INTRODUCTION

Versed (midazolam HCl) is a water-soluble, short-acting benzodiazepine that depresses the central nervous system. It is 95% plasma-protein bound and subject to approximately 55% first pass metabolism. Midazolam is currently approved for three indications: preoperative sedation; intravenous induction of anesthesia; and conscious sedation during therapeutic procedures. A supplemental application (No. 029) to the manufacturer's previous NDA was submitted on 13 September 1995 providing data for a new indication – continuous intravenous infusion for sedation of intubated, mechanically ventilated patients.

Since the late 1980s, intensivists in the US have been using midazolam off-label in order to sedate critically ill patients receiving mechanical ventilation. Independent audits of hospital practices suggest that 25% of the current use of midazolam in the US is for sedation of ICU patients. Midazolam is used as a sedative for over 2,000,000 ICU patient-days yearly. Continuous infusions account for approximately 45 percent of this use. In 30 percent of cases, the duration of administration is for three days or longer.

The Review Task

There is no doubt that midazolam is safe and effective. Questions that need to be answered with respect to continuous infusions include the following:

- What is the minimum effective dose required to sedate post-surgical patients and ICU patients?
- What are the side-effects of prolonged midazolam infusions?
- Is there tolerance to, or withdrawal from, midazolam infusions?
- What drug interactions (eg, prolonged elimination) are observed when midazolam is administered to ICU patients?

To answer dosing and safety concerns, the sponsor provided data from a variety of supported studies: i) three pivotal dose-finding studies [Martineau et al, Ralley et al, and Teasdale et al]; ii) two repeat-bolus studies [Leslie et al, Ramsey et al]; iii) one continuous infusion study (safety data only)[White et al]; and iv) eight open-label, uncontrolled investigations. In addition, the sponsor generated a detailed literature review of the adult ICU population that included 26 prospective, randomized, controlled, continuous infusion studies (22 of which included a comparitor, usually propofol); 23 uncontrolled studies; and more than almost 200 miscellaneous papers (abstracts, case reports) from the world literature. One study, still ongoing, is a pharmacokinetic study using a computer-assisted controlled infusion (CACI).

CHEMISTRY

Compatibility data for midazolam with 5% dextrose and 0.9% sodium chloride in PVC bags was submitted as a supplement in the application, S-020, dated 4 February 1991 and approved 19 September 1991. The compatibility data show that midazolam Injection, 5 mg/mL, when diluted to a midazolam concentration of 0.5 mg/mL with 5% dextrose or 0.9%sodium chloride is chemically and physically stable for ≥24 h.

For this NDA, the sponsor has prepared midazolam infusion solutions with PVC tubing to compare its compatibility with the tubing. Midazolam infusion solutions were made up at midazolam concentrations of 0.3 mg/mL and 0.5 mg/mL, diluted with 5% dextrose and 0.9% sodium chloride. The concentration of midazolam was assayed over a 24 h period using HPLC. The data recorded is within the specification limits of %.

From a chemistry viewpoint, the supplement can be approved.

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CLINICAL PHARMACOLOGY

Three dose-ranging studies supported by the sponsor investigated midazolam infusions in ICU patients (for a more complete description of these studies see "Summary of Clinical Studies", below). Two of these (Ralley et al and Teasdale et al) 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. Steady-state plasma concentrations measured in the third study (Martineau et al), in which the dose of midazolam was essentially unchanged throughout the study (whereas the dose of narcotic analgesia was varied), ranged from a mean of 76 ng/mL (range 31-140 ng/mL), 130 ng/mL (40-270), and 205 ng/mL (100-470) for the low, medium, and high treatment groups, respectively. Interim analysis of data collected from a partially completed CACI study indicates that midazolam has a therapeutic window between 50-100 ng/mL for sedation following coronary artery bypass surgery. Similar values were obtained for the low, moderate, and high dose groups with respect to clearance rate, volume of distribution, and elimination half-life and agreed with other studies in the literature.

In their literature review, the sponsor found studies in volunteers that lasted as long as 26 h with infusion rates up to 40 ug/kg-h. Mean plasma clearance in this group ranged from 6.1 to 9.6 mL/min-kg. Mean volume of distribution ranged from 1.0 to 2.7 L/kg. Studies in patients undergoing cardiac, abdominal aortic, and maxillofacial surgery demonstrated a mean plasma clearance and volume of distribution that were similar to those in volunteers, ie, 3.4-10.5 mL/min/-kg and 1.0-3.1 L/kg, respectively. For ICU patients, corresponding values were 0.4-10.3 mL/min/-kg and 0.7-4.6 L/kg, findings that are not unexpected in patients with hepato-renal dysfunction who are typically edematous and hypoalbuminemic. Because of the high variability in Vd and Cl in critically ill patients, cautious dosing should be emphasized. This is reflected in the observation that 14% of patients in the sponsor-supported studies experienced hypotension, most of these cases occurring immediately following the midazolam loading dose.

Midazolam undergoes hepatic metabolism to 1-hydroxy midazolam which is then conjugated and excreted by the kidneys. In the literature review, the sponsor presented several studies that measured levels of the unconjugated metabolite, which were considerably lower than those of the parent compound. This finding, together with the lower receptor affinity and lower relative brain uptake of 1-hydroxy midazolam relative to the parent compound, make it likely that the net pharmacological effect of midazolam administration is attributable to the parent compound. Since the glucuronide is excreted by the kidney, its plasma levels will rise in patients with renal insufficiency. This is not of clinical importance, however, since the glucuronide conjugate is pharmacologically inactive.

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SUMMARY OF CLINICAL STUDIES*

Protocol, Enrollment, Randomization, and Evaluability

Data for three dose-finding, controlled clinical trials were submitted under the sponsor's IND. Two of these were in post-CABG patients (one of which also included 4 patients who had valve replacement), whereas the third was in patients undergoing abdominal aortic aneurysm (AAA) surgery. Except for the first 7 (pilot) patients in Teasdale's CABG study in whom the loading doses were clearly too high, the only patients dropped from any study after being enrolled were in Ralley's group: one low-dose patient had to return to the OR for bleeding <3 h after the infusion was started; two high-dose patients were dropped, one who received the incorrect dose, the other who required a muscle relaxant for excessive shivering.

