Surveillance of Midazolam Infusions in ICU

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ABSTRACT

In order to determine the utilization of midazolam (MDM) infusions and to assess for the development of tachyphylaxis and withdrawal reactions with MDM, 17 mechanically-ventilated patients who received 18 courses of MDM infusions during their stay in ICU were studied retrospectively.

With a mean age of 52 years (range: 22-78), the average starting, maintenance and peak infusion rates were 1.0 ± 0.6, 1.9 ± 1.3, and 3.8 ± 4.6 mcg/kg/min, respectively. Patients received the infusion for a mean of 9.1 days (range: 0.6-16.1).

An inverse relationship was found between age and mean lowest daily Glasgow Coma Scale (GCS) scores (r=-0.60, n=14,p=0.02). Increases in the mean daily MDM infusion rate, suggestive of tachyphylaxis, were also noted (n=18, p<0.01). Ten patients were studied for use of CNS drugs after MDM discontinuation. Three patients who required haloperidol during the 24 hours following MDM discontinuation received larger doses of MDM than the remaining seven patients (3.6 ± 1.8 versus 1.2 ± 0.6 mcg/kg/min, n=10, p=0.05). Concurrent use of diazepam during the 24 hours prior to MDM discontinuation was documented in seven of ten patients.

The inverse relationship between age and GCS scores is suggestive of decreased clearance or enhanced sensitivity to MDM in older patients. Concurrent use of diazepam, possible development of tachyphylaxis and withdrawal reactions to MDM were also found. These findings may be useful in developing guidelines for use of MDM infusions.

Key Words: *midazolam infusion, tachyphylaxis, withdrawal reactions.*

RÉSUMÉ

Une étude rétrospective de 17 patients mis sous ventilation assistée et ayant reçu 18 perfusions de midazolam (MDM) durant leur séjour aux soins intensifs a été effectuée pour que l'on puisse définir l'utilisation des perfusions de MDM et évaluer les conditions de survenue de tachyphylaxie et de réactions de sevrage associées au MDM.

Les patients étaient âgés en moyenne de 52 ans (écart de 22 à 78 ans). Les vitesses de perfusion initiale, de maintien et maximale étaient de 1,0 ± 0,6, de 1,9 ± 1,3 et de 3,8 ± 4,6 µg/kg/min, respectivement. Les perfusions ont été administrées en moyenne durant 9,1 jours (écart de 0,6 à16,1).

Un rapport inverse a été observé entre l'âge et les scores quotidiens moyens les plus faibles (r = 0,60; n = 14; p = 0,02) à l'échelle de «coma» de Glasgow (GCS). On a aussi remarqué que des augmentations de la vitesse moyenne quotidienne de la perfusion de MDM pouvaient laisser prévoir la tachyphylaxie (n = 18; p < 0,01).

Dix patients ont été évalués relativement à l'utilisation de dépresseurs du SNC après le retrait du MDM. Les trois patients qui ont eu besoin d'halopéridol dans les 24 heures suivant le retrait du MDM avaient reçu de plus fortes doses de MDM que les sept autres patients (3,6 ± 1,8 versus 1,2 ± 0,6 µg/kg/min : n = 10, p = 0,05). L'usage concomitant de diazépam dans les 24 heures précédant le retrait du MDM a été documenté chez sept des dix patients.

Le rapport inverse entre l'âge et les scores à l'échelle GCS semble indiquer une clairance réduite ou une sensibilité accrue au MDM chez les patients plus âgés. On a également noté un usage concomitant de diazépam, un risque de tachyphylaxie et des réactions de sevrage associés au MDM. Ces résultats pourraient être utiles dans l'élaboration de lignes directrices sur l'utilisation des perfusions de MDM.

Mots clés : *perfusion de midazolam, réactions de sevrage, tachyphylaxie*

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INTRODUCTION

Continuous midazolam (MDM) infusions are sometimes used in the management of agitation and anxiety in ventilator-dependent patients in the cirtical care setting.[1,2] Some of the advantages of MDM infusions over diazepam include a short duration of action, avoidance of frequent intravenous (IV) bolus administration, low incidence of local irritation at the site of injection and the lack of active metabolites.[3] Due to the short duration of effect, some authors have documented faster recovery and extubation with MDM than with diazepam in coronary artery bypass patients.[2]

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Unfortunately, there is little information on dosing of the drug in critically ill patients and what has been published indicates marked inter-individual variability.[3-5] Furthermore, there have been reports in the literature of prolonged elimination half-life ($t_{1/2}$) and accumulation of MDM in mechanically ventilated patients, especially those with altered hepatic function.[6-8]

Like other benzodiazepines, MDM has been associated with the development of tolerance.[9-10] Several cases of withdrawal reactions with MDM have also been reported in the literature, including convulsions, anxiety and tachycardia.[11-13]

Finally, since MDM is also more expensive than other benzodiazepines, surveillance of the current utilization of MDM was undertaken to assist in the development of guidelines and criteria for its use.

