults:

- continuous intravenous infusion for sedation of intubated, mechanically ventilated patients.

2. SYNOPSIS

The pharmacokinetic component of this submission included a summary of 21 publications of the pharmacokinetics of midazolam administered by continuous intravenous infusion and four studies supported by the sponsor. The literature submission reaffirmed the ranges of the Vd and Cl parameters for midazolam in healthy adults. These were 1-3 L/kg and 3-10ml/min/kg, respectively. Infusions ranged from 0.01-0.2mg/kg/hr, which is well within the range disseminated in the package insert. No life threatening adverse events were reported and all adverse events resolved after treatment was discontinued.

In critically ill patients the Cl may well be reduced (range 0.4-10ml/min/kg) and the Vd may either increase or decrease (range 0.7-4.6L/kg). The infusion rate in these patients ranged from 0.003-0.21mg/kg.

Three dose ranging studies investigated infusions of 0.03, 0.06 and 0.09 mg/kg/hr to ICU patients who were mechanically ventilated following abdominal aortic surgery. This is the infusion range reflected in the package insert (i.e. 0.02-0.1mg/kg/hr). These were really safety studies rather than true dose response studies, because if patients were not at a predetermined level of sedation, the infusion was increased or decreased accordingly. The number of dosage adjustments for each treatment group for each center and each study was similar. There is marginal evidence that there were fewer dosage adjustments for the low dose treatment group.

Steady state plasma concentrations measured in study 912 (Ottawa center) ranged from 31 to 140 ng/ml (mean 76ng/ml), 40 to 270ng/ml (mean 130ng/ml) and from 100 to 470ng/ml (mean 205ng/ml) for the low medium and high treatment groups respectively. There was no clinically significant difference in sedation levels, although the optimum sedation level was more rapidly obtained with the high infusion rate treatment group. Tolerance to midazolam was not apparent in these infusion studies.

Interim analysis of data collected from a partially completed computer assisted continuous infusion study indicated that midazolam has a therapeutic window between 50 and 100 ng/ml for sedation following coronary artery bypass with underlying residual opioids from the anesthesia. Modeling pharmacokinetic data with NONMEM indicated that midazolam PK was best described by a three compartment model. Using the PK parameters determined from this, the desired therapeutic window was simulated using the a dosing schedule of 5-10 mg/hr for the first hour, 3-6mg/hr for the second and third hours and 2-4 mg/hr beyond 3 hours.

3. COMMENTS & RECOMMENDATIONS (not to be sent to the sponsor but to be discussed with review team).

1) The "Continuous Infusion" paragraph in the pharmacokinetic section of the label conveys no useful information and should be removed.

2) The continuous infusion section in the dosing section of package insert should be amended to indicate that the loading dose be infused over 2-several minutes as opposed to "given slowly or infused over several minutes".

3) Because of the high variability in Vd and Cl in critically ill patients, cautious dosing at the lower end of the suggested dose ranges should be emphasised.

4) Tolerance is not addressed in the package insert. This should be noted together with the fact that increases in doses to account for this will be accompanied by prolongation of the half-life.

4. TABLE OF CONTENTS

5. PHARMACOKINETICS

5.1. literature review

The number of subjects studied in the 21 reports amounted to 282. This included 43 healthy volunteers in 6 studies, 109 surgical patients in 5 studies and 130 critically ill patients in 10 studies. Midazolam infusion was continued for up to 27 days. The ranges of administered doses generally were;

loading dose; 0.02-0.5mg/kg
maintenance dose; 0.01-0.4mg/kg/hr

5.1.1. studies of healthy volunteers

Infusion durations in healthy volunteers were up to 26 hours with infusion rates up to 0.04mg/kg/h. The range of mean plasma clearance in healthy volunteers was 6.1- 9.6 ml/min/kg. The range of mean volume of distribution was 1.0-2.7 L/kg. Details of the studies conducted in healthy volunteers are displayed in table V1-B-7; Appendix 1.

5.1.2. midazolam kinetics after surgical procedures

The pharmacokinetics of midazolam were evaluated when midazolam was used in the postoperative period following surgical procedures, as a component of anesthesia during the procedure itself, or both. Infusion durations generally fell in the range of 4-24 hours. When a loading dose was administered it ranged from 0.01-0.05mg/kg. The time frame over which this was administered was not specified. The maintenance dose administered ranged from 0.01-0.2 mg/kg/hr. The duration of infusion ranged from 8-24 hours.

