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ORIGINAL ARTICLE

Adverse Drug Reaction with Midazolam Use in Emergency Department

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ABSTRAK

Midazolam adalah salah satu ubat yang paling biasa digunakan sebagai ubat pelali di Jabatan Kecemasan (ED). Ini adalah satu kajian retrospektif yang dijalankan ke atas 380 pesakit dari Disember 2012 hingga Mei 2014 di ED, Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Objektifnya adalah untuk mendapatkan kekerapan kesan sampingan dan korelasi kepada pelbagai faktor iaitu sosio-demografi, kumpulan umur dan penyakit-penyakit utama. Daripada 380 pesakit, 35 pesakit mempunyai kesan sampingan (20 pesakit dengan midazolam sahaja, 15 pesakit dengan kombinasi ubat-ubatan). Umur purata adalah 42 tahun dan dos purata midazolam adalah 3.5mg. Ubat lain yang paling biasa di gabung adalah fentanyl. Kadar komplikasi keseluruhan midazolam adalah 5.3%. Kesan sampingan yang paling biasa yang dicatatkan adalah somnolen (1.6%). Kesan sampingan yang lain adalah reaksi alergi kulit (1.1%), muntah (0.8%), sakit kepala (0.8%) dan tekanan darah rendah (0.5%). Tidak ada hubungan yang signifikan antara faktor-faktor sosio-demografi dan kombinasi ubat-ubatan dengan kesan sampingan midazolam pada pesakit. Kesimpulan daripada kajian ini ialah midazolam adalah dadah yang sangat selamat kerana ia tiada kesan sampingan yang mengancam nyawa. Terdapat kemungkinan bahawa kesan-kesan sampingan direkodkan boleh disebabkan oleh faktor-faktor lain seperti kecederaan atau penyakit dan kombinasi dengan ubat-ubatan lain.

Kata kunci: Midazolam, somnolen, tekanan darah rendah, reaksi alahan kulit, sakit kepala, muntah

ABSTRACT

Midazolam is one of the most commonly used drugs for sedation in Emergency Department (ED). This was a retrospective study conducted on 380 patients from

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December 2012 to May 2014 in ED of Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The objective was to elicit the frequency of side effects and correlation to various factors i.e. socio-demography, co-morbidities, age groups and underlying illnesses. Out of 380 patients, 35 patients experienced side effects (20 patients with midazolam alone, 15 patients with combination of drugs). The average age was 42 years and the average dose of midazolam was 3.5mg. The most common other drug combined was fentanyl. The overall complication rate for midazolam was 5.3%. The most common side effect recorded was excessive somnolence (1.6%). Other side effects included local skin reactions (1.1%), vomiting (0.8%), headache (0.8%) and hypotension (0.5%). There was no significant association between the socio-demographic factors and drugs combination with the side effects of midazolam on patients. It was concluded that midazolam was a safe drug due to absence of any life-threatening side effects. There are possibilities that most side effects recorded could be caused by other comfounding factors e.g. underlying injuries or disease and combination with other drugs.

Keywords: Midazolam, excessive somnolence, hypotension, local skin reaction, headache, vomit

INTRODUCTION

Midazolam is a water-soluble imidazobenzodiazepine derivative which is commonly used for sedation in the Emergency Department (ED) (Ramoska et al. 1991). The reason attributed to this is that it possesses potent anxiolytic, amnesic, hypnotic and sedative properties (Khanderia & Pandit 1987; Olkkola & Ahonen 2008; Barash et al. 2009). The present study was to assess the incidence of adverse effects following intravenous midazolam given to patients in the ED. Reasons for sedation in the ED are chemical restrains of violent patients and procedural sedation and analgesia (PSA). PSA is the administration of sedatives to induce a depressed level of consciousness while maintaining cardio respiratory functions. This is done so that a medical procedure can be done (Godwin et al. 2005). Procedural sedation is commonly used for outpatient medical procedures and done by non-anesthesiology physicians (Knape et al. 2007).

