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Review

Midazolam: Safety of use in palliative care A systematic critical review

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ABSTRACT

Purpose: The undesired effects of midazolam can be life-threatening. This paper delineates the findings related to the pharmacokinetics, adverse effects and drug-drug interactions as well as associated therapeutic implications for safe midazolam use.
Methods: A systematic review of literature was conducted.
Results: The pharmacokinetics of midazolam depends on hepatic and renal functions, fat tissue mass, route and duration of administration, as well as potential drug-drug interactions. Palliative care patients constitute a high-risk group prone to side effects of drugs, due to polytherapy and multi-organ failure.
Conclusion: Midazolam is one of three most frequently administered drugs in palliative care. The indications for its use include anxiety, dyspnea, seizures, vomiting refractory to treatment, agitation, myoclonus, status epilepticus, restlessness, delirium, pruritus, hiccups, insomnia, analgosedation, palliative sedation and preventing or counteracting undesired effects of ketamine.

1. Introduction

In palliative care, patients are prone to intractable symptoms, most frequently fatigue (88%), anorexia (56%), pain (45%), dyspnea (39%), dizziness (38%), xerostomia (34%), anxiety (30%) constipation (29%), confusion (24%), nausea (17%) and insomnia (14%) [1]. Midazolam is one of three most frequently administered drugs in palliative medicine, the others being morphine and haloperidol. According to some reports, midazolam was administered to 11% of patients on admission to a palliative care unit and used in 58% of patients on the day of their death [2]. The indications for administering midazolam include: anxiety, insomnia, restlessness, agitation, delirium, dyspnea, analgosedation, myoclonus, seizures, status epilepticus, palliative sedation, pruritus, hiccups, refractory vomiting, and preventing or counteracting the undesired effects of Ketamine [3–28]

Rising incidence of neoplastic diseases is closely related to the increase in the number of patients under palliative care. In view of the growing scale of the problem, we decided to systematize available information about one of the most commonly used drug in palliative medicine - midazolam. In clinical work we noticed problems associated with the use of the drug: its side effects, drug-drug interactions, effects of polypharmacy, concomitant multiple organ failure in patients undergoing palliative care - particularly kidney failure and liver.

1.1. Methods

We decided to search the PubMed database with the aforementioned slogans in order to clarify these problems and provide better quality of care for patients. We used the materials published between 1978-2018. The work also includes information from medical literature both English and Polish. The material from the websites contained content available in January 2019.

2. Midazolam - biochemistry and pharmacokinetics

Midazolam is a short-acting benzodiazepine affecting GABA-ergic

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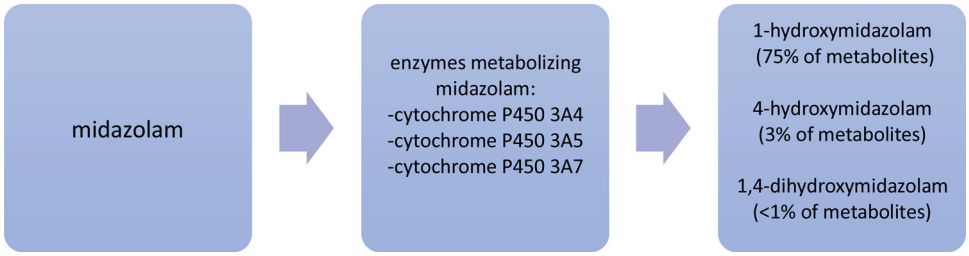

Fig. 1. Midazolam, enzymes involved in its metabolism and its metabolites [40,68,70].

