



Clinical Use of Midazolam Midazolam

John Schou, M.D.

Alix

John Schou, M.D.
County Hospital of Loerrach
Spitalstr. 25
D-79539 Loerrach, Germany

Alix Publishing

Wallbrunnstr. 106E · D-79539 Loerrach · Germany

Clinical Use of Midazolam

John Schou

Midazolam brought benzodiazepines to a prominent place in anaesthesia and related disciplines. While generally used according to previous standards, the partially unexpected features of this drug also helped to define new clinical options. These greatly enlarged the clinical field that could profit from utilization of this unique drug.

Having had occasion to work with midazolam right from its introduction in Germany in 1984, the author actively participated not only in defining new standards for the use of this drug, but also in coping with its adverse effects. Any useful drug poses side-effects, and full comprehension of these are a precondition for an optimal use. Although all drugs may be claimed to have negative properties, these may often derive simply from incorrect usage.

This booklet is not a strict review; it reflects the author's experiences which may occasionally appear to be in contrast to some study results. This depends in part on, how the defined questions were studied. An effort has been made to avoid obscure comparisons and to focus instead on practical clinical aspects as they have appeared in the author's use of midazolam.

Contents

General pharmacology	6
Premedication of children	9
Premedication of adults	11
The paradoxical reaction	12
Sedation for regional anaesthesia	13
Sedation for diagnostic procedures	14
General anaesthesia	15
Intensive care	16
Use as an anticonvulsive	18
Emergency medicine	19
The benzodiazepine-antagonist	21
Synopsis: indications and dosages	22
Conclusion	25
References	27

General pharmacology

With its introduction into anaesthesia 20 years ago, midazolam displayed two unique features, which remain relevant today: it is the shortest-acting and the only water-soluble benzodiazepine-agonist [BZD] available. It engenders the general BZD effects, causing *anxiolysis*, *muscular relaxation* and *amnesia* in lower doses and *sedation* or *hypnosis* in higher ones. In addition, it has distinct *anticonvulsive properties*. This may be interesting but it does not make clear what are the practical consequences for the use of this drug.

Water- and lipid-soluble BZD-agonist	
Year of synthesis	1976
Elimination half-life	1.5-2.4 h
Active metabolite (α -OH-midazolam)	10 %
- metabolite elimination half-life	0.7-0.8 h

Table 1. Key midazolam data

The drug has an elimination half-life of about 2 h (1.5-2.4). Only 10 % is transferred to one sole active metabolite with lower potency and an even shorter half-life [1]. This is in contrast to the old BZD diazepam with 3 metabolites and a half-life of 48-72 h. An even longer acting BZD, dipotassium-chlorazepate, has strangely enough gained favour among other anaesthetists.

The water-solubility of midazolam allows for an unproblematic galenic preparation for painless injection or mixture with common infusion solutions. It also explains the fast resorption after IM injection. After 10 min, similar plasma levels are reached as after IV injection of the same dose, without the latter's high initial peak levels. Bioavailability of an IM dosage amounts to 90%. Crossing the blood-brain barrier demands lipid solubility, also found in this drug.

Midazolam is not an analgesic; still, it exerts an important effect on *central nociception* (perception of pain) which, in clinical use, sometimes makes it difficult to tell the difference to analgesia. The combination of midazolam with opioids leads to a useful, but possibly also dangerous synergism – at least then dirigable through repeated dosage of fractional amounts.

Adverse effects are similar to those of other BZD. Contrary to many BZDs, including the two mentioned above, midazolam is considered not *porphyrrhoigenic*. A respiratory depressant effect is not profound in lightly sedated patients. Strong sedation, in particular in combination with opioids, may yield problematic *respiratory depression* [2]. For the same reason, any BZD should not be used in patients with chronic respiratory failure and possible hypercapnia.