OBJECTIVES

A retrospective review of MDM infusions administered to patients in the Intensive Care Unit (ICU) was conducted with the following objectives:

1) To determine the utilization of MDM with respect to dose, duration of therapy and patient demographics and to assess relationships between certain demographics, such as age and MDM dose requirements.
2) To determine if tachyphylaxis occurs in patients receiving MDM infusions.
3) To monitor for withdrawal reactions to MDM and to assess whether the occurrence of these can be influenced by the means of discontinuing the drug (i.e., weaning).

METHODS

All patients administered MDM infusions in the ICU during a five-week study period were included in the study. The following information was collected for all the patients and analysed retrospectively: demographics and primary diagnosis; dosing, duration and means of discontinuation (weaning versus abrupt discontinuation) of MDM infusions; orders for concurrent and subsequent use of other central nervous system (CNS) depressants (i.e., benzodiazepines, narcotics, barbiturates and neuroleptics); daily serum creatinine, aspartate aminotransferase (AST), total bilirubin concentrations and lowest Glasgow coma scale (GCS) scores during MDM infusion; and time to extubation with respect to discontinuation of MDM. Elevations in direct bilirubin and prothrombin time (PT), in the absence of warfarin therapy or documented disseminated intravascular coagulopathy (DIC), were also recorded. Since neuromuscular blocking agents lower GCS scores, lowest daily GCS scores were not recorded on days patients received either infusions or bolus doses of pancuronium or vecuronium.

Due to the potential effects of renal/hepatic impairment on MDM dosing requirements, patients with such condition(s) were identified according to the following definitions: renal dysfunction was defined as calculated creatinine clearance (CrCl, Cockcroft & Gault formula) equal to or below 0.33 mL/sec on two consecutive measurements during MDM infusion or the need for dialysis. Patients were considered to have hepatic dysfunction if they fulfilled two or more of the following criteria: elevated AST (>40U/L), elevated total bilirubin (>17 umol/L) in the absence of blood transfusions or hemolysis, elevated direct bilirubin (>10 umol/L) and elevated PT (>12 sec) in the absence of warfarin therapy or documented DIC.

Tachyphylaxis was assessed by relating mean daily MDM infusion rates (per kg of body weight) with respect to time (days of MDM infusion). The occurrence of withdrawal reactions was measured by recording additional doses of CNS depressants administered during the 24 hours following discontinuation of MDM infusion. The difference in requirements for additional CNS depressants between patients who were weaned and patients who were not weaned off MDM was also assessed. Patients were considered to be 'weaned' if there was at least one dose reduction in MDM infusion, during the 24 hours prior to discontinuation of the infusion.

STATISTICAL ANALYSIS

Linear regression analysis and calculation of Pearson's correlation coefficient 'r' were used to determine the relationships between demographic data (i.e., age and GCS scores) and mean MDM infusion rates. Linear regression was also utilized in evaluating the development of tachyphylaxis. *Epistat Statistical Package* for IBM personal computer was used for these statistical calculations. The mean MDM infusion rate in patients who required haloperidol following MDM discontinuation versus those who did not was assessed by Mann-Whitney U test (one-way). Fisher's Exact test was used to compare the proportion of weaned patients versus those not weaned, who required additional CNS depressants following MDM discontinuation.

RESULTS

Utilization and Dose/Demographic Relationships

Seventeen patients received a total of 18 treatment courses of MDM infusions during the study period. All patients were ventilator-dependent at the start of MDM infusion. One patient (#10) received MDM infusion twice, six days apart. She was not extubated during that time. (Table I)

The mean age was 52 ± 18 years (range: 22-78). Four patients expired while on MDM and two patients (#12,17) died subsequent to MDM discontinuation. Time to extubation