(Gamma Aminobutyric Acid) transmission. Benzodiazepines possess an electronegative halogen substituent at position 7 which is indispensable to providing sedative and hypnotic effects. Midazolam contains an alkaline nitrogen atom in position 2 of the imidazobenzodiazepine ring system, which facilitates the formation of water-soluble salts (pKa = 6.15). Owing to its lipophilicity, its onset of action is rapid (1.5–15 minutes) following a single dose administered intravenously (i.v.) or intramuscularly (i.m.). Benzodiazepines rapidly cross the blood-brain barrier (BBB), easily cross the placenta (category D) and are secreted into breast milk. Midazolam can be administered in constant infusion or in boluses i.v., i.m., subcutaneously (s.c.), per os (p.o.), buccally, intranasally (i.n.) and per rectum (p.r). The volume of distribution (Vd) of Midazolam is equal to 1–2.5 L/kg, and is higher in the elderly and obese patients.

The metabolites of Midazolam are products of oxidation of the imidazole ring by the cytochrome P450 enzymes (Fig. 1). The active metabolite of midazolam is 1-hydroxymidazolam with biological activity equal to 10% of midazolam activity. The half-life (t½) of midazolam in the elimination phase is 1.36–4 h but t½ for 1-hydroxymidazolam is 1 h. Midazolam and its active metabolite are both referred to as a short-acting benzodiazepine (< 10 h) [5,29–32].

With high concentrations of midazolam in the blood serum, its metabolite, 4-hydroxymidazolam, accumulates, inhibiting the pathway of 1-hydroxymidazolam formation [7]. Fig. 1 presents the proportion of midazolam metabolites. Increased activity of CYP3A5 (cytochrome P450 3A4) results in 1-hydroxymidazolam production, whereas dominance of CYP3A4 leads to higher proportion of 1,4-dihydroxymidazolam [33,34].

Only 0.03% of midazolam is eliminated in its unchanged form. 63–80% of administered dose is coupled with glucuronic acid, and the metabolites are excreted with urine within 24 h. The lethal dose, leading to the death of half of the population following oral administration can be as high as 1600 mg/kg [35–43].

T ½ D – distribution half-life; Vd – distribution volume; Cl – clearance; i.v. – intravenous administration; p.o. – oral administration; i.m. – intramuscular administration; s.c. – subcutaneous administration; p.r. – per rectum administration; i.n. – intranasal administration

CYP 3A constitutes 40% of hepatic and 82% of intestinal CYP. Therefore its role in midazolam metabolism is crucial. The oral administration of midazolam lowers its bioavailability by 36–40% [40,64].

Grapefruit juice intake increases the bioavailability of midazolam administered orally by over 10%. This effect can lead to drug-related reactions in some patients, especially in those whose pharmacokinetics is impaired due to other clinical conditions [65].

Subcutaneous drug administration is frequent in palliative care patients [32]. A comparison of geometric means: AUC (Area under the curve) (0, ∞), following subcutaneous and intravenous administrations pointed towards bioequivalence [51].

Lower peak concentration following one midazolam i.v. bolus (5 mg) administration was observed in obese patients in comparison to patients with proper body weight (BMI < 25), which is justifiable by the higher Vd in the former. The drug's half-life is extended in obese patients following long-term (10-day) constant i.v. infusion at 2.5 mg/h. This effect, i.e. obtaining a stable level of clearance in both groups (patients with obesity and normal body weight), is related to the drug's accumulation in adipose tissue [66].

The results of a cohort study on patients with obesity showed a 1.7-fold greater systemic clearance of midazolam (0.65 vs. 0.39 l/minute) one year after bariatric surgery. This change was most probably related to decreased adipose - inducing proinflammatory factors (IL-6 and TNF-α) which are responsible for fall the activity of CYP 3A [67].

The half-life of midazolam following a 4-hour infusion was equal to 70 min while its half-life following a long-term infusion was as much as 100 min (*context sensitive half-life*) [68].

No impact of hypothermia on the clearance and half-life of midazolam was reported [69].

Albrecht et al. studied the pharmacokinetics and pharmacodynamics of midazolam in young people (24–28 yo) taking 40 ng/ml/min and the elderly (67–81 yo) taking 20 ng/ml/min. The results revealed significant individual variation in midazolam plasma concentrations constituting clinical endpoints. The endpoints were formulated as obtaining EEG mean frequency of < 4 Hz and the loss of response to acoustic stimuli. EC50 was 522 ± 236 ng/ml in the younger population and 223 ± 56 ng/ml in the elderly one [71].

