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A Review on the use of Midazolam as a Co-induction Agent

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The practice of delivering a small amount of sedative or another anesthetic drug to lessen the dose of induction agent necessary has been known as co-induction. In other terms, employment of two or more medications to generate anaesthesia is referred to as co-induction of anaesthesia [1,2]. As a coinduction agent, various medications have been trailed out. We'll look at the drug midazolam, its pharmacology, and how successful it is as a coinduction agent in this article. Midazolam has been proven to minimize the amount of propofol required to produce anaesthesia by up to 50% without compromising the recovery profile when administered in this fashion [3,4]. We looked at the literature on the drug midazolam and coinduction agents that was available on different platforms such as PubMed, medline, Scopus, Web of Science, and Google Scholar. We looked at several articles about midazolam and coinduction agents, as well as articles where midazolam was utilized as a coinduction agent. Prior observational studies and case reports using midazolam as a coinduction agent were mentioned in this article. After studying about midazolam's pharmacology, usage, indications, contraindications, as well as past observational studies and case reports, The substance can be used as a coinduction agent and has a variety of purposes in anaesthesia.

Keywords: Anesthetic drug; pharmacology; coinduction agent; Midazolam.

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1. INTRODUCTION

The technique of delivering a minor amount of sedative or another anesthetic agent to lower the dose of induction agent required has been dubbed co-induction. The employment of two or more medications to generate anaesthesia is referred to as co-induction of anaesthesia [1].

The term was coined in 1986 to describe the unintentional induction of anaesthesia by non-anaesthetically trained sedationists, as well as unintentional anaesthesia in an improper environment, which resulted in numerous deaths [2]. Currently, anaesthesiologists use intentional co-induction of anaesthesia to take advantage of medication interactions, particularly synergism.

There are two arguments in favor of co-induction. First, to enhance the balance of desired vs unfavorable consequences, and then to save money [1,2].

Midazolam has been proven to minimize the amount of propofol required to produce anaesthesia by up to 50% without compromising the recovery profile when administered in this fashion [1,3].

The use of two or more hypnotic medications to aid in the induction and maintenance of general anaesthesia has become increasingly popular. The goal of mixing medications in anaesthesia is to create more "precise target responses while avoiding adverse effects and facilitating speedy and predictable recovery," according to one argument [4].

Currently, no one intravenous anaesthetic medication can offer hypnosis, analgesia, or forgetfulness efficiently and safely. Thus, especially for total intravenous anaesthesia, clever mixtures of hypnotics and opioids are required (TIVA) [5]. Inevitable interactions occur, the majority of which are synergistic and should be assessed for the best patient care. This synergism varies a lot depending on the medications, the different anesthetic endpoints, and the different combined dosages of both anaesthetic agents [6].

In this article, we'll look at the pharmacology of midazolam and how it can be used as a coinduction agent.

C18H13ClFN3 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-Imidazo (1,5-a) (1,4)benzodiazepine, midazolam hydrochloride. Imidazo benzodiazepine is a water soluble imidazo benzodiazepine [7-10]. Anxiolysis, sedation and anti-convulsant are only a few of the effects. These activities are based on its interaction with central nervous system receptors.

The inhibitory impact of g-aminobutyric acid is amplified when these receptors are activated (GABA). In physiological pH, midazolam is lipid-soluble and promptly enters the central nervous system [7,8]

Fryer and Walser were the first to synthesize it in 1976 [7,9,10].

Because the imidazole ring is open at low pH, midazolam is water soluble. When it's in a solution with a pH higher than 4, the imidazole ring closes and it becomes much more lipid soluble, allowing it to enter nerve tissue more quickly. This helps to explain its quick onset of action and strong blood protein binding (up to 97 percent) [8-10].

The molecular weight is 325.767g/mol, the melting point is 159°C, the water solubility is 40.0mg/ml, the state is solid (white crystalline powder), and the half-life is 2.2-6.8 hours [9,10].

Pharmacodynamics: Sedative, anxiolytic, amnesic, and hypnotic actions are among the pharmacodynamic features of midazolam and its metabolites, which are comparable to those of other benzodiazepines. The pharmacologic effects of benzodiazepines appear to be due to reversible interactions with the (gamma)-amino butyric acid (GABA) benzodiazepine receptor in the CNS, which is the central nervous system's principal inhibitory neurotransmitter. Flumazenil, a benzodiazepine receptor antagonist, can easily reverse the effects of midazolam [9,10].