The use of midazolam in the ED is unique in terms that the location possess different issues and risks to the physician. Among issues that is different to normal outpatient clinic is the occurrence which is unpredictable, the timing is time dependent and sometimes emergent, gastric state is variable (either fasted or not). Patients are unselected and may have underlying systemic disease (Godwin et al. 2005). Hence, even though the adverse effects of midazolam was extensively studied in various clinical locations, the data for midazolam use in ED especially throughout Malaysia, is still lacking.

Adverse reactions from midazolam use include urinary retention, nausea, vomiting and excessive somnolence

(Ramoska et al. 1991). Few serious incidents were reported with the administration of midazolam. In 1989, Roche Laboratories received 74 deaths reports with regard to midazolam use. Majority of the midazolam deaths were used as an adjunctive agent, which complicated with respiratory arrest. Overdosage, co-morbidities, old age and use in adjunct to other central nervous depressants are the main factors which lead to this mortality (Ramoska et al. 1991).

MATERIALS AND METHODS

This was a retrospective study conducted on 380 patients who received intravenous midazolam in ED, UKMMC from December 2012 to May 2014. Data collection commenced following receiving approval from UKMMC'S Ethical Committee. Registration numbers of the patients that fulfilled all inclusion criteria were collected from the controlled drugs record. Data was then collected from the Records Department. Data was documented in the data collection sheet and then analyzed using Statistical Package for Social Sciences (SPSS) Windows Version 20.0. Chi-square test was used to analyze the association between the side effects of midazolam and factors studied. P value of <0.05 was described as statistically significant.

The main objective of the was to look into the incidence of adverse effects after intravenous midazolam administration in the ED.

We also aimed to (i) determine the association between adverse effects of intravenous midazolam with socio-demographic factors (ii) determine the association between adverse effects of intravenous midazolam with co-morbidities and underlying illnesses (iii) compare adverse effects of midazolam when used alone with certain drug combinations (iv) determine the occurrence of life threatening adverse effects with intravenous midazolam administration.

SAMPLE SIZE CALCULATION

Formula by Cochran (1963),

$$n = \left(\frac{z}{\Delta}\right)^2 \times p\,(1 - p)$$

95% confidence level
z = degree of confidence value (1.96 for 95% confidence level) = 1.96
Δ = Error of margin 0.005 (0.5%)
p = expected prevalence

Based on an earlier study (Khanderia & Pandit 1987), the overall complication of side effects midazolam was 1% and the error of margin 0.01[5]

$$n = \left(\frac{1.96}{0.01}\right)^2 \times 0.01(1 - 0.01)$$

= 380 patients (rounded to zero decimal points)

INCLUSION CRITERIA

Patients administrated intravenous midazolam in the ED, UKMMC from December 2012 to May 2014.

EXCLUSION CRITERIA

1. Midazolam indicated for rapid sequence intubation (RSI) – due to its use as an induction agent,

not for procedural sedation and analgesia or chemical restrain of violent patients.
2. Patient transferred to another hospital.
3. Midazolam dependence.

RESULTS

This study involved a total of 380 patients. The mean age was 42 years with minimum of one year and maximum of 108 years. Majority were males (64.7%) and Malays (43.2%) were the highest population involved. Other populations included Chinese (39.2%), Indians (9.2%) and others (8.4%). According to races, Chinese (5.0%) was the most population associated with side effects of midazolam use while Malays (43.2%) were the highest population involved in the midazolam use (Jabatan Perangkaan Malaysia 2010) (Table 1). For patients aged 40 years and below, the adverse effects were 6.3% (13 out of 206 patients), whereas for age 41-60 years, it was 11.5% (10 out of 87 patients) and 61-80 years were 10.6% (7 out of 66 patients). Incidence of side effects in patients more than 80 years is significantly higher (38/1%), (8 out of 21 patients (Table 1).

Two hundred and thirty nine (63%) patients had midazolam combined with other drugs. The drugs combined with midazolam were fentanyl (28.7%), morphine (16.6%), haloperidol (8.7%), propofol (6.1%), ketamine (2.1%) and diazepam (0.8%). Overall number of patients who suffered adverse effects recorded with midazolam administration was 35 (9.2%).