3. Midazolam - pharmacokinetics in hepatic failure

The elimination and pharmacokinetics of many lipophilic drugs change in chronic disease, especially in the case of sedatives to which CNS (central nervous system) may become more sensitive. Elimination of drugs by the liver is related to hepatic blood flow (the elimination index of midazolam can vary from 0.3 to 0.5, depending on this flow [72,73]), enzyme ability to oxidize and couple, metabolite elimination with bile and the amount of plasma protein able to bind with drugs, which also affects the drug's distribution. Portosystemic shunts, as a result of bypass flow, decreases the first pass effect, at the same time leading to increased oral midazolam plasma concentration [74–76]. In addition, enzyme-containing cell mass decreases in chronic disease. At the same time, midazolam pharmacokinetics can be easily affected by the changes in hepatic blood flow.

The outcome of a study comparing pharmacokinetics of midazolam in healthy population and in patients suffering from alcoholic liver cirrhosis showed impaired psychomotor functions and increased level of sedation lasting up to 6 h following the administration of 0.075 mg/kg of midazolam in the group with impaired hepatic function. By the same token, the drug's elimination was delayed. T½ in patients with alcoholic cirrhosis and healthy individuals was equal to 1.6 ± 0.3 h and 3.9 ± 0.8 h, respectively [77]. Selected pharmacokinetic parameters of midazolam are presented in Table 1.

4. Midazolam pharmacokinetics in renal failure

The renal elimination of midazolam in its unchanged form in close to none (< 1%) [35]. The results of a study comparing the pharmacokinetics of midazolam in healthy population and in patients suffering from chronic renal disease, following the administration of 0.2 mg/kg of midazolam within 15 s, point to major differences primarily in free

Table 1
Selected pharmacokinetic parameters of midazolam [32,36,38–40,45–63].

T ½ D	6-15 minutes
T ½	1-4 hours for parent compound; variable for metabolites: 105-108 mins, approx. 1 -3 hrs; context sensitive half-life should be taken into account during chronic treatment or repeated drug administration
Vd	1-2.5 l/kg
Plasma protein binding	97%
Cl	0.25-0.54 l/kg/h
Onset of action	i.v.: 2-2.5 minutes (1.5 minutes after pre-medication) i.m.: 15 minutes p.o.: 20 minutes s.c. 5-10 minutes

Bioavailability		Concentration peak
i.v.	100%	
p.o. (in tablets)	up to 50% (strong first-pass effect), in children up to 27%	44–55 min
p.o. (in solution)	40-50%	22 min
i.m.	> 90%	20 min
s.c.	96%	31 min
p.r.	~50%	31 min
for colostomy	52%	10 min
buccal pills	75%	30 min
i.n.	64-83%	20–25 min

Table 2
Midazolam pharmacokinetic parameters in chronic renal disease and differences in midazolam pharmacokinetics between healthy individuals and patients with acute renal failure. [78,79].

Parameters	Control group	Patients with CRD
Age [yo]	47.1 ± 4.7	47.4 ± 3.9
Weight [kg]	70.5 ± 3.5	75.1 ± 3.4
Elimination t 1/2 of midazolam [h]	4.93 ± 0.8	4.58 ± 0.75
Vd of midazolam [l/kg]	2.18 ± 0.22	3.79 ± 0.31
Clearance [ml/kg/min]	6.74 ± 0.85	11.40 ± 1.55
Midazolam FF [%]	3.93 ± 0.12	6.51 ± 0.74
Vd FF of midazolam [l/kg]	55.6 ± 5.7	63.5 ± 6.8
Clearance of midazolam FF [ml/kg/min]	176 ± 24	189 ± 27