The effects of midazolam on the central nervous system vary depending on the dose, mode of administration, and presence or absence of concomitant drugs [9,10]. Time to eye opening, time to extubation, time in the recovery room, and time to discharge from the hospital have all been used to assess time to recovery after premedication with midazolam. The majority of placebo-controlled trials (8 in total) found no effect of midazolam on recovery time from general anesthesia, while a few additional placebo-controlled studies (5 in total) found some delay in recovery time after premedication with oral midazolam. It is possible that recuperation

will take a long time connected to the length of the surgical operation and/or the use of additional central nervous system depressive drugs Several investigations have shown that midazolam causes partial or total recall impairment [11]. When administered as a premedication, amnesia for the surgical experience was greater after midazolam than after placebo, which was usually regarded as an advantage [12]. In one trial, 69 percent of midazolam patients did not recall applying the mask, compared to only 6% of placebo participants [12].

Following premedication, episodes of oxygen desaturation, respiratory depression, apnea, and airway obstruction have been reported [13]; the risk of such adverse events is greatly increased when midazolam is combined with other central nervous system depressing agents and in patients with abnormal airway anatomy, cyanotic congenital heart disease, sepsis, or severe pulmonary disease [9,10].

Pharmacokinetics: Midazolam is readily absorbed following oral administration and undergoes extensive first-pass metabolism in the intestine and liver. Its main metabolite, (alpha)-hydroxymidazolam [14].

Midazolam has a moderately high level of plasma protein binding that is concentration independent. Midazolam is 97 percent bound to plasma protein, primarily albumin, in adults and children over the age of one year. The mean steady-state volume of distribution ranged from 1.24 to 2.02 L/kg in healthy volunteers, indicating that (alpha)- hydroxymidazolam is bound to an extent of 89 percent [9,14].

Human cytochrome P450 IIIA4 (CYP3A4) metabolizes midazolam to its pharmacologic active metabolite, (alpha)-hydroxymidazolam, in the liver and gut, followed by glucuronidation of the (alpha)-hydroxyl metabolite, which is found in unconjugated and conjugated forms in human plasma. The glucuronide of (alpha)-hydroxymidazolam is then eliminated in the urine [10,14].

The pharmacodynamic parameter values of the maximum effect (E max) and concentration eliciting half-maximal effect (EC 50) were identical in a research in which adult volunteers were given intravenous midazolam (0.1 mg/kg) and (alpha)-hydroxymidazolam (0.15 mg/kg). Midazolam is also broken down into two minor metabolites: 4-hydroxy metabolite (approximately 3% of the dosage) and 1,4-dihydroxy metabolite (about 1% of the dose), which are eliminated in urine as conjugates in modest proportions [10,14,15].

Elimination: After single oral dosages of 0.25, 0.5, and 1.0 mg/kg of midazolam, the mean elimination half-life ranged from 2.2 to 6.8 hours. Following IV injection of 0.15 mg/kg of midazolam (6 months to 16 years old), similar results (ranged from 2.9 to 4.5 hours) for the mean elimination half-life were observed. Total clearance ranged from 9.3 to 11.0 mL/min/kg on average [9,14,15].

Renal impairment: Although the pharmacokinetics of intravenous midazolam differed from those of persons with normal renal function, there were no differences in the distribution, elimination, or clearance of unbound medication in renal failure patients [14,15].

Hepatic dysfunction: Midazolam's pharmacokinetics are altered by chronic hepatic dysfunction. C max and bioavailability values in adult patients with hepatic cirrhosis were 43 percent and 100 percent higher, respectively, after oral administration of 15 mg of midazolam than in adult individuals with normal liver function. In the same patients with hepatic cirrhosis, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% compared to those with normal liver function after IV administration of 7.5 mg of midazolam. In individuals with chronic hepatic illness, midazolam should be titrated to get the desired effect [10,15].

Dizziness, headache, and discomfort or redness at the injection site, as well as fainting, confusion, mental/mood changes, difficulty breathing, muscle twitching, and uncontrollable movements, are all possible side effects. Symptoms include a sore throat, trouble breathing, a rash on the skin, hives, and itching [16,17].

Midazolam can produce any level of cardiovascular and respiratory depression, depending on the dose. High i.v. doses have resulted in cardiac and respiratory collapse, both of which can be fatal. Typical doses result in a slight drop in blood pressure and oxygen saturation [18,19]. The required amnesia, for example, during endoscopies, might persist much longer than the procedure itself,

sometimes even for hours (semi consciousness). Daydreams with sexual content do occur from time to time. Midazolam can produce visual abnormalities and nausea in addition to a variety of central nervous system symptoms (vertigo, dizziness, headaches, and infrequently hallucinations) [20]. Within weeks of repeated treatment (for example, as a sleeping aid), tolerance and dependency develop; withdrawal syndrome is common if the drug is abruptly stopped [17,18].