DOSE-FINDING TRIALS IN ADULT ICU PATIENTS CONDUCTED UNDER THE SPONSOR'S IND

First Author	Setting	Opioid Technique (ug/kg)	Patients	Loading Dose (mg/kg)	Maintenance Dose (ug/kg-min)
Martineau	AAA Surgery	Load: Fentanyl: 2-10 or Alfentanil: 10-50 or Sufentanil: 1. Maintenance Total: Fentanyl ≤15; Alfentanil: ≤125; Sufentanil: ≤3.	30 (10 in each of 3 treatment groups)	Low: 0.03 Moderate: 0.06 High: 0.10	Continuous Infusion: Initial: 0.5; Optimal: 0.66 Initial: 1.0; Optimal: 0.83 Initial: 1.5; Optimal: 1.33
Ralley	CABG + Valvular Surgery	Load: Fentanyl: 2-10 or Alfentanil 10-50 or Sufentanil 1. Maintenance Total: Fentanyl: ≤15; Alfentanil: ≤125; Sufentanil: ≤3.	45 (15 in each of 3 treatment groups)	Low: 0.03 Moderate: 0.06 High: 0.09	Continuous Infusion: Initial: 0.5; Optimal: 0.25 Initial: 1.0; Optimal: 0.45 Initial: 1.5; Optimal: 0.40
Teasdale	CABG Surgery	Load: Fentanyl 30. Maintenance Total: Fentanyl ≤75.	30 (10 in each of 3 treatment groups)	Low: 0.015** Moderate: 0.03 High: 0.050	Continuous Infusion: Initial: 0.5; Optimal: 0.25 Initial: 1.0; Optimal: 0.28 Initial: 1.5; Optimal: 0.23

**First 7 patients dropped and excluded from the analysis: Low: 0.03; Moderate: 0.06; High: 0.09 mg/kg.

Coronary Artery Bypass Graft Surgery

Methodology for the two studies conducted in patients undergoing CABG surgery, ie, Ralley et al and Teasdale et al, were similar in many respects. Patients were randomized into low, moderate, and high dose midazolam loading and maintenance infusion groups. The patients were comparable in terms of age, body surface area, duration of surgery, and ASA status. Subjects were premedicated with morphine and underwent a "moderate-dose" narcotic regimen with low dose inhalation agent as "background" anesthetic.

They were different, however, in two key respects: i) Teasdale's patients were induced with moderate-dose fentanyl (30 ug/kg), whereas Ralley's patients received either low-dose fentanyl (2-10 ug/kg), or moderate-dose sufentanil or alfentanil; ii) the two studies used inverse sedation scales. A four-step scale was used for Ralley's study (1=unresponsive; 2=asleep, responds to pain; 3= asleep, responds to verbal command; 4=awake), whereas a six step scale was used for Teasdale's study (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=unresponsive). The goal was to achieve the same level of sedation, ie, 2-3 in Ralley's study and 3-5 in Teasdale's. For the purposes of this review, Ralley's sedation scores have been transformed to comply with the results of the other two studies.

*Throughout this review, conversion to ug/kg assumes patient weight=70 kg.

The following tables show that all three dosing groups had a marked change in sedation scores and that even before they received a revised (downward) midazolam bolus, Teasdale's patients were within the targeted range for sedation of 3-5 (in bold):

SEDATION SCORES FOR CABG PATIENTS: RALLEY / TEASDALE*							
HOUR	0	0.25	0.5	1	2	4	6
Low Dose	2.3/3.4	4.7/5.3	4.7/5.5	3.6/5.4	3.1/4.4	2.8/3.1	2.6/3.0
Moderate Dose	2.2/3.6	5.3/6.0	5.4/6.0	4.7/6.0	3.6/4.5	2.6/3.9	2.6/3.4
High Dose	2.3/3.5	5.6/5.8	5.6/5.8	5.1/6.0	3.5/5.7	3.6/4.2	2.8/3.6

* Numbers in bold=sedation within the target range for the study.

MIDAZOLAM INFUSION DOSE (ug/kg-min) FOR CABG PATIENTS: RALLEY / TEASDALE							
HOUR							
Low Dose	0.5/0.5	0.52/0.33	0.3/0.3	0.26/0.28	0.21/0.21	0.22/0.21	0.16/0.24
Moderate Dose	1/0.9	0.97/0.4	0.57/0.4	0.35/0.37	0.23/.0.25	0.30/0.21	0.32/0.28
High Dose	1.5/1.5	1.45/0.74	0.75/0.74	0.42/0.62	0.30/0.35	0.32/0.34	0.32/0.25

Rather than reduce the loading dose further in subsequent patients, Teasdale et al elected to reduce the maintenance dose by half. Regrettably, their subjects remained heavily over-sedated (ie, sedation score >5) for almost 2 hours, until the infusion rate was reduced to 12-18 ug/kg-h (0.2-0.3 ug/kg-min). Even though the degree of over-sedation in Ralley's patients was much less, the desired level of sedation was not attained until the dose was decreased to the same rate as in Teasdale's patients, ie, 12-18 ug/kg-h (0.2-0.3 ug/kg-min).

It is likely that pharmacodynamic differences among the synthetic opioids accounted for this observation. Fentanyl, especially in doses as high as 30 ug/kg, has a sedating effect, as opposed to sufentanil or alfentanil. Moreover, the duration of fentanyl's sedative effects is longer than its congeners.

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- **Abdominal Aortic Aneurysm Surgery**

The study by Martineau et al was the only dose-finding study conducted in this population. In many respects, the methodology closely resembled that of Ralley et al. For example, the demographics of the patient populations were similar in terms of age, body surface area, duration of surgery, and ASA status. Choice of opioid consisted of low-dose fentanyl or medium-dose sufentanil, or alfentanil. An inhalation agent was used to provide "background" anesthesia. The midazolam dosing schedule was virtually identical, with subjects randomized to receive a midazolam loading dose of 0.03, 0.06, or 0.10 mg/kg, followed by corresponding midazolam infusion rates of 0.5 ug/kg-min (low dose), 1.0 ug/kg-min (moderate dose), or 1.5 ug/kg-min (high dose). There was one noticeable difference -- the sedation scoring system was the same one as Teasdale used (6-step).