Parameters	Control group	Patients with acute renal failure
Infusion rate [mg/h]	9.4	8.7
CL 1-HM [ml/min]	136	3.9
Elimination t 1/2 of midazolam [h]	7.6	13.2

fraction (6.5% vs. 3.9%), distribution volume (3.8 l/kg vs. 2.2 l/kg) and clearance (11.4 ml/min vs. 6.7 ml/min) [72]. Details are presented in Table 2. CRD - chronic renal disease, FF – free fraction, Vd- volume of distribution, Cl 1-HM – 1-hydroxymidazolam glucuronide renal clearance

Differences in the pharmacokinetics between patients with chronic renal disease and healthy individuals are probably rooted in different protein binding.

No changes in the pharmacodynamics of midazolam and 1-hydroxymidazolam following the drug's p.o. administration in patients with end-stage renal disease were reported [80].

Another team investigated the pharmacokinetics of midazolam in emergency unit patients with acute renal failure, on mechanical ventilation, who took midazolam in constant i.v. infusion. The authors observed significant differences in the pharmacokinetics of midazolam and its metabolites (Table 2).The results of studies presented above indicate that midazolam should be used cautiously in patients with acute renal failure [79]. Drug dosage of midazolam in selected diseases/clinical conditions are presented in Table 3.

5. Dosage

PRN – on demand; CSCI – constant subcutaneous infusion; BDZ - Benzodiazepines

6. Midazolam interactions

The main metabolic pathway of midazolam is via CYP3A4, therefore inhibitors or inducers of this enzyme largely affect the pharmacokinetics of the drug [82,83]. Table 4 shows the most important interactions of midazolam with other drugs. Drug–drug midazolam interactions are presented in Table 4.

GCS- Glucocorticoids

The interaction between midazolam and grapefruit juice (CYP 3A4 inhibitor) must be emphasized [100].

7. Side effects

As seen with other benzodiazepines, administration of midazolam carries a risk of undesired effects. Often, however, they are taken concomitantly with other drugs or alcohol, which intensifies their toxic effects.

The main side effects of midazolam include: excessive sleepiness, sedation and confusion, difficulty concentrating, dizziness and related falls and fractures, impaired motor coordination, speech disorders, double vision, hiccups, nausea and vomiting [101].

Midazolam impairs the consolidation of new memories and may be associated with retrograde and anterograde amnesia [102]. Significant drop in blood pressure may be observed in patients with comorbid cardiovascular diseases, on antihypertensive therapy. Increased

Table 3
Midazolam dosage in selected diseases [4–28,81].

Symptom	Dose	Practical remarks
Anxiety/terminal restlessness/ agitation	• 0,25-0,5 mg i.v. • 0,5-1 mg s.c. PRN • 10-60 mg CSCI/ 24 hrs.	• start with smaller doses, gradually increasing the dose • if the patient does not respond to the dose of 60 mg CSCI, consider the administration of antipsychotics (e.g. levomepromazine)
Dyspnea	• 0,25-1 mg i.v. • 0,5- 1 mg s.c. PRN	• start with smaller doses, gradually increasing the dose • the dose can be increased up to 2.5 to 5 mg s.c./i.v. PRN or 30-60 mg / 24 hours CSCI • add morphine – modification of the central perception of dyspnea by the inhibition of the respiratory centre's response to hypercapnia and hypoxia • Simon and colleagues believe that the use of BDZ in the treatment of dyspnea should be 2nd- or 3rd-line treatment (after opioids and other methods), because there is inconclusive evidence for the effectiveness of BDZ in the treatment of dyspnea
Palliative sedation	• initial dose 0.25 mg i.v. or 0.5 mg s.c.	• following the starting dose, introduce constant infusion: 0.25-1.0 (and more) mg/h (usually 0.02-0.1 mg/kg mc./h) • onset of action after 1-3 min (i.v.) or 10-15 min (s.c.) • administration aiming at palliative sedation should be performed at hospital; in exceptional cases the drug can be administered at home by an experienced nurse in contact with the physician who introduced the treatment
Seizures/myoclonus	• 5-10 mg s.c. • 1-2,5 mg i.v. • 7,5 mg s.l. or 7,5 mg bucally PRN • 10-20/ 24 hrs. mg CSCI	• start with smaller doses, gradually increasing the dose • dose may be increased up to 30-60 mg CSCI • if the patient does not respond to the dose of 60 mg CSCI, consider phenobarbital • consider the cause of myoclonus (consider the possibility of accumulated toxic metabolites of medications in diseases that are associated with renal failure) • drug administered s.l. or buccal is recommended for children
Hiccups	• 1 mg i.v. or 2,5 mg s.c. • 10 mg /24 hrs CSCI	• start with small doses, gradually increasing dose • target 10-60 mg / 24 h CSCI • midazolam can be the cause of hiccups • 0,5-4 mg every 4-6 hrs s.c./s.l
Vomiting	• 0,5-4 mg every 4-6 hrs s.c./s.l	• midazolam affects the cerebral cortex • especially useful in cases of nausea and vomiting associated with fear
Addition to ketamine	• initial dose 0.25 mg i.v./ 1 mg s.c.	• alleviating undesired effects of ketamine • dose is ketamine- and patient respiratory status-dependent