The patients in these studies tended to be young adult or elderly. Most appeared to be healthy at the time of surgery, but were undergoing major procedures such as myocardial revascularization, abdominal aortic reconstruction or other intra-abdominal procedures, or maxillofacial surgery. Midazolam was generally one of many pharmacologic agents administered. Other classes of coadministered medications included opiates, anticholinergics, neuromuscular blockers, barbiturates, and volatile general anesthetics.

The range of mean plasma clearance was 3.4-10.5 ml/min/kg. The range of mean volume of distribution was 1.0-3.1 L/kg. The pharmacokinetics of midazolam determined in these studies are displayed in Table VI-B-8, Appendix 1. These are similar to values reported in Supplement 30 where it was reported that for individuals between 1-18 years of age, the mean CL ranged from 3-13ml/min/kg. Similarly the mean Vd ranged from 0.6-2.7 L/kg.

5.1.3. Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation

Most patients confined to intensive or critical care units receive mechanical ventilation for various reasons including postoperative recovery, serious medical illness, or trauma. Ten studies included this patient population. Most of these studies included elderly patients suffering from dysfunction of multiple organs and major abnormalities of cardiac output, and receiving multiple medications. Kinetic parameters for midazolam in these studies were quite variable, with clearances ranging from values in the normal range to those that are substantially reduced from normal. Likewise, values of elimination half-life ranged from those usually expected for individuals of corresponding age to values that were greatly prolonged.

The range of mean plasma clearance was 0.4- 10.3 ml/min/kg. The range of mean volume of distribution was 0.7-4.6 L/kg. The infusion duration ranged from 23 to 649 hours. The loading dose where administered ranged from 0.07-0.5 mg/kg. The maintenance dose ranged from 0.003-0.21 mg/kg/hr. Details of dosing and pharmacokinetic parameters determined in theses studies are displayed in Table VI-B-9; Appendix 1.

5.2. Midazolam Metabolites

Plasma concentrations of α-hydroxy-midazolam were reported in some of these studies. When levels of the unconjugated metabolite were described, they were considerably lower than those of the parent compound (Crevat-Pisano et al 1986; Driessen et al 1989; Dirksen et al 1987; Miller et al 1994). This finding, together with the lower receptor affinity and lower relative brain uptake of "α-hydroxy-midazolam relative to those of the parent compound (Arendt et al 1987), make it likely that the primary pharmacological effect of midazolam administration is attributable to the parent compound. In some studies plasma levels of "α-hydroxy-midazolam glucuronide were also reported (Driessen et al 1991; Vree et al 1989; Dirksen et al 1987; Oldenhof et al 1988). Levels of the glucuronide conjugate exceeded those of intact "α-hydroxy-midazolam. Since the glucuronide is excreted by the kidney, its plasma levels will rise in patients with renal insufficiency. This is not of clinical importance in short term infusion (<24 hrs), since the glucuronide conjugate is pharmacologically inactive. However with prolonged infusion in very sick ICU patients (e.g with accute renal failure due to circulatory shock or hypotension), this accumulation may displace the equilibrium to deglucuronidation resulting in elevated α-hydroxy-midazolam. Driessen et al., 1991, who studied the pharmacokinetics of midazolam, the hydroxltaed metabolite and its conjugate in ICU patients patients administered prolonged midazolam infusions, reported that in 6 patients who developed accute renal failure, unconjugated hydroxy midazolam levels were lower than the parent drug. This suggests that the deglucuronidation is unlikely to be of any clinical importance.

5.3. Studies Supported by the Sponsor

Pharmacokinetic investigations were undertaken as part of three dose-ranging studies and one prospective, open-label study of midazolam administered by continuous intravenous infusion that were supported by the sponsor. The three dose-ranging studies (by Martineau and Miller; Teasdale et al; and Ralley et al) are completed. The prospective, open-label study (Reves et al) is ongoing; this is a multi-center trial of the safety and efficacy of midazolam administered to patients following cardiac surgery by computer-assisted continuous infusion (CACI).