SEDATION SCORES FOR ALL THREE DOSE-FINDING STUDIES: RALLEY / TEASDALE / MARTINEAU							
HOUR							
Low Dose	2.3/3.4/1.9	4.7/5.3/3.8	4.7/5.5/3.4	3.6/5.4/3.8	3.1/4.4/3.4	2.8/3.1/3.7	2.6/3.0/3.4
Moderate Dose	2.2/3.6/2.6	5.3/6.0/4.9	5.4/6.0/4.5	4.7/6.0/4.8	3.6/4.5/4.4	2.6/3.9/4.1	2.6/3.4/3.8
High Dose	2.3/3.5/1.4	5.6/5.8/5.1	5.6/5.8/4.7	5.1/6.0/4.8	3.5/5.7/4.4	3.62/4.2/3.9	2.8/3.6/4.0

*Numbers in bold=sedation within the target range for the study.

The hypothesis was that each group would titrate to a common infusion dose as occurred in the CABG studies. This did not happen, as the treating physicians altered the dose of narcotics analgesics from high (43 mg morphine dose-equivalents) to moderate (34 mg) to low (18 mg) across treatment groups. Accordingly, even though the ultimate infusion rates ranged from ug/kg-h ug/kg-min) for the three treatment groups, sedation scores were in the desired range as early as the first 30 min of infusion and remained there throughout the study period.

MIDAZOLAM INFUSION DOSE (ug/kg-min) FOR ALL THREE DOSE-FINDING STUDIES: RALLEY / TEASDALE / MARTINEAU							
HOUR							
Low Dose	0.5/0.5/0.5	0.52/0.33/0.5	0.3/0.3/0.5	0.26/0.28/0.47	0.21/0.21/0.55	0.22/0.21/0.6	0.16/0.24/0.6
Moderate Dose	1.0/0.9/1.0	0.97/0.4/1.0	0.57/0.4/1.0	0.35/0.37/0.78	0.23/.0.25/0.75	0.30/0.21/0.9	0.32/0.28/0.9
High Dose	1.5/1.5/1.49	1.45/0.74/1.49	0.75/0.74/1.49	0.42/0.62/1.49	0.30/0.35/1.15	0.32/0.34/1.34	0.32/0.25/1.34

Effect on Concurrent Medication

Since patients enrolled in the two cardiac surgery studies underwent the same procedure and ultimately received the same infusion rate (12-18 ug/kg-h=0.2-0.3 ug/kg-min) of midazolam, it is not unexpected that they would require roughly the same total amount of narcotic analgesia in the post-operative period.

A problem arises when these results are compared with those from the aortic surgery study. At first glance, it might appear that low, moderate, and high dose midazolam groups in Martineau's study ultimately had the same level of sedation. What actually occurred was that low-dose midazolam patients received a total dose of narcotics (morphine equivalents) that was substantially higher than that received by their high dose cohorts. While the practice of using midazolam to reduce analgesic requirements cannot be condoned, it does illustrate midazolam's opioid-sparing effect.

INTEGRATED ANALYSIS OF EFFICACY

What is the minimal effective dose for sedation in the ICU population?

Cardiac Surgery

i) **Loading Dose:** The fact that Teasdale's patients were too heavily sedated for several hours has important clinical implications. As mentioned previously, even the lowest midazolam loading dose (0.015 mg/kg), combined with the lowest infusion rate (0.5 ug/kg-min), was too large, given putative CNS tissue fentanyl concentrations and fentanyl's pharmacodynamic profile. Accordingly, when moderate-dose fentanyl (eg, 25-75 ug/kg loading dose + supplements prn) is used to induce patients, the recommended midazolam loading dose is approximately 0.010 mg/kg. The fact that Ralley's patients (who received a loading dose of 0.030 mg/kg) were less heavily sedated than Teasdale's during the first hour, lends support to the recommendation that in subjects induced with low-dose fentanyl (ie, ≤10 ug/kg) or medium-dose sufentanil or alfentanil, a midazolam loading dose of 0.020 mg/kg is appropriate.

ii) **Infusion Dose:** Cardiac surgery patients in these dose-finding studies ultimately achieved the desired level of sedation at a constant infusion rate of 12-18 ug/kg-h (0.2-0.3 ug/kg-min). Accordingly, the recommended initial infusion rate in this population is 15 ug/kg-h (0.25 ug/kg-min).

Major Vascular Surgery

Recommendations for AAA patients are less clear. Data from Martineau's study of 30 patients are confounded by a more than two-fold difference (18 mg vs 43 mg) in concurrently administered morphine equivalents between the high and low dose midazolam group. Assuming pain management is being adequately addressed by epidural narcotics/local anesthetics, intravenous opioid infusions, non-steroidals, or PCA, an appropriate dose of midazolam for AAA patients during mechanical ventilation appears to be similar to that for cardiac surgery patients, ie, approximately 0.020 mg/kg loading dose + 15 ug/kg-h (0.25 ug/kg-min) infusion rate.

ICU Patients

This seems an appropriate place to outline the demographics of the ICU patient population.

Broadly speaking, this group can be stratified into two subgroups. The first consists of post-operative surgery patients who require short-term mechanical ventilation (ie, <12 h) until they recover from the effects of surgery (eg, blood loss) and anesthesia (ie, drugs that induce acute *ventilatory* failure – inability to eliminate sufficient CO_2 – by reducing level of consciousness). Results of the three dose-finding studies supported by the sponsor fall into this category.