1.1 Risk Groups for Midazolam

1. **Pregnant women:** It should be avoided if possible, despite the fact that a link between benzodiazepines and malformations has yet to be proven. [21,22]
2. **Breastfeeding mother's:** It is excreted in breast milk therefore should be avoided [21].
3. **Children:** 0.08 to 0.15 mg/kg (maximum of 0.20 mg/kg) is the usual parenteral single dose. Rectal administration of 0.35 to 0.45 mg/kg is possible. Senior citizens: In the elderly (and when overall health is compromised), extreme caution is advised: do not exceed 50% of the usual dose at first! Renal failure may necessitate a dose reduction (individual adjustment). In the case of liver insufficiency, a dose reduction may be necessary (individual adjustment) [23].

2. INDICATIONS AND APPLICATIONS

1. Preoperatively it can be given intramuscularly or intravenously- it provides sedation / anxiolysis / amnesia;
2. Intravenously as a sedative/anxiolytic/amnesic agent before or during diagnostic, therapeutic, or endoscopic procedures such as bronchoscopy, gastroscopy, cystoscopy, radiologic procedures, coronary angiography, cardiac catheterization, oncology procedures, , suture of lacerations, and other procedures, alone or in combination with other CNS depressants;
3. It can be given as premedication prior to induction of general anaesthesia, a relatively narrow dose range and in a short period of time with the use of opioid premedication. Midazolam can also be utilized as a component of intravenous nitrous oxide and oxygen augmentation (balanced anesthesia);
4. It can be given as continuous intravenous infusion as part of anesthesia or in critical care settings for sedation of intubated and mechanically ventilated patients.

3. METHODOLOGY

We looked at the literature on the drug midazolam and coinduction agents that was available on different platforms such as PubMed, medline, Scopus, Web of Science, and Google Scholar.
We looked at several articles about midazolam and coinduction agents, as well as articles where midazolam was utilized as a coinduction agent. Prior observational studies and case reports using midazolam as a coinduction agent were mentioned in this article.

4. FINDINGS OF THE REVIEW

1. M. A. Khan et al. found that co-induction of anaesthesia with midazolam 0.02 $mg.kg^{-1}$ and thiopentone 3 $mg.kg^{-1}$ was associated with a smoother and significantly faster induction, better airway control, greater haemodynamic stability, and a lower incidence of untoward effects when compared to midazolam 0.02 $mg.kg^{-1}$ and thiopentone 2 $mg.kg^{-1}$ or thiopentone 4 $mg.kg^{-1}$ alone. The drawbacks of propofol are its higher price when compared to thiopentone, as well as discomfort on injection (50-100%) and more hypotension when compared to thiopentone [24].
2. Short TG. et al.. found that with the presence of midazolam, the dose of propofol necessary to generate anaesthesia was lowered by 52 percent. The cause of synergism was unknown, but it could have been due to interaction at GABA(A) receptors in the CNS [25].
3. In 1995, Amrein R, et al.. looked into midazolam and propofol as prospective partners. The synergy between midazolam and propofol could be used to improve the connection between intended effects and undesirable effects. When compared to monotherapy, co-induction of anaesthesia and co-administration of long-term sedation can improve therapeutic outcomes [26].
4. R. Howard-Griffin et al.. examined midazolam-alfentanil-thiopentone and midazolam-alfentanil-propofol co-induction

in 1997. Patients were given equal doses of thiopentone or propofol after receiving pre-induction doses of midazolam 0.04 mg.kg-1 and alfentanil 10 microgm/.kg. When adopting a co-induction approach, propofol was found to be superior to thiopentone at these levels for laryngeal mask airway insertion [26].