Table I: Patient Demographics and Primary Diagnosis

Patient Number	Age (years)	Gender	Condition	Renal (R) or Hepatic (H) Dysfunction	Outcome
1.	35	M	multiple trauma		
2.	56	F	inferior MI		
3.	60	M	postop. bowel infarction	R+H	expired
4.	58	M	respiratory failure, asthma		
5.	51	M	infected carotid endarterectomy		
6.	28	M	multiple trauma		
7.	23	M	intraabdominal sepsis		
8.	78	M	acute bowel obstruction		expired
9.	42	M	sacroiliac abscess, sepsis		expired
10.A	61	F	anteroseptal MI		
10.B	61	F	anteroseptal MI		expired
11.	75	F	mitral valve repair		
12.	69	M	cardiac failure post MI	H	expired
13.	22	M	multiple trauma		
14.	34	M	toxic shock	R	
15.	62	M	double CABG		
16.	41	M	anoxia to brain due to hanging		
17.	73	M	postop. retroperitoneal bleed	R+H	expired

CABG = Coronary Artery Bypass Graft
MI = Myocardial Infarction

Table II: Midazolam Infusion Data

Patient Number	Initial Infusion Rate mcg/kg per min	Mean Infusion Rate mcg/kg per min	Peak Infusion Rate mcg/kg per min	Mean Lowest Daily Glasgow Coma Score	Duration of Infusion days	Means of Midazolam Discontinuation	Time to Extubation hours
1.nb	0.49	0.32	0.59	9.8	14.8	W	-21
2.	1.60	1.67	2.56	9.0	7.0	NW	72
***3.nb	0.91	1.97	4.54	6.9	9.2	-	-
4.	0.71	2.11	2.38	10.0	1.9	NW	3
5.	1.09	1.09	1.09	11.3	12.2	W	-24
6.nb	2.32	4.68	6.48	7.2	12.9	NW	4
7.nb	1.09	4.65	21.79	9.0	15.9	NW	48
8.nb	0.43	0.53	1.07	4.2	10.9	-	-
9.nb	0.42	0.42	0.42	9.7	12.7	-	-
10.A	1.25	3.22	4.17	7.8	6.2	NW	-
10.B	0.83	2.64	5.21	6.3	13.2	-	-
11.	0.62	0.62	0.62	7.7	2.1	W	100
**12.nb	0.47	1.02	2.34	7.8	9.2	NW	-
13.nb	1.12	1.29	2.23	12.8	16.1	W	260
*14.nb	0.33	1.55	1.67	8.0	9.3	W	130
15.	1.00	1.70	2.00	8.0	2.3	W	44
16.	1.11	1.11	1.11	9.5	0.6	NW	2
***17.nb	2.56	3.32	7.76	4.8	8.0	W	-
MEAN:	1.0	1.9	3.8	8.3	9.1		74
SD:	0.6	1.3	5.0	2.1	5.0		

*/** = renal/hepatic dysfunction, respectively; *** = renal and hepatic dysfunction; **nb** = patient received neuromuscular blocker during midazolam infusion; **W** = weaned; **NW** = not weaned; Time to extubation is measured from the time of midazolam infusion discontinuation, where a negative number indicates the patient was extubated prior to discontinuation of midazolam.

was documented for the remaining 11 patients.

MDM was prepared in a 5% dextrose or normal saline solution at a concentration of 0.5-2 mg/mL. The starting, mean (excluding weaning rates) and peak infusion rates for each patient are summarized in Table II. As a result of concurrent use of neuromuscular blockers, 42 patient days of GCS data (25.5%) were excluded from a total of 164.5 days studied.

There were no statistically significant relationships between age and mean MDM infusion rate ($r=-0.25$, $n=18$, $p=0.31$) nor between mean MDM infusion rate and the mean lowest daily GCS scores ($r=-0.24$, $n=18$, $p=0.33$). However, an inverse relationship was found between age and the mean lowest daily GCS scores ($r=-0.63$, $n=18$, $p=0.005$). Upon excluding the four patients with hepatic and/or renal impairement, the correlation coefficient between age and MDM infusion rate improved but was still not statistically significant ($r=-0.37$, $n=14$, $p=0.19$). The correlation between age and GSC scores persisted in this patient group ($r=-0.60$), $n=14$, $p=0.02$).