The second subgroup is comprised of medical and surgical patients who require long-term mechanical ventilation (ie, days to months) for acute *respiratory* failure – inadequate oxygen uptake in the lungs – subsequent to life-threatening systemic illness, eg, systemic inflammatory response syndrome (ie, ARDS). Acute respiratory failure can last a week or it can last months. Unless patients develop acute respiratory failure on the first day after surgery, hospitalized patients who become hypoxemic acutely *rarely* receive opioids prior to endotracheal intubation for fear that respiratory drive will be blunted,

necessitating intubation prematurely for iatrogenic reasons. Because this group is extremely heterogenous with respect to several important variables, eg, nature of their illness, number and the extent to which various organs are affected, premorbid physiologic function, age, and mental status, the recommended bolus and infusion doses will, by necessity, cover a wide spectrum. On one end are frail, elderly patients who may require an initial IV bolus as small as 0.5 mg (7 ug/kg). At the other end of the spectrum are young adults, who may require up to 200 ug/kg-h (3.3 ug/kg-min). These doses should be divided and administered over ≥2 minutes. It is important to point out that in following these dosage recommendations, caution is advised in those instances when midazolam administration is initiated in preparation for endotracheal intubation.

As the inflammatory response increasingly impairs hepatic and renal function, appropriate infusion rates often fall below the recommended infusion rates for post-CABG/AAA patients. This phenomenon is most likely due to higher free drug levels resulting from the combined effects of hepato-renal dysfunction, ie, hypoalbuminemia, impaired hepatic glucuronide conjugation, and/or diminished excretion of the major metabolite, 1-hydroxy-midazolam (20% activity of the parent compound). Less well understood as a contributing factor are potential drug interactions specific for the ICU population (see side-effects and drug interactions, below).

INTEGRATED SUMMARY OF SAFETY

Is Midazolam Safe to Administer by Continuous Infusion?

There were no deaths or serious injuries attributable to study drug in either Ralley's or Teasdale's investigation. The most frequent adverse event was hypotension, which resolved with conventional treatment. A transient (ie, 15 minute) 50 mmHg decline in systolic blood pressure was noted, however, in the first 15 min of Teasdale's study (due to excessive bolus doses). Transient arrhythmias, one episode of elevated cardiac enzymes, and a pneumothorax also were seen in Teasdale's group, none of which is unexpected in this type of surgery.

One patient [redacted] low dose group) in Martineau's study had an adverse event. He experienced postoperative hemorrhage, resulting in hypovolemia, non-cardiogenic pulmonary edema, and a perioperative myocardial infarction. He recovered and was discharged to home. It is unlikely that these events were related to drug infusion. In addition, five patients experienced hallucinations, confusion, or agitation, with no apparent relation to dose. There were no treatment-related alterations in vital signs or laboratory test, despite careful examination for acute withdrawal phenomena.

In formulating this part of the review, the reviewer requested all adverse events associated with midazolam administration reported to the Agency up until 26 February1996. Key words were "withdrawal," "somnolence,"and "prolonged effect." Fourteen cases were identified in which patients (aged 12-60) receiving continuous Midazolam infusions averaging 5-10 mg/h for agitation during mechanical ventilation experienced "withdrawal symptoms," ie, tachycardia, agitation, restlessness, combativeness, sleeplessness, sweating, hallucinations, and, in at least one instance, a grand mal seizure. A common thread running through these reports is that long-term (ie, one or more weeks) infusions were stopped abruptly or weaned from the patient overnight. In many cases, appearance of symptoms was delayed until 12-36 h after termination of the infusion. Typical management included reinstitution of the midazolam infusion and a second weaning trial that lasted several (eg, 3-5) days. Successful outcome with no sequelae was achieved in all cases using this approach.

A review by the sponsor of data supporting the safety of midazolam by continuous infusion to adult ICU patients included material from four primary sources: 1) publications of controlled and uncontrolled trials; 2) publications of clinical pharmacology studies designed to investigate the pharmacokinetics of midazolam; 3) controlled and uncontrolled trials supported by the sponsor, including dose-finding studies; and 4) results of the sponsor's worldwide postmarketing safety monitoring system. Their review of controlled (vs propofol, in most cases) trials published in the medical literature revealed the following. Nine of the studies reported a number of deaths in the respective treatment groups. In the midazolam group (n=299), 1 patient (0.33%) died, whereas in the comparative (propofol by continuous infusion) group (n=270), 8 patients (2.96%) died.

SPONSOR'S SUMMARY OF STUDIES IN WHICH ADULT ICU PATIENTS RECEIVED MIDAZOLAM BY CONTINUOUS INFUSION		
Source of Safety Data	**Patient Population**	**Number of Patients**
Controlled Clinical Studies	Medical/Surgical Postoperative Recovery	430 (+ 139 additional patients in 4 controlled studies that did not report the number of patients per treatment group)
Dose-finding Studies	Postoperative Recovery	163 (includes 105 patients from the pivotal Canadian dose-finding studies and studies comparing intermittent bolus vs continuous infusion)
Uncontrolled Studies	Medical/Surgical Postoperative Recovery	319
Pharmacokinetic Studies	Medical/Surgical Postoperative Recovery Healthy Volunteers	325

What Are The Side-Effects Associated with Continuous Midazolam Infusions?

Because sedation during mechanical ventilation is the primary indication for continuous infusion of midazolam, none of the studies included ventilatory management of the patient among outcome measures. Insofar as time to extubation can be considered a measure of the need for ventilatory support, in studies that compared continuous infusions of midazolam vs propofol, the former was associated with a substantially longer time from termination of infusion to extubation.

Many drugs administered to ICU patients on a routine, round-the-clock basis, inhibit the same enzyme responsible for hepatic 1-hydroxylation of midazolam: cytochrome P450 3A. These include certain histamine-2 antagonists (cimetidine), antibiotics (erythromycin), calcium channel blockers (diltiazem, verapamil), and anti-fungal agents (ketoconazole, fluconazole). Even though this reviewer could not find any published reports of adverse interactions involving midazolam by continuous infusion, it is as yet unclear whether administration of one or more of these substances decreases midazolam metabolism and intensifies its effect, in the face of unchanged infusion rates. None of the dose-finding studies reviewed in this NDA was designed to evaluate drug interactions.