5.3.1. Study by Martineau and Miller (Otawa site) and Study by Teasdale (Toronto site)

The 60 patients in this 2 center study received midazolam by continuous intravenous infusion during mechanical ventilation in the ICU, following abdominal aortic surgery. The patients were 50 to 75 years of age, with a mean age of 67.6. They were randomly assigned to one of six dosage groups. Three dosage regimens were at an Ottawa center and three dosage regimens at a Toronto center. Dosage regimens are detailed in Table 1 and Table 2.

Table 1; Theoretical and Actual Infusion Rates Studied; Toronto site

group	bolus	infusion (mg/kg/hr)	time to optimal sedation (mins)
	mg/kg	theoretical	
1	0.015	0.03	
2	0.03	0.06	
3	0.05	0.09	

Table 2; Theoretical and Actual Infusion Rates Studied; Ottawa site

group	bolus	infusion (mg/kg/hr)		time to optimal sedation (mins)	mean plasma conc at end of infusion
	mg/kg	theoretical	actual		
1	0.03	0.03	0.036 ± 0.011		76.1 ± 31.6
2	0.06	0.06	0.054 ± 0.031		132.7 ± 70.5
3	0.1	0.09	0.080 ± 0.041		206.6 ± 106.2

Mean duration of infusion was approximately 17 hours for both centers. (Further details of the patients and methods are shown in Table VI-B-3 and Table VI-B-4, under Miller et al.) For the Ottawa site, the differences in infusion rates were associated with differences in midazolam plasma concentrations (see Table 2). There was no significant difference in the time to optimal sedation although the time to recovery was faster for the low and medium dose groups compared to the high dose group at 2 hours ($p=0.3$). There was no significant difference between duration of artificial ventilation, postoperative sedation and stay in the ICU for any group.

Pharmacokinetic variables were independent of infusion rates. Similar values were obtained for the three groups with respect to total clearance rates, volumes of distribution, and elimination half-lives. The values are within the ranges

determined in other studies. (These latter values are shown in Table VI-B-8, under Miller et al.)

Plasma samples were collected at the Toronto center and analyzed. Data for 5 patients indicated that plasma concentrations of midazolam persisted or increased in the 24 hours following termination of infusion. The sponsor speculates that this was a consequence of poor chromatography by the contract research organization. This reason is speculative because chromatographic records could not be accessed for appraisal because they had been discarded. There was no pharmacokinetic analysis of this data.

The mean time to optimal sedation at the Toronto center was reported as approximately 200 minutes. This is inconsistent with the results reported by the Ottawa center. No explanation is offered by the sponsor and does not appear consistent with the sedation scale scores during midazolam administration. Mean sedation scores during the recovery period were very similar for the three treatment groups.

5.3.2. Study by Ralley et al. (protocol no 910)

This study was similar in design to the two previous studies reported. Results from this study supported the previously mentioned findings; i.e. no clinically significant difference in sedation. The time to optimum sedation was similar to the results obtained at the Ottawa site in study 912. Plasma samples were also collected at this site but there was no PK analysis of the data.

Table 3; Theoretical and Actual Infusion Rates Studied; Montreal site

group	bolus	infusion (mg/kg/hr)	time to optimal sedation (mins)
	mg/kg	theoretical	
1	0.015	0.03	
2	0.03	0.06	
3	0.05	0.09	

5.4. PK-PD relationship

Mean midazolam concentration-time curves during sedation and decay curves for midazolam, and α-hydroxy-midazolam, for patients representative of each group were obtained from the publication by Miller et al 1994 and are shown in Figure 1. For low rate infusion, steady state plasma concentrations ranged from ng/ml (mean 76ng/ml), for the medium infusion rate, steady state plasma concentrations were between 40 to 270ng/ml (mean 130ng/ml) and for the fast infusion plasma concentrations ranged from ng/ml (mean 205ng/ml). Despite the differences in infusion requirements all groups were optimally sedated 95% of the time). **The obscurity of the PK/PD relationship in this instance is likely to be attributable to the coadministration of narcotics during the postoperative sedation period.**

The proportion of patients requiring dosage adjustments in the three groups did not differ significantly. Upon discontinuation of midazolam, a relatively rapid decline in the level of sedation was observed in all groups (see Figure 2). However the early recovery phase was prolonged in the higher infusion rate treatment groups.