Tachyphylaxis

For all but four patients (#5,9,11,16) there was an increase in MDM infusion rate with time, with day zero (i.e., the initial infusion rate, $n=18$) being significantly lower than day ten ($r=0.92$, $n=10$, $p<0.01$). (Figure 1)

Withdrawal

Seven patients were weaned off MDM infusion, while seven patients had MDM abruptly discontinued. Weaning was usually done by 1 to 2 mL (i.e., 0.5-4 mg) hourly decrements in infusion rate, over 4 to 19

hours. Data on doses of other CNS depressants administered concurrently (i.e., 24 hours prior to) and subsequently (i.e., 24 hours after discontinuation of MDM infusion) were collected on ten patients. (Table III)

Eight of the ten patients received additional doses of CNS depressants in the first 24 hours following MDM discontinuation-two of four 'weaned' patients and six of six patients in whom MDM was abruptly discontinued (Fisher's Exact: p=0.13). Three patients received haloperidol during the 24 hours following MDM discontinuation. The mean MDM infusion rate was greater in these patients (3.6 ± 1.8 mcg/kg/min) than in patients who did not receive haloperidol (1.2 ± 0.6 mcg/kg/min, n=7; Mann-Whitney U test, one-tailed: p=0.05).

While all seventeen patients were prescribed diazepam (2.5-5 mg IV every 15 minutes as necessary for agitation), and morphine (2-5 mg IV every 10 to 15 minutes as needed) at some point during MDM infusion, seven of the ten aforementioned patients received doses of diazepam (5-55mg) during the 24 hours prior to MDM discontinuation. Five of these seven patients still received doses of diazepam during the 24 hours following MDM discontinuation.

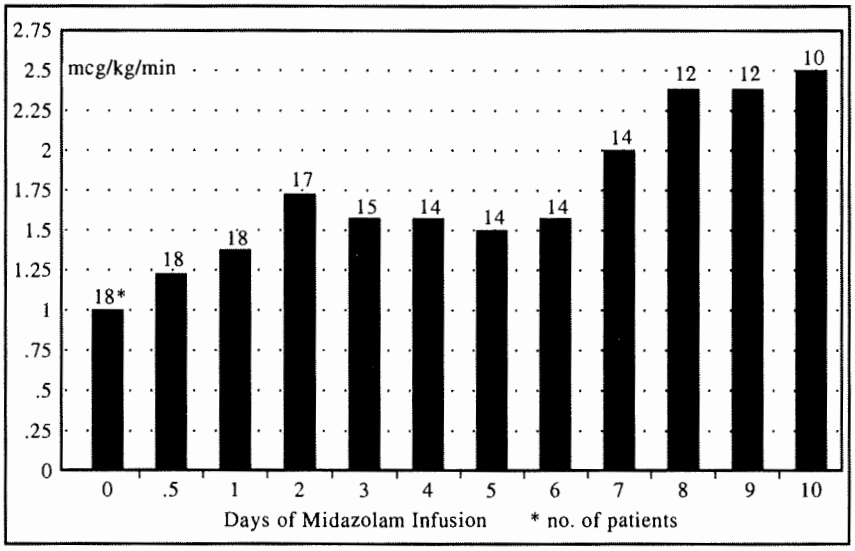

Figure 1: Mean Daily Midazolam Infusion Rate

Table III: Additional Doses of Other CNS Depressants Administered During the 24 Hours Following Midazolam Infusion Discontinuation (Numbers indicate how many more milligrams of each drug were given during the 24 hours following discontinuation of midazolam infusion compared to doses administered during the 24 hours prior to midazolam infusion discontinuation.)

Patient Number	Diazepam IV (mg)	Haloperidol IV/IM (mg)	Lorazepam SL/PO mg	Morphine IV (mg)
Patients Weaned				
1.				
5.				
13.	25			
14.	10	33		
Patients not Weaned				
2.	12.5			
4.	5		1	
6.		25		
7.	115	54		121
12.				52
16.				6

DISCUSSION

A number of limitations and difficult-to-control variables would exist in any study of dose/demographic relationships, tachyphylaxis and withdrawal reactions to benzodiazepines in the critical care setting. Varying need for pain control among patients, subjective determination of optimal sedation by attending nurses and medical staff, concurrent use of muscle relaxants, previous use of benzodiazepines by the patient prior to hospital admission, increased agitation due to increasing recovery of consciousness or increased stress secondary to weaning patients off mechanical ventilation, withdrawal reactions to narcotics and the occurrence of ICU psychosis are only some of these variables. The control of such variables was beyond the scope of this retrospective review. However, some trends and observations can be useful in developing guidelines for MDM use in ICU — an area where few such guidelines are currently in existence.