A few years after its introduction, midazolam experienced an important safety development with the introduction of the BZD-antagonist flumazenil. In 1977 a specific BZD-receptor was demonstrated, which is localized in association to the GABA-receptor [3,4]. BZDs thus augment the inhibitory GABAergic stimulation, which is an indirect effect and only possible to a certain level. They do not exert any direct inhibitory action.

Galenically, midazolam is distributed in aqueous solution void of any preservation agents. It exists in ampoules of

- 1 ml, 5 mg (Multiple purposes)
- 3 ml, 15 mg (see: Role in general anaesthesia)
- 5 ml, 5 mg (see: Sedation for regional anaesthesia and diagnostic procedures)
- 10 ml, 50 mg (see: Role in intensive care).

In addition, 7.5 mg tablets are available for oral premedication. Rectal and nasal premedication of children is performed with the ampoule solution (5 mg/ml) while a syrup for oral (including sublingual/buccal) premedication of children may be prepared in the local pharmacy (registered in the US).

A neglected topic in clinical studies is the relative potency of the BZD on various BZD-effects. Although animal studies indicate that there are such differences, the rationale for claiming some BZDs to be more useful for sedative purposes and others to be better suited as anticonvulsives, is inconclusive. One difference is found with the classification of some drugs as partial antagonists (e.g., bromazepam), thus limiting the sedative component in comparison to the anxiolytic one. In this relation, midazolam must be considered a strong agonist.

Premedication of children

Ideally, the physician specifies what he requires and the substances meeting these requirements are subsequently found. In real life, the desired drug effects are often found incidentally while expecting other manifestations with the use of new drugs. That is what happened to us when we started using midazolam for the premedication of children.

We had expected a strong sedation, as was required then, giving the anaesthetist an advantage in achieving sleep induction. At first, we were disappointed, because the children usually arrived quite awake. It appeared that the smaller the children, the less sedated they were, even when the dose of midazolam was adjusted to body surface. Fortunately, it was also noted that, despite the absence of sedation, the children arrived in the operating room in a cooperative mood. Indeed, they were often rather euphoric, making a "drunken" impression. Although nobody would claim analgesic properties from a BZD, school children are often surprisingly calm at the attempt of establishing an IV line [5,6].

In a rather short time, the desired aim of paediatric premedication changed. Not deep sedation and reduced combative qualities were now the desired properties but rather anxiolysis and cooperation. It was also realised that not only drugs but also organisational measures (e.g. verbal preparation, motivation, cooperation with parents) were of importance for obtaining these qualities. In contrast, we did not miss the anticholinergic effects, previously considered a "must" in premedication. It was only a somewhat uneasy feeling that in leaving the pharmacological effects of morphine-scopolamine as the target of any premedication, we were now about to define other drug effects as a therapeutic aim.

The search for a suitable application and then a relevant dosage soon resulted in the following recommendations [Table 2]. The intramuscular route was widely abandoned. The best results were obtained with rectal administration of the concentrated ampoule solution. Oral administration was hampered by the problem that midazolam has a disgusting taste which it proved difficult to cover up by taste-modifiers - still, this succeeded to some better than to others.

Larger children will usually take the tablet, under the threat of other applications. Some may prefer the nasal route (again directly from the ampoule) which, next to direct intravenous injection, works fastest. It is impossible to predict which route of administration may be the best in a certain hospital since also non-pharmacological factors are of importance and all routes have been proven effective [7].

Route of administration	Age (year)	Dose (mg/kg)	Max (mg)	min before operation
Intramuscular or Nasal	0.5-2	0.2	3	15
	2-6	0.15	5	
	6-12	0.1	7.5	
	12-	0.075	7.5	
Rectal	0.5-2	0.7	10	20
	2-6	0.6	15	
	6-12	0.4	15	
	12-	0.3	15	
Oral (mixture) (tablet)	4-6	0.6	10	30
	6-12	0.4	10	
	8-		7.5	

Table 2: Route of administration and dosage of midazolam for premedication of children

Newborns and infants below 6 months are not given any premedication. Some felt that this border should lie even lower, at 3 months. The question is a double one, never really answered: is there a need, and is there any effect of midazolam in less mature brains? Obviously, this is felt by some pediatricians [8] since there is a recommendation for the use of midazolam in neonates.