Table 1: Association of socio-demographic factors with side effects of Midazolam use

	Group		Total n (%)	p value
	Side Effects n (%)	No Side Effects n (%)		
Age (years)				
1-20	4 (1.1)	59 (15.5)	63 (16.6)	0.48
21-40	9 (2.4)	134 (35.3)	143 (37.6)	
41-60	10 (2.6)	77 (20.3)	87 (22.9)	
61-80	7 (1.8)	59 (15.5)	66 (17.4)	
>80	8 (0.8)	18 (4.7)	21 (5.5)	
Gender				
Male	18 (4.7)	228 (60.0)	246 (64.7)	0.20
Female	15 (3.9)	119 (31.3)	134 (35.3)	
Race				
Malay	12 (3.2)	152 (40.0)	164 (43.2)	0.10
Chinese	19 (5.0)	130 (34.2)	149 (39.2)	
Indians	1 (0.3)	34 (8.9)	35 (9.2)	
Others	1 (0.3)	31 (8.2)	32 (8.4)	

p value age 0.48; gender 1.20; race 0.10, Chi-Square test

Table 2: Association of interaction of midazolam with one specific drugs and side effects

Drugs	Group		Total n (%)	P value
	Side Effects n (%)	No Side Effects n (%)		
Midazolam + Fentanyl	5 (4.2)	51 (43.2)	56 (47.4)	0.38
Midazolam + Propofol	0 (0.0)	8 (6.8)	8 (6.8)	0.43
Midazolam + Ketamine	0 (0.0)	6 (5.1)	6 (5.1)	0.50
Midazolam + Morphine	1 (0.8)	19 (16.1)	20 (16.9)	0.73
Midazolam + Haloperidol	2 (1.7)	24 (20.3)	26 (22.0)	0.83
Midazolam + Diazepam	0 (0.0)	2 (1.7)	2 (1.7)	0.70

p value Midazolam + Fentanyl 0.38; Propofol 0.43; Ketamin 0.50; Morphine 0.73' Haloperidol 0.83; Diazepam 0.70, Chi-Square test

Table 3: Association of interaction of midazolam with various drugs combination and side effects

Side effects	Midazolam only (N=20) n (%)	Midazolam and others (N=15) n (%)	p value
Local skin reaction	4 (1.1)	2 (0.5)	0.51
Hypotension	2 (0.5)	5 (1.3)	0.18
Excessive somnolence	6 (1.6)	4 (1.1)	0.67
Vomit	3 (0.8)	1 (0.3)	0.38
Headache	3 (0.8)	2 (0.5)	0.77
Others	2 (0.5)	1 (0.3)	NA

Breakdown of overall adverse effects were excessive somnolence 10 (2.6%) patients, hypotension 7 (1.8%) patients, drug hypersensitivity reaction 6 (1.6%) patients, headache 5 (1.3%) patients and vomiting 4 (1.1%) patients and 3 (0.8%) patients had tachypnea, increased blood pressure and ECG changes.

Midazolam and fentanyl were the mostly combined drugs (47.4%) and it had the highest combination (4.2%) with side effects of midazolam use. Six patients who received this combination of drugs had transient hypotension. However, there was no significant association with p value of 0.38. Combination of midazolam with propofol or ketamine recorded no side effects. Table 2 showed the association of interaction of midazolam with one specific drugs and side effects whereas Table 3 showed the association of interaction of midazolam with various drugs combination and side effects. The total side effects with midazolam used alone was 20 (5%) compared to 15 (3.9%).