Utilization and Dose/Demographic Relationships

Seventeen critically ill patients who received 18 courses of MDM infusions were studied. The MDM infusion rates used in these patients were comparable to those reported by others in the literature, ranging from 0.5 to 6 mcg/kg/min.[1,3,5,10,11,14,15] Also, as noted by others, the dose requirements varied markedly among different patients.[5,8,16]

Decreased total clearance of MDM in older males but not females has been documented.[17,18] Greenblatt and

colleagues reported prolonged elimination half-life of 5.6 hours in males, aged 60 to 74 years, compared to that of 2.1 hours in younger males, aged 24 to 33 years. As a result, the authors recommended a 25 to 50% reduction in MDM infusion rates in elderly males.[17] In another study by Greenblatt et al, the authors found greater EEG changes at any dose or plasma level of MDM in patients over 60 years compared to patients under 40 years of age. The MDM median effective concentrations (EC_{50}) were statistically different between these two groups, indicating increased intrinsic sensitivity to MDM in older patients.[19]

In this study, no statistically significant linear relationships were found between age and patient's mean MDM infusion rate, even when the four patients with hepatic and/or renal dysfunction were excluded (r=-0.37). Exclusion of female patients in addition to patients with hepatic and/or renal impairment, yielded a higher correlation coefficient for age and mean MDM infusion rate (r=-0.46, n=10, p=0.18). While these findings may be suggestive of an inverse relationship between age and MDM dose requirements, especially in male patients, they have not been statistically substantiated in this study. Consideration should also be given to the intentional and unintentional differences in dose-titration endpoints to the sedative or hypnotic effects of MDM, which could largely affect this type of a relationship.

No relationship was found between MDM dosing and mean daily lowest GCS scores. This is not surprising when one considers the potential differences in the desired level of CNS suppression and the concurrent use of other CNS suppressants. An inverse relationship between age and mean daily lowest GCS scores was noted (r=-0.60, n=14, p=0.02). This could be a possible indicator of a decreased elimination or increased sensitivity to MDM in the elderly, as described by Greenblatt et al.[17,19] However, since serum MDM concentrations were not measured, one cannot determine whether accumulation of this drug occurred in elderly patients. Furthermore, the lower CGS scores in older patients could also represent poorer neurological status due to age, underlying condition, or impaired clearance of other drug therapies.

Tachyphylaxis

Figure 1 depicts mean daily MDM infusion rates for all patients, from the start of the infusion (n=18) and up to ten days thereafter (n=10). There was a statistically significant doubling of the mean MDM infusion rate by the seventh day of infusion (n=14, p<0.01). While this may constitute tachyphylaxis, serum MDM concentrations would be needed to confirm these findings.

Meyer et al have briefly reported on the occurrence of tachyphylaxis with MDM in a study of 18 pediatric ICU patients on ventilators. Patients receiving the infusion beyond 72 hours required higher doses of MDM. However, the authors did not mention the statistical significance of their findings.[10] Shelly and colleagues noted significant increases in MDM dose in adult ICU patients on continuous MDM infusions.[20] It would appear, then, that the potential for tachyphylaxis with MDM exists.

Withdrawal

Withdrawal reactions are more commonly seen with shorter acting drugs than with longer acting agents. MDM, one of the shortest-acting benzodiazepines available today, would be expected to produce similar effect. In fact, reports on cases of withdrawal reactions with MDM indicate the need for gradual tapering of the drug in patients who have received MDM for one to two weeks.[12,13]

Due to the subjective assessment usually involved in documenting a withdrawal reaction, doses of additional CNS depressants administered during the 24 hours following MDM discontinuation were recorded in this study. Ideally, a control group similar in all aspects to the MDM group would be needed to assess the issue of additional CNS medications. Because of the logistical problem of identifying and adequately matching the groups, the cited number of CNS medications was chosen (Table III). The number of patients was too small, however, (n=10) to assess for differences in doses of additional CNS depressants administered following the discontinuation of MDM infusion in weaned versus not weaned patients.

Of note, the three patients who were prescribed haloperidol received larger doses of MDM than the other seven patients (Mann-Whitney U Test, one-tailed, n=10, p=0.05). As with other benzodiazepines, the risk of withdrawal reactions increases with higher doses. It would, therefore, seem prudent to wean MDM in such patients.[13] Unfortunately, in this study, the influence of weaning MDM infusion on the occurrence of withdrawal reactions was not statistically detectable.

The final finding was that diazepam was administered concurrently to patients on MDM infusions. Seven of the ten patients received doses of diazepam during the 24 hours prior to stopping MDM infusion. The redundance of the double benzodiazepine therapy, with potential loss of the anticipated short-term effects of MDM is of serious concern. An inclusion of a cautionary statement regarding this issue should be given consideration in the development of dosing guidelines for MDM infusions.

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