The major side-effect appearing in these dose-finding studies was hypotension, reported in the range of 0-14.3% of patients. Current labeling indicates that the sedative effect of midazolam is accentuated by narcotics administered as premedication for surgery, and therefore recommends that the dosage be adjusted in accord with their use. In patients who have received fentanyl in the 30 ug/kg range, a 14% incidence of hypotension is significant but not unexpected. On the other hand, in ICU patients with acute respiratory failure who are in the initial stage of their disease, hypotension should raise suspicions that other factors are at play.

No neurological or dermatological side-effects were noted in the studies cited.

Is There Tolerance To, Or Withdrawal From, Continuous Midazolam Infusions?

In the dose-finding studies, there was no evidence that the doses of midazolam specified in the protocols were increased to compensate for tolerance. If anything, the initial doses were titrated down to reach the therapeutic endpoint.

As mentioned previously, there have been a number of reports of symptoms interpreted as signs of withdrawal following prolonged midazolam treatment. Admittedly, this represents a tiny fraction of less than one percent. The fact that most clinicians wean midazolam infusions over several days probably accounts for the low number of AE reports.

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Are There Effects of Prolonged Administration on Steroidogenesis or Hepatic Function?

Several literature studies looked at the effect of prolonged midazolam infusion on steroidogenesis and found no effect. One controlled trial specifically investigated the effects of continuously infused midazolam on hepatic function and found no adverse effects. Hepatic dysfunction in critically ill patients is more likely due to their underlying disease.

CONCLUSION

Findings from the sponsor's three pivotal trials indicate that midazolam administration by continuous infusion is safe and effective for sedating intubated, adult ICU patients during mechanical ventilation. This is consonant with a number of well-designed studies from the literature and corresponds to the clinical impression of intensivists who have been administering midazolam by continuous infusion off-label for more than 5 years.

In particular, the data show that loading doses and infusion rates depend upon a number of factors. These include the setting, plasma levels of opioids, if any, already present in the circulation; patient's age and premorbid status; and severity of disease. Appropriate loading doses (administered over ≥2 minutes in divided doses) range from mg/kg in patients undergoing cardiac and major vascular surgery, and from 0.05 up to 0.2 mg/kg in intubated critically ill patients with acute respiratory failure. In the postopeţative setting, corresponding infusion rates are approximately 15 ug/kg-h; in the critically ill population, rates range from approximately 30 ug/kg-h in frail, elderly patients to as much as 200 ug/kg-h in tolerant, young adults. It should be noted that for the average adult, a loading dose of 0.01 mg/kg is less than the 1 mg initial dose recommended in the label. The revised label for this NDA will need to emphasize that extra caution is advised when larger doses are administered to *unintubated* patients in respiratory failure in prepartion for endotracheal intubation in the ICU.

In conclusion, within these recommended guidelines, approval of midazolam by continuous infusion should be granted.

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APPENDIX

A) Literature Search by Sponsor

Not Supported by the Sponsor: A literature search to identify publications appearing by April 1994, and presenting original data relevant to the use of midazolam by continuous infusion in adult ICU patients, was conducted by the sponsor. The result was a total collection of 26 publications, with a total enrollment of 1071 patients; of these, 430 actually received midazolam. Of this group, 383 patients received midazolam as the only sedative, while an additional 18 received a combination of Midazolam and morphine and 29 received a combination of midazolam and fentanyl.

All 26 studies were prospective, controlled, parallel-group trials. Eighteen of the studies compared midazolam with propofol, two with isoflurane, and one study each compared midazolam with diazepam, ethanol + clonidine, flunitrazepam, alfentanil + propofol, and morphine. The remaining study compared two dose regimens of midazolam with saline. All but four were randomized (it was not stated whether these four were randomized), one was double-blind, one reported a blinded assessor, and all but one study were conducted a single center.

In 22 of these studies, the actual number of patients receiving a continuous infusion of midazolam was reported, ie, 430 patients. Midazolam was administered as the only sedative to 383 patients, while an additional 18 received midazolam + morphine and 29 received midazolam + fentanyl. In these same studies, there were 327 patients who received propofol, 60 who received isoflurane, 20 who received morphine, 11 who received flunitrazepam and fentanyl, 9 normal saline, and 7 diazepam. In addition, 40 patients received intermittent bolus doses of midazolam as part of the parallel-group design and 20 patients received a combination of morphine by continuous infusion and intermittent midazolam boluses.

In these 22 studies, the breakdown by patient population was as follows: 8 were in post-cardiac surgery patients, 4 in non-cardiac surgery patients, 1 in a respiratory ICU, and 9 in a mixed medical/surgical ICU.

CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR

First Author	Citation	Report Type	# of Patients	Study Design	Treatment Groups	Patient Population
Aitkenhead	*Lancet*	Full	101	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Med/Surg/ Trauma
Barvais	*Acta Anaesth Belg*	Full	14	Prospective, Randomized, Comparative	Midazolam vs Diazepam	CABG
Beyer	*Anaesthesist*	Full	20	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg
Boeke	*J Drug Develop*	Full	10	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg

CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR						
Boyle	*J Drug Develop*	Brief	58	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Med/Surg
Carrasco	*Chest*	Full	88	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg/ Trauma
Chaudhri	*Br J Anaesth*	Brief	40	Prospective, Randomized, Comparative	Midazolam vs Propofol	CABG
Clarke	*J Drug Develop*	Brief	20	Prospective, Randomized, Comparative	Midazolam vs Propofol	Neurosurg
Degauque	*J Drug Develop*	Brief	11	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med (Resp Failure)
Du Gres	*J Cardiothoracic Anesth*	Abstract	38	Prospective, Randomized, Comparative	Midazolam vs Propofol	Cardiac Surg
Geller	*Anesthesiology*	Abstract	51	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg
Glew	*J Drug Dev*	Brief	29	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg
Higgins	*Anesthesiolgy*	Abstract	80	Prospective, Randomized, Comparative	Midazolam vs Propofol	CABG
Huber	*Langenbecks Arch Chir*	Brief	52	Prospective, Randomized, Comparative	Midazolam vs Ethanol vs Clonidine	Post-op alcoholic
Kocks	*Eur Congress of Anaesth*	Abstract	23	Prospective, Comparative	Midazolam + Fentanyl vs Fentanyl + Flunitrazepam	Trauma
Kong	*Br Med J*	Full	60	Prospective, Randomized, Comparative	Midazolam vs Isoflurane	Surg/Other
Kox	*Br J Anaesth*	Abstract	30	Prospective, Randomized, Comparative	Midazolam vs Alfentanil vs Propofol	Med/Surg
Ledingham	*Resuscitation*	Interim	36	Prospective, Randomized, Comparative with Blinded Assessor	Midazolam Bolus + MS infusion vs Midazolam Infusion +MS Bolus vs MS infusion + MS bolus	Med/Surg
Lehmkuhl	*J Drug Dev*	Brief	60	Prospective, Comparative	Midazolam Bolus vs Midazolam Infusion vs Propfol Infusion	Med/Surg