Figure 1; Midazolam and hydroxy-midazolam plasma concentration decay curves for representative patients in the low medium and fast infusion rate treatment groups

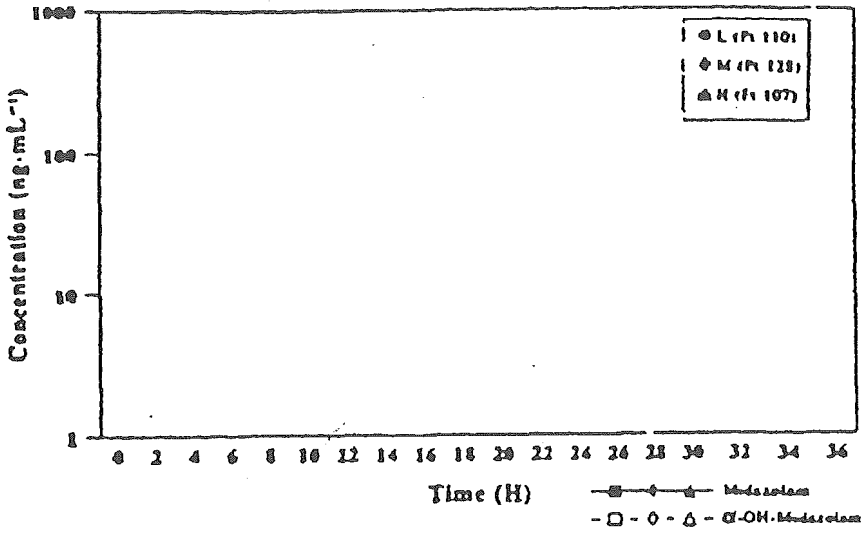
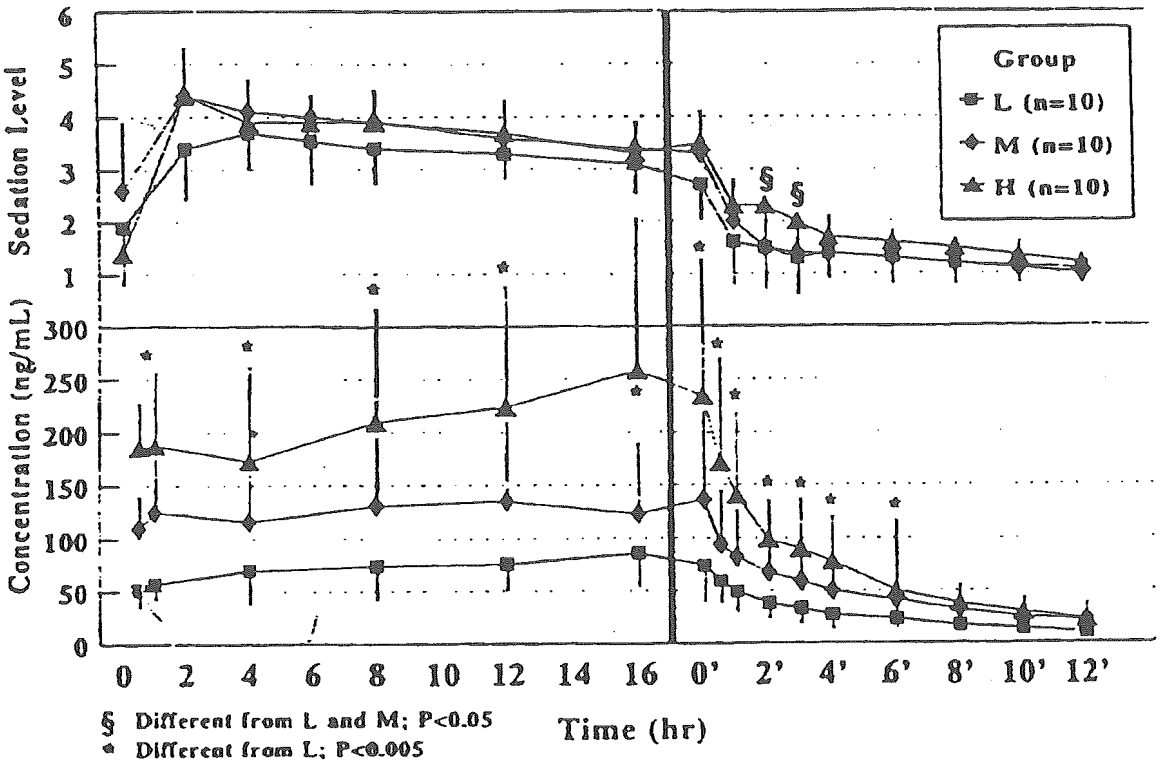