Among the comorbidities, hypertension (1.6%) was the highest comorbidity associated with midazolam use followed by asthma and diabetes mellitus which was 0.5% respectively. Other comorbidities were tabulated (Table 4). There were seven indications of midazolam and sedation (58.9%) was the highest

Table 4: Comorbidities with side effects of Midazolam use

Comorbidities n (%)	Group		Total
	Side Effects n (%)	No Side Effects n (%)	
Hypertension	6 (1.6)	61 (16.1)	67 (17.7)
Asthma	2 (0.5)	13 (3.4)	15 (3.9)
Diabetes Mellitus	2 (0.5)	36 (9.5)	48 (10.0)
Schizophrenia	0 (0.0)	11 (2.9)	11 (2.9)
Cerebrovascular Accident (CVA)	1 (0.3)	13 (3.4)	14 (3.7)

indication of midazolam to be used. Other indications were orthopaedic procedures (17.9%), psychotic disturbances (10.5%), anticonvulsants (9.5%), anxiety (2.4%) and chest tube insertion (0.8%). Midazolam was given intravenously with dosage varying from 1.0 mg to 10.0 mg and the mean dose was 3.5 mg.

DISCUSSION

We managed to gather a sample size of 380. The study population ethnicity breakdown comprised Malays-43.2%, Chinese-39.2%, Indians-9.2% and others-8.4% and it did not resemble the ethnicity of the Cheras region. This region has a population breakdown of 25.4% (3,101) Malays, 40% (4,910) Chinese, 7.6% (932) Indians and others (non-malay bumiputra, Malaysian nationals and foreigners) 27% (Jabatan Perangkaan Malaysia 2010). It resembles the population of Kuala Lumpur as a whole, which has a breakdown of 40.6% (644,406) Malays, 39.1% (621,805) Chinese and 9.3% (148,300) Indians. Although Chinese (5.0%) were more associated with side effects, there was no significant association between races and side effects of midazolam use (p=0.1). The highest gender associated with side effects was males (4.7%), and it correlated to the majority male patients who had midazolam administered. The correlation between gender and side effects was not significant (p=0.2)

Out of total 35 patients who experienced side effects, 13 patients (37% out of total with side effects) were below 40 years. Ten patients were between the age of 40 to 60 years and the rest (12 patients) were above 60 years old. There was no significance in the relation of age and adverse effects, as the distribution could be seen as nearly equal. However, when used in the extreme ages (above 80 years), a higher proportion of adverse effects were observed (38.1% - 8 out of 21 patients) as shown in Table 1. Elderly patients receiving midazolam 0.06 mg kg^{-1} showed significant reductions in mean blood pressure, respiratory rate and SpO_2 (Sun et al. 2008). Elderly patients (>70 years) previously on diazepam in particular has a higher propensity of falls compared to other benzodiazepam users (Ballokova et al. 2014). There was also an increase in fracture risk with short term benzodiazepine usage, (RR = 1.21; 95 % CI, 1.13–1.30) with a weak significance.

This was also observed in the elderly age group (>65 years) (Xing et al. 2013). Extra caution should be practiced when administering benzodiazepine among elderly, especially at extreme ages (>80), as they are more susceptible to adverse effects. However, in the young (pediatric and adolescent), significant adverse effects are rare. A review by Papineni et al. (2014) showed that after oral administration of midazolam among the pediatric and adoloscents during dental procedure, the most common effect was paradoxical reaction, including aggressiveness.

There were five side effects which were encountered during the study and these were excessive somnolence, hypotension, headache, vomiting and allergy. However, none of them were life-threatening i.e. coma, respiratory arrest or cardiovascular effects. This study was comparable to the study by which reported no serious respiratory or cardiovascular events while using midazolam intravenously (Ramoska et al. 1991; Wenzel et al. 2002; Xing et al. 2013). Our study is similar to a previous study which included intravenous midazolam used for critical patients such as head injury, sepsis, meningitis and all types of drug combinations, which is sedative in nature (propofol and opioids) (Ramoska et al. 1991). Other neurological effects such as euphoria, aggressiveness, depression and intense hiccups were not documented in the clinical case notes, neither it was undetected nor classified as somnolence. As comparison to a study by Wenzel et al. (2002) neuropsychiatric effects including aggressive, euphoria and depressive behaviors made up to 6% of cardiac cases undergoing transesophageal echocardiography.