LANDOW

CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR						
Pappagallo	*Minerva Anestesiol*	Full	22	Prospective, Comparative	Midazolam vs Propofol	Med/Surg
Plainer	*J Drug Dev*	Interim	6	Prospective, Randomized, Comparative	Midazolam + Sufentanil vs Sufentanil + Propofol	Neurosurg
Roekaerts	*J Cardiothoracic & Vasc Anesth*	Full	30	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	CABG
Snellen	*Int Care Med*	Full	40	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	CABG
Spencer	*Int Care Med*	Full	60	Prospective, Randomized, Open, Comparative	Midazolam vs Isoflurane	Med/Surg
Westphal	*Anesthesiology*	Full	27	Prospective, Randomized, Double Blind, Comparative	Midazolam vs saline	CABG
Wolfs	*J Drug Dev*	Full	34	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg/Trauma

B) Trial by Trial Reviews

Twelve of these controlled trials from the literature were published as original articles. Three of these – two in ICU patients (Aitkenhead et al; Carrasco et al), and one in cardiac surgery patients (Westphal et al)a midazolam loading dose of 0.020 mg/kg is appropriate – appearing in leading peer-reviewed journals were carefully examined by this reviewer.

Aitkenhead AR, Pepperman ML, Willatts SM, et al. Comparison of propofol and midazolam for sedation in critically ill patients. Lancet 1989;1:704-709.

Introduction: This prospective, randomized, multi-center, open-label comparative study of propofol vs midazolam for short-term (≤24 h) sedation of ICU patients looked at effectiveness of sedation (Ramsey Score), impact on adrenal function, and time required for weaning from mechanical ventilation.

Methods: Patients (n=101) aged 16-80 yrs in five institutions were randomized to receive either propofol or midazolam by continuous infusion. A "synacthen test" (ie, known in this country as a Cosyntropin test) was performed immediately after termination of the infusion.

Results: One patient never received sedation and was not included in the study data. Four propofol patients died during the study for reasons judged unrelated to sedation.

Conclusions: "Propofol and midazolam were comparable in safety and efficacy for sedation; neither drug impaired production of adrenal corticosteroids; recovery time was less variable after discontinuation of propofol than midazolam; weaning from the respirator (*sic*) was achieved faster in propofol patients than in midazolam patients."

Reviewer's Comments: The sponsor's review was generally accurate. It omitted the fact that the difference between the groups in terms of weaning following termination of infusion was highly significant – $p<0.001$ – in favor of propofol.

Carrasco G, Molina R, Costa J, Soler JM, and Cabre L. Propofol vs midazolam in short-,

medium-, and long-term sedation of critically ill patients: a cost-benefit analysis. Chest 1993;103:557-564.

Introduction: This randomized, prospective; open label, comparative study of midazolam vs propofol in short-, medium-, and long-term sedation of critically ill patients compared the effectiveness and cost-benefit of the two drugs.

Methods: Patients >16 yr old (n=102) were randomly assigned to receive either propofol (n=46) or midazolam (n=42). Within each group, patients were classified into candidates for short-, medium-, or long-term sedation. Desired levels of sedation were defined as end-points. Safety was assessed through hemodynamic parameters, lab test results, recovery time from termination of the infusion to extubation and total time before the patient could be transferred to the floor. Statistics: Unpaired t-test or Mann-Whitney U test for between-group comparisons; linear regression to correlate sedation time with extubation and recuperation times, defined as the time when the patient could be transferred to a step-down unit or the floor.

Results: Ten patients were ineligible due to exclusion criteria, but it is not clear whether they were randomized ant/or exposed to medication. Four patients died during the study period but there is no mention whether they were in the propofol or midazolam group. The remaining 88 patients were analyzed.

Mean Recover Times (h)

	Event	Midazolam	Propofol	p Value
Short-term group	Time to Extubation	2.5	0.3	<0.05
	Total Recovery Time	3.6	1.0	<0.05
Medium-term group	Time to Extubation	13.5	0.4	<0.05
	Total Recovery Time	21	1.4	<0.05
Long-term group	Time to Extubation	36.6	0.8	<0.05
	Total Recovery Time	54.7	1.8	<0.05

Conclusion: "The percent of adequate sedation time was greater for propofol than for midazolam ($p<0.05$). The time to extubation and recovery to full consciousness was faster with propofol than with midazolam. The time to extubation and time to full recovery correlated with the duration of sedation in patients treated with propofol but not with midazolam."

Reviewer's Comment: Review of the study compared to the sponsor's summary was accurate and complete except for the absence of one important finding: as indicated in the accompanying chart (which was provided in the sponsor's review), there was a clinically meaningful and statistically significant shorter time from termination of infusion to transfer out of the ICU in favor of propofol, especially in the medium- and long-term groups.

Westphal LM, Cheng EY, White PF, Sladen RN, Rosenthal MH, Sung M-L. Use of midazolam infusion for sedation following cardiac surgery. Anesthesiology 1987;67:257-262.

Introduction: This randomized, prospective, open label, placebo-controlled, dose-effect study of midazolam in sedation of post-CABG surgery patients.