A persistent and bigger problem remains the "paradoxical reaction" [PR] of about 5% of the children, occasionally calling for IM ketamine induction. This failure of effect differs from the phenomenon of PR defined below in not relating to any interactions and therefore perhaps calls for another term to be used. Still, to those who remember what paediatric anaesthesia induction was like previously, introduction of midazolam represents an enormous advantage.

Premedication of adults

Previous means for premedication mainly included opioids, anticholinergics and neuroleptic agents. This might produce an outwardly calm patient but some of these later reported suffering serious panic ("I would have run away but I couldn't") [9,10]. Regrettably, the prolonged use of neuroleptic drugs betrays that many anaesthetists did not routinely interview their patients postoperatively. This phenomenon changed convincingly with the introduction of midazolam for premedication.

As for the children, the effect of premedication in adults initially gave rise to disappointment with the expected degree of sedation. But then it was readily recognized that sedation is not a feature required in premedication - anxiolysis, preferably without any dangerous sedation, is the superior quality. Slowly emerged another recognition, in sharp contrast to earlier standards: there is no need for analgesics (exception: acute or chronic pain), neither are anticholinergics generally required; indeed, when they are not strictly needed, these two drug compounds may rather be the reason for adverse effects.

As a consequence of altered clinical options, the dose recommended was altered to 7.5 mg orally, which is equipotent to about 3 mg IM. Even then, the anaesthetist was repeatedly confronted with amnesia when the patient the following day claimed not to have experienced anything since leaving the ward. Declaring amnesia to a target of premedication is, however, not reasonable and represents a repetition of older mistakes when the pharmacological effects of other drugs were declared the desirable target of any premedication. A less charming manifestation of amnesia can be experienced when a patient claims that he did not feel any pain from the needle last time. Generally, the anaesthetist may then restore his pride when asking the patient about his experiences the following day.

Even 3.75 mg orally has been shown to blunt the immunological response [11]. A dose reduction is recommended for old patients. Very old patients and those with chronic respiratory depression should not receive any premedication at all. Caution is necessary when opioids are required.

The paradoxical reaction

In contrast to the expected sedation, as experienced with higher doses of midazolam, restlessness and confusion occasionally occurred when used for facilitating regional anaesthesia. This soon came to be feared as "the paradoxical reaction" [PR]; and when titrated during regional anaesthesia, slight restlessness turned worse and occasionally made a general anaesthesia necessary, simply in order to keep the patient on the operating table. An adverse effect of the drug, we thought, until we found out that we were provoking it unknowingly ourselves [12]. We had initially utilized a traditional premedication with phenothiazines and atropine, fearing that sedation would complicate the cooperation of the patient (later we learned that it did not). Under the assumption to antagonize midazolam - before flumazenil was available, - the patients with a PR were given 0.4-1.2 mg of physostigmine IV, which did not only calm them down but resulted in what you might well call a "paradoxical sedation". From the success of physostigmine, it was evident that the PR was to be considered an expression of a central anticholinergic syndrome [13] and as such the result of a drug interaction between the BZD on the one side and an anticholinergic or neuroleptic drug on the other. So this experience demonstrated both how to treat the PR and how to prevent it. Besides, using midazolam alone for premedication, we did not experience such effects.