5. In a 1992 study, McClune S. et al. examined the synergistic effects of propofol and midazolam in 140 ASA 1 and 2 female patients (18-60 years). Loss of command response, loss of eye lash reflex, and failure to respond to anaesthetic face mask application were among the clinical end goals. In 50 percent of patients, 25 percent ED 50 midazolam followed by 50 percent ED 50 propofol resulted in loss of responsiveness to command, whereas 50 percent ED 50 midazolam followed by 25 percent ED 50 propofol resulted in the same effect [27].
6. Caba F. et al.. investigated the synergy of midazolam and propofol in anaesthesia induction in 1993. The ED 50 in the propofol group was 1.56 mg/kg, while the ED 50 in the midazolam group was 0.24 mg/kg, according to a double-blind trial of 90 ASA 1 and 2 women undergoing elective surgery. The ED 50 of midazolam was reduced by about a fourth in the midazolam propofol group, and the reduced dose was 0.068 mg/kg [28].
7. The notion that the "synergistic interaction that occurs when midazolam and propofol are combined for i.v. sedation is produced by an increase in the free plasma concentration of one of the medications" was tested by Teh J, Short TG, et al.. in 1994. Six patients had general anaesthesia and got a propofol infusion, followed by a midazolam infusion 30 minutes later. Another six individuals had a midazolam infusion followed by a propofol injection 30 minutes later. The observed synergism with this combination could not be explained only by changes in free plasma concentrations of any of these medications when they were given simultaneously, the researchers found [29].
8. The hypnotic effects of propofol, midazolam, and alfentanil were studied by Vinik HR, et al.. in 1994. In a randomized, double-blind study, 130 unmedicated subjects were exposed to their binary and triple combinations. The ability to open one's eyes in response to a spoken instruction was utilized as a benchmark. A probit approach was used to determine the dose-response curves for the three medications given separately and in combination, and the ED50 values were compared using an isobolographic analysis. The ratios of a single-drug fractional dosage to a combination fractional dose, which indicate superadditivity (synergism), were 1.4 for propofol-alfentanil, 1.8 for midazolam-propofol, 2.8 for midazolam-alfentanil, and 2.6 for propofol-midazolam-alfentanil. The findings show that the propofol-midazolam-alfentanil combination causes a powerful hypnotic synergism that is comparable to that of the binary midazolam-alfentanil combination. When compared to monotherapy, co-induction of anaesthesia and co-administration of long-term sedation can improve therapeutic outcomes. These enhancements include a better effect profile, a better ratio of beneficial effects to adverse effects, optimization of the time course of effects, and lower costs [30].
9. Martlew RA, et al.. established the dose-response curves and effective doses of propofol for insertion of the laryngeal mask airway (LMA) in 50 unmedicated children and 60 children premedicated with midazolam in a study conducted in 1996 [28]. The children were given one of several propofol doses i.v. over 15 seconds, and the circumstances for LMA implantation were assessed at 60 seconds. The doses required for acceptable LMA insertion in 50% and 90% of unpremedicated patients (ED50, ED90), respectively, were 3.8 mg kg-1 and 5.4 mg kg-1; for premedicated patients, the doses were 2.6 mg kg-1 and 3.6 mg kg-1.
10. In 1998, McAdam LC, et al. studied the effects of propofol and midazolam on GABA(A) receptor activation in embryonic hippocampus neurons. The patch clamp method was used to investigate the effects of midazolam and propofol on peak current induced by submaximal GABA concentrations. Isobolographic study was performed by first creating concentration-response curves for midazolam and propofol alone, and then assessing the potency of midazolam and propofol combos. In other studies, GABA concentrations were raised and flurazepam was used instead of midazolam.

Midazolam and propofol interact synergistically to augment currents induced by low GABA concentrations, according to isobolographic studies (1 microM). The interaction was additive when the concentration of GABA was increased to 3 microM. For the increase of currents elicited by 3 microM GABA, the interaction between flurazepam and propofol was likewise additive. The concentration of GABA was found to be a crucial factor in the interaction between midazolam and propofol: At low GABA concentrations, synergism was shown, but when the concentration of GABA was increased, an additive interaction was observed. The synergistic interaction between propofol and midazolam for clinical effects such as hypnosis may be due to changes in GABA(A) receptor activity. The findings have clinical implications in that the synergistic advantages shown at one concentration ratio of these medications may not be seen at another [31].

11. Cressey DM, et al.. examined the effects of pretreatment with midazolam at two different doses (0.025 and 0.05 mg / kg with placebo) on the induction dose requirements of propofol in two different age groups in a double-blind, randomised experiment. 60 patients between the ages of 18 and 35 and 60 individuals beyond the age of 65 (aged over 60 years). All of the patients were given 0.75 micrograms of fentanyl per kilogram of body weight, as well as a blinded pretreatment with either saline or one of two doses of midazolam. The induction was continued with a propofol infusion at a set rate [32].
12. G.F. Stegmann et al. [33] used propofol (4 mg/kg) after intravenous premedication with or without midazolam (0.1 mg/kg) in a group of 8 dogs scheduled for ovariohysterectomy in a clinical trial. The amount of propofol required, as well as cardiovascular parameters and the occurrence of severe apnoea (> 60 seconds), were all documented. In both younger and older patients, pretreatment with midazolam was linked to a considerable reduction in propofol dose requirements. The decrease in older patients was substantially bigger than the drop in younger patients. There was no discernible advantage in terms of better cardiovascular stability or reduced apnoea incidence. In the elderly, caution should be exercised while using midazolam as a co-induction drug with propofol [33]. After propofol induction, midazolam injection caused rapid behavioural alterations and enhanced reflex suppression. The dose necessary to achieve loss of the pedal reflex was lowered by 37%, and the end-tidal isoflurane concentration during maintenance was reduced by 23% compared to the control group.

5. CONCLUSION

After analyzing the literature on the drug midazolam, it has been determined that it can be utilized as a coinduction agent in the induction of anaesthesia, and that it has a synergistic effect with other inducing medicines such as propofol and thiopentone. It also reduces the induction dose of other inducing agents, making them more cost-effective and reducing their negative effects.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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