Methods: Patients (n=27) were randomly assigned to receive either saline, low-dose midazolam (load=0.03 mg/kg + infusion=1.7 mg/kg-h), or high-dose midazolam (load=0.06 mg/kg + infusion=3.4 mg/kg-h) for a duration of 8 h. Statistics: X^2; ANOVA with Bonferroni adjustment; linear regression analysis.

Results: All 27 patients were enrolled and completed the study. The control group required significantly more morphine than the two midazolam treatment groups, but the midazolam groups did not differ with respect to morphine requirement. Time to eye opening and response to command was signficantly longer in the high dose-dose midazolam than in the control group. Time to spontaneous

ventilation was significantly longer in the low-dose midazolam group than in the control group. There was no significant difference in length of ICU stay among the three study groups.

Postoperative Recovery Times (h) After Arriving in the ICU (Mean± SEM)*

Group	First Movement	Eye Opening	Response to Command	Spontaneous Ventilation	Extubation
Saline (placebo)	2.6± 0.6	2.9± 0.6	3.9± 0.6	7.6± 1.1	16.2± 1.3
Low-dose Midazolam	5.9± 1.0	5.9± 1.0	6.4± 0.8	14.1± 1.4	19.2± 1.8
High-dose Midazolam	6.2± 1.0	6.8± 1.0	7.9± 1.1	11.9± 1.2	19.4± 1.4

* Bold=Significantly different from placebo, $p<0.05$.

Conclusion: Midazolam infusion resulted in a significant decrease in the requirement for morphine. Midazolam infusion increased postoperative recovery time.

Reviewer's Comment: Review of the study compared to the sponsor's summary was accurate and complete except that the original article was more balanced in discussing costs (prolonged emergence time) vs benefits (sedation, amnesia, and anxiolysis) of midazolam administration.

Laurence Landow MD — *Date* 30 August 1996

Curtis Wright MD — *Date* 8/30/96

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

Protocol 910 Ralley (Montreal)

NDA- 18-654 Midazolam
Sponsor- Hoffmann La Roche INC.
Primary Reviewer- Curtis Wright
Secondary Reviewer- Laurence Landow
Date of Review- 8/5/96
Material Reviewed- Jacket 6

Summary

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 45 coronary artery bypass graft patients (3 groups of 15 each), who received 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.). Physicians titrated all three groups to the range of mcg/kg/hr with acceptable safety.

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

This protocol started as an open-label study, and was altered to a dose controlled study in a series of amendments before the protocol began. It was supposed to be a patients undergoing single-valve or CABG surgery, but there were only 4 valvular patients out of the 45 studied. Patients scheduled to undergo elective cardiac 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 & scopolamine), pentothal induction, and enflurane balanced anesthesia with one of the fentanyl's for analgesia during the procedure and a midazolam bolus of 0.035 mcg/kg just prior to bypass. Patients were then taken to the ICU where they were given morphine 2 mg IV prn for pain. Midazolam was

mixed in one of three strengths, (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 FOUR step scale: 4 = Awake, 3 = Asleep, responds to verbal command, 2 = Asleep, responds to pain, 1 = Unresponsive. Physicians were advised to titrate the patients to a target score of 2 or 3 (Asleep but responsive), reduce dosage for a score of 1 (Unresponsive), and increase dosage for a score of 4 (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 4-6 hours, with a 12 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

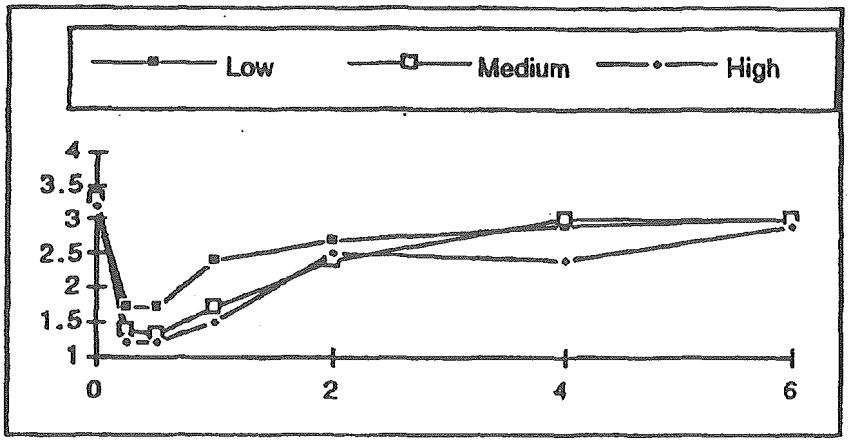
Enrollment, Randomization, and Evaluabilty

48 patients were enrolled, two in the high dose group were replaced (patient given non-protocol medication for shivering, patient given wrong midazolam concentration). Of the 45 patients who were eligible some had minor protocol violations, but all were included in the analysis.

Item (MEAN & SD)	Low Dose	Medium Dose	High Dose
AGE	65 (6)	64 (6)	65 (6)
WEIGHT	73 (9)	73 (13)	71 (12)
HEIGHT	68 (2)	66 (4)	66 (2)
DURATION OF SURGERY	204 (41)	215 (47)	206 (29)
MALE	13	11	11
FEMALE	2	4	4
ASA III	13	15	12
ASA IV	2	0	3
CAUCASIAN	15	15	14
Occlusive Disease	14	13	14
Valvular Disease	2	2	1

Results

All three groups showed a marked change in sedation scores:

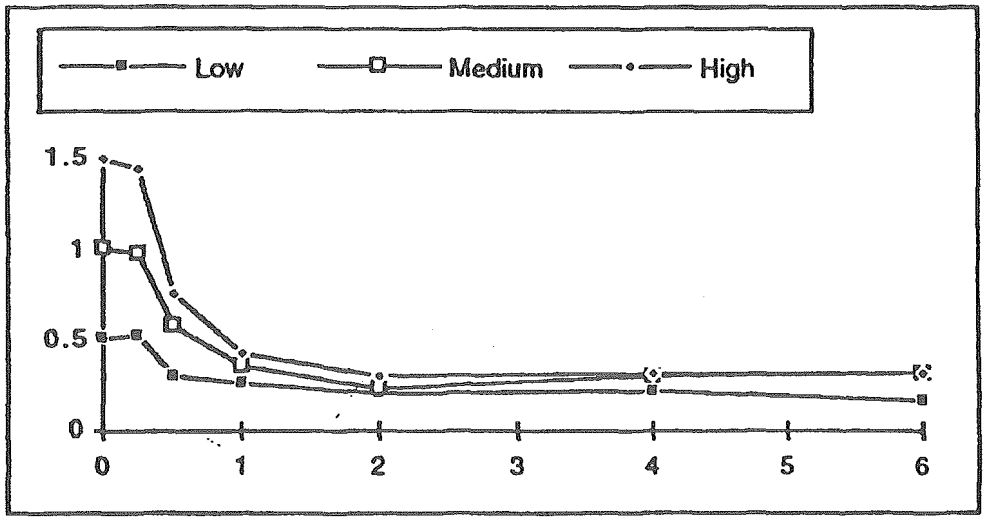


Hours	0	0.25	0.5	1	2	4	6
Low	3.2	1.7	1.7	2.4	2.7	2.9	3
Medium	3.3	1.4	1.3	1.7	2.4	3	3
High	3.2	1.2	1.2	1.5	2.5	2.4	2.9

Except for the inversion, caused by the different scale, the picture is quite similar to trial 912, although far more patients became heavily sedated following the initial bolus dose. This may reflect the addition of both the scopolamine premedication and the bolus of midazolam prior to bypass, or it may reflect a generally deeper anesthesia with greater carry-over of anesthetic effects.

Dose of Midazolam by group

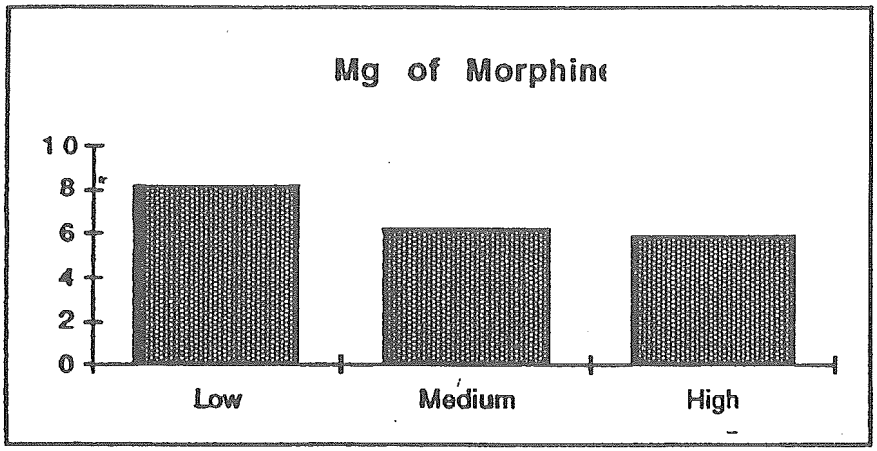
In this study, there was an unequivocal trend toward downward titration in dose (infusion rates in mcg/kg/min).



Hours	0	0.25	0.5	1	2	4	6
Low	0.5	0.52	0.3	0.26	0.21	0.22	0.16
Medium	1	0.97	0.57	0.35	0.23	0.3	0.32
High	1.5	1.45	0.75	0.42	0.3	0.32	0.32

Effect on Concurrent Medication

We see all three groups down-titrating, and this effect is still reflected in the analgesic usage during midazolam administration.



Subjective effects

The results of the questionnaires given the subjects were illuminating:

	Low dose	Medium	High Dose
Failed to remember ICU admission	15/15	10/15	15/15
Did not know if it was day or night	1315	8/15	10/15
No recall of visitors	12/15	10/14	12/14
No recall of anxiety	13/15	8/14	13/15

The impression from the patient questionnaire was that the patients were heavily sedated and amnestic for the period of midazolam administration.

Efficacy Conclusion

The midazolam infusions caused a dramatic change in level of consciousness, taking the population from "half awake & half drowsing" to "half unresponsive & half responsive only to painful stimuli". In this trial, doses above 0.3-0.5 mcg/kg/min were clearly overly sedating. No efficacy differences beyond downward titration were seen between the groups, as the doses given all patients rapidly converged.

Safety

There were no deaths or serious injuries during the trial. One patient had a post-operative hemorrhage requiring re-operation, unrelated to the study drug. The most frequent adverse event was mild hypotension, which resolved in all cases with conventional treatment. One patient had marked shivering, treated with vecuronium.

Follow-up lab values were consistent with the surgery performed.

Conclusion

This was an adequate and well-controlled study. The sponsor's interpretation was that the doses of midazolam were too high. Given group mean scores of 1.2 & 1.4 for the medium and high dose groups, corresponding to 2/3 or 3/4 of the patients being unresponsive to painful stimuli, I agree.

The message from this study is that the dose of midazolam for infusion will need to be titrated, depending on patient factors and on the particular anesthetic technique used. Techniques that involve deeper anesthesia, long-lasting agents or intraoperative benzodiazepines may require lower doses.

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 Martineau & Miller (Ottawa)

NDA- 18-654 Midazolam
Sponsor- Hoffmann La Roche INC.
Primary Reviewer- Curtis Wright
Secondary Reviewer- Laurence Landow
Date of Review- 8/5/96
Material Reviewed- Jacket 6

Summary

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 30 patients (3 groups of 10 each), who received 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.). This did not happen, as the treating physicians altered the dose of narcotic analgesics from high (43 mg) to moderate (34 mg) to low (18 mg) across the treatment groups.

The study showed that all three doses of the drug could safely substitute for opiate-induced sedation, with slightly shorter recovery times for the two lower doses.

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 abdominal aortic 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, pentothal induction, and isoflurane balanced anesthesia with one of the fentanyl's for analgesia during the procedure. Patients were then taken to the ICU where they were given morphine 2 mg IV prn for pain, agitation, "fighting the respirator, or tachycardia. Midazolam was mixed in one of three strengths,