The term PR has been (ab-)used in a broader sense. It seemed that alcoholics occasionally reacted to BZD without needing other drugs for creating a PR. Also the PR found in children seems to arise from another genesis. In such cases, using the experiences from emergency medicine [14], another synergism can be used: the sedative effect of nalbuphine (even when no analgesics were required) with midazolam. For an effective utilisation of this interaction, it is essential that *nalbuphine is given first* (adult dose 20 mg) whereupon midazolam is titrated in mg-doses. That, however, demands that it is suspected in advance that the patient will cause problems. Nalbuphine is not a drug for titration; therefore, its application at a later time, after midazolam has proved insufficient, may lead to an unpredictable sedation.

Sedation for regional anaesthesia

The lesson learned from the PR was to titrate midazolam and, perhaps more importantly, change the options. The fearless and relaxed, not the sleepy patient was our target; these, at least, were the new options to which the patients also could easily be persuaded. Occasionally, it proved more difficult to convince the surgeon that this was feasible.

In order to avoid any PR, the patients were premedicated with midazolam. Many brave men and women did not want it at all but vasovagal reactions became rare when you insisted on it. Atropine may be the treatment required when the pulse-rate suddenly goes down but it has no preventive action, on the contrary. Then, of course, the regional anaesthesia must be convincing. Only with these preconditions, you can proceed.

The key to success lies in adding tiny doses of 1 mg (or even 0.5 mg) midazolam in a titrated fashion. Probably adding to the effect of 7.5 mg orally as a premedication, patients would generally require 1.5–2 mg. This made another formulation preferable, that of 5 mg in 5 ml ampoules. The patient would even snore loudly, but assuming sleep or amnesia in advance would lead to instant disappointment and should therefore not be a declared therapeutical option. Music on headphones (according to the patient's personal choice) can be an excellent supplement, even if the experience is later found to be buried in amnesia.

In the cases where, for some reason, a sleep seems mandatory, the author prefers the combination with nalbuphin as described in the previous chapter. Using these modifications (and acting for consequent prevention and treatment of post-dural puncture headache), regional anaesthesia could be offered on a larger scale than previously seemed suitable.

Sedation for diagnostic procedures

Sedation for endoscopy shows much resemblance to the challenge of adjoining regional analgesia. Preferable seems the IM premedication with 5 mg, but some physicians are not afraid to meet the tablet again in the stomach (this encounter was never reported to me). In most cases, an IV line is then not required. It is, of course, possible to perform gastroscopy without any sedation, but patients clearly prefer midazolam to nothing [15]. For a day-case patient, early ambulation is an essential quality; however, midazolam should not be given to patients who, in spite of all warnings, insist on driving by themselves after the examination. The doctor should refuse to take any co-responsibility for the traffic events that day.

Midazolam certainly acts with before-mentioned BZD-effects: anxiolysis, sedation and (at least to a certain degree) amnesia. It does, however, also contribute to a reflex depression of the upper airways [16,17].

When a more sophisticated gastroscopy is required (for banding of oesophageal varices), the patient is often of a certain constitution that makes a deeper sedation necessary. This is occasionally also necessary for facilitating coloscopy, often a rather painful matter. Here, again, the above-mentioned sedative synergism between an opioid and midazolam has proved useful. Certainly, such strong sedation is not quite suitable for day-case patients, but neither are bleeding oesophageal varices, and it still proved possible to avoid a general anaesthesia in most of these cases.

For other diagnostic measures, when sedation is indeed needed (e.g. in children), it is advisable to use premedication as described above and/or in a titrated fashion of mgs of midazolam IV.

In case of the need for stronger sedation, the combination of low doses of midazolam and propofol may make a regimen with spontaneous ventilation (under oxymetry monitoring) possible through favourable synergism [18] (compare with co-induction in general anaesthesia).

General anaesthesia

It is possible to induce hypnosis with 0.15–0.2 mg/kg midazolam IV; however, what is possible is not always preferable. Generally, a rather awake patient is preferred soon after surgery and using a full induction dose of midazolam is not the correct way to achieve this. Personally, I have used the high dose only in patients where post-operative ventilation was expected.