Table 4
Significant drug interactions with midazolam [84–99].

Drug	Mechanism of Interaction	Practical remarks
Buprenorphine	Drugs' additive effect	• increases the depressant effect on respiratory system • ↑ risk of opioid overdose – lower the dose adjusting it to the patient's condition • intensification of sedation
Dexamethasone	CYP3A4 inducer	• In patients chronically using GCS, noticeable ↓ AUC and ↓ of clearance midazolam and ↑ excreted in the urine of 1-hydroxymidazolam glucuronide - consider increasing the dose of midazolam
Haloperidol	CYP3A4 Inhibitor	• ↑ toxicity risk midazolam • intensification of depressive action on the respiratory center
Carbamazepine	CYP3A4 inducer	• significantly lowers the effect of oral midazolam – use other route of administration or titrate dose to patient's condition
Clarithromycin	CYP3A4 inhibitor	• ↑ risk of midazolam toxicity • concomitant administration of midazolam with clarithromycin increases the AUC of midazolam by 174% after i.v. and by 600% after p.o. administration
Diltiazem	CYP inhibitor	• ↑ plasma concentration of midazolam - start with smaller doses of midazolam
Fentanyl	CYP3A4 substrate	• inhibits the metabolism of midazolam competing for CYP3A4
Fluoxetin/Olanzapine	CYP3A4 and/or 2C19 inhibitor	• ↑ CNS hypersensitivity to midazolam • increases respiratory depressant effect • ↓ blood pressure
Fluconazole	CYP3A4 inhibitor	• slight increase in plasma concentration of midazolam, possible prolonged sedation and ↑ psychomotor function impairment – lower the dose of midazolam or consider other BDZ which are not metabolized by CYP3A4 (e.g. lorazepam, oxazepam)
Ketoconazole/Itraconazole/ Voriconazole	CYP3A4 strong inhibitor	• significant ↑ AUC of midazolam – consider changing antifungal drug or observe the guidelines given above
Miconazole gel	CYP3A4 inhibitor	• topical administration of the drug in gel does not exclude drug-drug interactions, especially midazolam p.o.

respiratory depressant effect leading to respiratory failure, can also occur in individuals with respiratory diseases, elderly patients, as well as patients taking CNS depressants (e.g. opioids) [101].

In addition, long-term administration of midazolam may be associated with increased risk of seizures related to the lower effectiveness of GABA-A receptors. Seizures can also act as markers of the drug's withdrawal, especially if the withdrawal was sudden [103].

Midazolam administration can be related to a paradoxical reaction, i.e. the occurrence of agitation leading to aggression, hostility and impulsiveness, with tendency to violence. The mechanism of this reaction is not completely understood. It is postulated, that this reaction is related to past alcohol abuse and mental disorders [6].