There were 6 (1.6%) cases reported on excessive somnolence involving midazolam alone and 4 (1.1%) cases reported with drug combination, which accounts to 10 cases (3.8%). Majority of excessive somnolence is due to repeated dosage given due to inadequate sedation from the initial dose. A 41-year-old male with clavicle and rib fracture was reported to have received total of 8 mg IV midazolam. The additional dosage was given due to his agitation at that time. He developed somnolence with duration of 2 hours with GCS 11/15. He was monitored later and did not develop respiratory or cardiovascular effects. The frequency is slightly higher than what was reported by (Ramoska et al. 1991) in which excessive somnolence was observed in (1.6%) of 120 patients.

The second side effect was 6 (1.6%) cases of drug hypersensitivity reaction. Two (1.1%) patients resulted dermatology effects with midazolam alone. Both cases developed itch and urticarial rash at a range of 1-2 hours after midazolam administration. The other 4 cases were in combination with other drugs i.e. opiates, hence cannot eliminate the combination or histamine release by opiods. The patient was stable afterwards after administration of hydrocortisone and piriton. Life-threatening laryngospasm or anaphylactic shock did not develop during the period of our study.

Hypotension was recorded in 7 (1.8%) cases. Patients with hypertension were found to have higher risk of developing

hypotension with the administration of midazolam, which correlates with previous studies (Shekerdemian et al. 1997). Hypotension after midazolam administration was due to cardiovascular depressant effect that results in minimal change in arterial blood pressure, heart rate and systemic vascular resistance (Shekerdemian et al. 1997). Other contributing factors to hypotension were co-morbidity, other combination of drugs given and underlying illnesses. Another case reported was a 87-year-female who had hypertension, chronic kidney disease and complete heart block. She was given a 1.5 mg midazolam and 0.5 mg fentanyl for sedation. She developed hypotension which her blood pressure falls from 191/61 mmHg to 96/35 mmHg with heart rate of 36 beats per min after 4 hrs. Temporary pacemaker was inserted and later blood pressure was stabilized. In this case, hypotension developed might be due to several factors such as elderly age which affect the renal clearance and her clinical conditions like bradycardia and heart block. All cases of hypotension which developed post intravenous midazolam administration were transient and resolved with supportive measures.

Three (0.8%) patients developed vomiting. This is lower than previous reports (2-3%) (American Hospital Formulary Service 1989). Three (0.8%) patients developed headache post midazolam administration which then resolved. Adverse effects will be considered severe or life-threatening if it results in permanent organ damage or death. Adverse effects that are selected in this category are cardiac arrest, apnoea, anaphylaxis and severe respiratory depression which resultes in hypoxia and neurological sequelae. Papineni et al. (2014) classified life-threatening as prolonged respiratory depression and hypoxia. No case was reported with such serious side effects.

A limitation of this study was the retrospective data collection. We could not obtain all the medical files requested in a short duration. Few of the medical records provided were incomplete and inconsistent as there were no proper documentations of certain side effects from the files. Not all adverse effects were documented and are most neuropsychiatric effects were labeled under the group of altered mental state, or low GCS, whereas it could mean euphoria, aggressiveness or somnolence. It was also impossible to compare when drugs used in combination, whether the effects were due to midazolam alone, or confounding effect with other drugs. There was no significant result. This study was more towards a role of an audit, in which the adverse effects of midazolam in our ED did not differ much from the general population.

CONCLUSION

Statistical values showed that there was no significant association with the demographic factors and the drugs combination towards the side effects of midazolam use in ED. No life-threatening side effects occured following the use of midazolam, in consideration of the wide variety of critical patients. Thus, we conclude that midazolam is a very safe drug used

in ED. In fact, special caution, close monitoring and precaution steps should be carried out during the administration of midazolam in ED. We should follow the guideline of management recommended in ED so that the usage of midazolam can be optimized with minimal side effects in clinical setting. Caution should be practiced in elderly. In addition, as in advent to introduction of new sedative agent such as propofol and etomidate, the role of midazolam is still considered to be safe.

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