Why, then, use it in anaesthesia at all? The answer is a philosophical one [19], therefore, not accessible to all. While the reader's patients may be heavily "asleep" (some comatized condition commonly understood as anaesthesia), the victims of the author's techniques might have been influenced by verbal stimuli. They did not complain of it afterwards but I knew it even then; in the meantime, there is solid evidence for the existence of cerebral activity in response particularly to auditory stimuli (speech). The "awareness in anaesthesia", as represented by the patient who then sues the anaesthetist for a wakeful condition when everybody assumed her or him to be asleep, is just an extreme, a rare event that is frequently obscured by amnesia.

Practically, the use of midazolam can be facilitated with "*co-induction*": Using 0.05 mg/kg of midazolam with 1.5 mg/kg of thiopental (a third of the usual dosage) produces a favourable synergism, by which the adverse effects of thiopental are reduced when midazolam is added at a crucial time. Somewhat disturbing, it has not been possible to measure the effect of midazolam when given in this context. Its use remains based upon philosophical considerations. Co-induction also make sense with other hypnotics [20].

In day-case patients, co-induction is not recommended. After all, these patients should regain vigilance more readily. This is then best assured by total intravenous anaesthesia based upon *propofol*.

When using *ketamine*, it has been recommended to add a BZD for suppressing the hallucinogenic effect. This effect has been reduced but not eliminated with the introduction of the racemate (s-ketamine), still the combination is recommended. For this type of anaesthesia, midazolam has proved preferable to diazepam [21,22].

Intensive care

We had already gained important experiences with midazolam when the drug was finally introduced in the intensive care unit [ICU]. Nonetheless, other anaesthetists were still making the same mistakes there as described in other fields. Midazolam was expected to produce a long-term anaesthesia which would then cover up some of the mess typically found within the ICU. Patients are often struggling with life-threatening conditions and have extreme pain and discomfort to cope with as well. This is then amplified through various organizational failures, e.g. an eternal disturbance through alarms, a special jargon adopted by the staff towards their speechless patients and more. Not surprising to lay people, this atmosphere more than occasionally results in serious psychic disturbances.

This seems to touch one of the frequent challenges met at ICUs - *delirant conditions* [23,24]. The occurrence of that is then often seen by the staff as a confirmation that the patient has an alcohol problem (which may, of course, be counted to the etiologies). Who is to blame? That the ICU had any co-responsibility in producing this condition is rarely recognized.

Midazolam is not an antipsychotic drug and such are necessary in the *treatment* of delirant conditions. It may, however, be useful in the *prevention* of psychotic reactions - not to cover up unpleasant circumstances in the ICU but along with organizational reshaping. Such non-pharmacological measures include a respectful behaviour to the patients, also apparently confused and unresponsive ones, a restriction of auditory disturbances and measures in support of a diurnal rhythm - let the patient, when possible, sleep without interruption from drug injection and other manipulations at short intervals. Other pharmacological interventions include pain treatment with systemic or regional measures.

Patients judged to be in need of prophylactic midazolam at the ICU [25,26] are given, for example, a continuous infusion of 0.2-1.0 mg/h from 04 am - 10 pm (*anxiolytic dose*) and 1-2 mg from 10 pm to 04 am (*hypnotic dose*). In the evening, the altered infusion rate is not producing higher plasma levels at once, therefore a bolus of 2.5 is added; similarly, changing the infusion rate in the morning does not instantly alter

the plasma level, but here you can calculate 2 hours for the adjustment. Certain measures, carried out thrice a day, are then confined to the hours 6 am, 2 pm and 10 pm, while the sleeping time is kept as free as possible from any intrusion.

The failure of midazolam to sedate a patient should not be understood as an adverse effect of the drug itself but indeed as a symptom of severe psychotic disturbances. Similarly, the failure of moderate doses of antipsychotic drugs (e.g. haloperidol) to influence the patients must be understood as a *symptom in itself*, not as a drug failure. Here, anaesthetists obviously have a lot to learn from psychiatrists.