The antidote used for the toxic effects of midazolam is flumazenil, administered at a dose of 10 mcg / kg (max. 0.2 mg / dose), can be repeated after 45 s, then every 1 min several times to a total dose of 50 mcg/kg or 1 mg; 5–10 mcg / kg / hour CCSI - stable solution at room temperature for 24 h [104]. The duration of single dose of flumazenil is shorter than midazolam (there is a need to repeat doses) [105].

8. Therapeutic implications

1 Avoid the use of midazolam in patients with severe respiratory failure or respiratory depression; with the exception of 1/ patients near death with chronic, incurable diseases in severe condition who suffer from intractable symptoms, refractory to the other treatment, and require midazolam for control and relief of their suffering (i.e., massive metastatic lung spread causing respiratory panic and dyspnea, dyspnea in lymphangitis carcinomatosa, or for palliative sedation), and 2/ patients with respiratory depression in agony- such patients require careful titration of midazolam doses and strict monitoring (indications for palliative sedation).
2 Use midazolam cautiously in patients with myasthenia gravis, chronic renal disease, impaired hepatic function, cardiovascular disorders and/or chronic respiratory failure.
3 Consider modification of the dose of midazolam in patients who are obese, extremely cachectic or suffer benzodiazepine/alcohol addiction.
4 Consider the possibility of physical dependence and drug tolerance developing along its long-term use.
5 While withdrawing midazolam, gradually discontinue (if possible) and inform the patient and his/her close relatives about possible rebound effect, characterized by anxiety, restlessness, agitation, irritability, confusion, hallucinations, headaches and seizures. Similar symptoms can occur following the introduction of a CYP3A4 inducer (e.g. dexamethasone, carbamazepine) during midazolam treatment.
6 Patients taking midazolam should not drive or operate machinery.
7 Limit polypragmasia/polypharmacy in order to avoid drug-drug interactions and undesired effects. Take into account the increased risk related to the concomitant administration of midazolam with clarithromycin, fluoxetine, olanzapine, azole antifungals or opioids.
8 Do not co-administer midazolam p.o. (entire dose reaches liver shortly after administration) and CYP inhibitors (i.e. antifungal azoles and miconazole gel- Daktarin; although used only topically) due to drug-drug interactions (via CYP3A4).
9 Should alarming symptoms occur, consider the reason for their occurrence (e.g. differentiation of neurological disorders in patients with diabetes mellitus - hypoglycemia or midazolam effect).

9. Conclusions

Midazolam is one of the most commonly prescribed drug in palliative care, with many indications in patients with limited organ reserve.

The drug (metabolized in the liver) and its active metabolite - 1-hydroxymidazolam, are short acting benzodiazepines but their half-life (t1/2) varies by mode of administration (p.o. administration results in decreased drug bioavailability by 40%), timing of administration (repeated vs. single dosing), dosage, adipose tissue mass (accumulation of the drug reflected by context-sensitive t1/2), hypoalbuminemia, decreased hepatic blood flow (regardless of etiology), chronic liver disease and renal impairment (excretion of active metabolite and parent drug is prolonged).

Midazolam undergoes drug - drug and drug - food interactions.

Polytherapy in palliative patients is common, thus safe treatment with midazolam is a challenge.

Sensitivity to midazolam is increased in elderly patients.

Special caution must be exercised when midazolam is co-administered with certain drugs that are often used in palliative care: buprenorphine, fentanyl, dexamethasone, haloperidol, clarithromycin, carbamazepine, fluoxetine, olanzapine, fluconazole, itraconazole, miconazole and diltiazem. All these factors should be considered with regard to midazolam dose adjustment.

Due to the high risk of dependance on midazolam, there is need for gradual withdrawal of the drug (if possible). Sudden discontinuation of midazolam or co-administration (of) CYP3A4 inducers may be followed by anxiety, agitation, confusion and/or seizures.

Conflicts of interest

None declared.

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