Figure 2; Mean sedation levels and corresponding mean midazolam plasma concentrations



5.5. *Adverse Events*

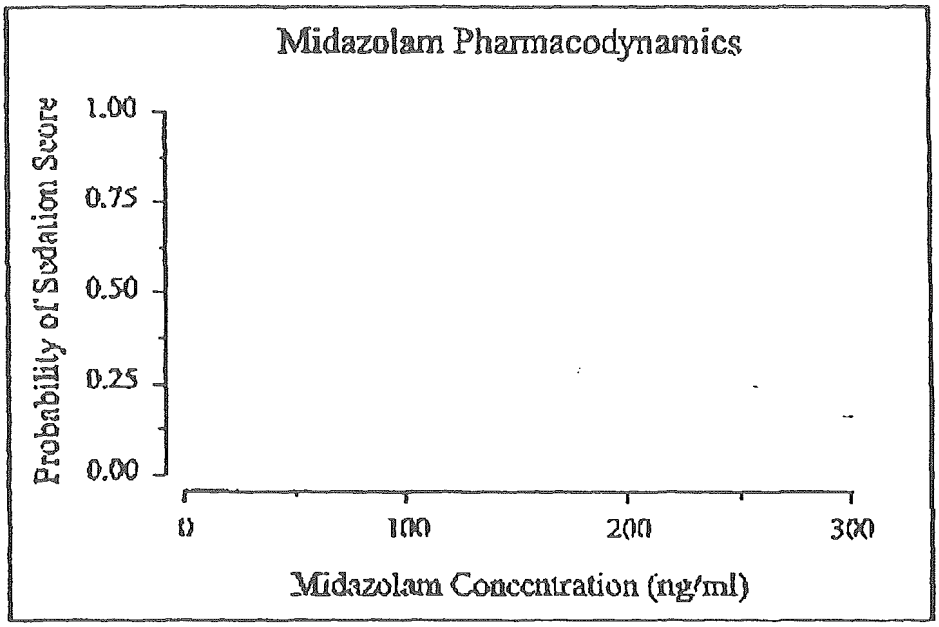
Most patients in these studies experienced at least one adverse event. None of these events were assessed to have a probable relationship with the study drug. Cardiovascular events were the most common. Both hypertensive and hypotensive events were apparent which resolved after cessation of treatment. No correlation was conducted between plasma levels and adverse events.

5.6. *Open Study of Computer-Assisted Continuous Infusion*

This is an ongoing multi-center study involving three study sites. Each site is to enroll thirty patients for a study of the safety, efficacy, pharmacokinetics, and

pharmacodynamics of midazolam administered by computer-assisted continuous infusion (CACI) for sedation during mechanical ventilation following coronary artery bypass grafting (CABG). An interim analysis has examined the pharmacokinetic data for twenty-five patients and the pharmacodynamic data for fifteen patients. The relationship between plasma concentration and sedation level was determined with logistic regression using NONMEM (see Figure 3).

Figure 3; Probability of a sedation score relative to midazolam plasma concentration determined by logistic regression



This suggests that the probability of obtaining a score greater than 2 ranges from 70%-90% at plasma concentrations of ng/ml. The probability of obtaining a sedation score < 5 at this concentration ranges from i%. This is the basis for the claim that the therapeutic window is between 50-100ng/ml. Using parameters determined from the fitting of a three compartment model to the pharmacokinetic data using NONMEM, the desired therapeutic window could be simulated using the following dosing schedule;

> First hour: 5-10 mg/hr, Second and third hours: 3-6 mg/hr, beyond 3 hours: 2-4 mg/hr. After infusions of more than 4 hours duration, return to a fully alert state may take 6-10 hours after stopping midazolam application.