A different, possibly more frequent use of midazolam is found in the production of *strong analgosedation of ventilated patients*. Here doses of 2-5 mg per hour are regularly used. Again, it is recommended to use small boluses (~2.5 mg) when an increased infusion rate is required, whereas a complete intermission for 1-2 hours will show the effect of a dose-reduction more rapidly.

For analgosedation (or sedoanalgesia, a suitable clinical concept), practically all opioids can be considered without caring for any possible synergistical respiratory depression [27], once the patient is anyhow ventilated.

Used under these criteria, it is possible to avoid the application of *continuous anaesthesia* (propofol infusion or combination with ketamine) in most cases but not all. The indiscriminate use of propofol for all ventilated patients can be understood as an indication that some organisational measures, as indicated above, need to be taken. Just calling it a "sedation" does not remove the adverse effects of anaesthesia.

Midazolam has now been used for many years in the ICU and has stood this test of time brilliantly. A recent European survey revealed 63% use of midazolam for sedation vs. 35% propofol and 2% others [28]. It needs attention that the pharmacokinetics of many drugs, including midazolam [29], is altered in intensive care patients. It may thus rarely be necessary to use the BZD-antagonist flumazenil. Personally, I understand this as only a theoretical option when using midazolam whereas I have experienced some "surprises" in patients who had been given chlordiazepoxid, diazepam or flunitrazepam for premedication even days before.

Use as an anticonvulsive

All BZD act as anticonvulsives and some are used for long-term preventive purposes. Midazolam is only to be considered for treatment of convulsive states and immediate prophylaxis thereafter (exceptions to be found in the ICU [30]). What then makes the drug a logical choice in emergency use is its fast action after IM application – it is difficult to establish an IV line on a jerking arm – and its short duration of action, making EEG examinations possible the following day.

The advantage of midazolam for emergency use was recognized shortly after its introduction [31], and its therapeutical use as an anticonvulsive has been confirmed in other studies [32]. It thus eliminates the need for any other BZD in the emergency equipment. The use includes a prophylactical IM application after the convulsions have stopped. The actual need of it has been challenged with the arguments that most convulsions are singular, and long-acting BZD may disturb diagnosis for a considerable time. All BZD may induce a beta-rhythm in EEG; it is therefore advisable to postpone electroencephalographic diagnostics to at least the following day – which would still not suffice for other BZD, requiring an interval of 3–7 days. Arguments for the prophylactic IM application are: 1) this makes the emergency physician ready for another prehospital mission and 2) it becomes unnecessary to search at length for an IV access in an infant (typically after febrile convulsions) which has in the meantime woken up.

The IM application had indeed a problem of acceptance among physicians who believed rectal diazepam should remain the method of choice. Recent studies have confirmed that also midazolam 0.2 mg/kg intranasal [33] or buccal/sublingual 0.3 mg/kg [34,35] are effective (though hardly advantageous) against seizures. A precondition for the use of midazolam as the sole BZD in emergency medicine is that it also acts as an effectful anticonvulsive.

Emergency Medicine

The use as an *anticonvulsant* is perhaps a minor topic in emergency medicine. If, however, that purpose can be fulfilled with a drug predominantly used for other indications, this is advantageous, given the limited drug supply.

Hyperventilation attacks can sometimes not be clearly distinguished from convulsions. A standard dose of 2.5 mg IV or 5 mg IM will generally solve the problem more rapidly than rebreathing measures and many comforting words. Except for this condition, the use as an *anxiolytic* should be restricted for patients anyhow to be admitted, since the brief action makes midazolam unsuitable for longer treatments and this is, in any case, beyond the scope of an emergency physician.

Midazolam is used very frequently along with an opioid in so-called "*analgo-sedation*" ("*sedoanalgesia*"). The rationale is that a rather small dose of midazolam (1.5–2.5 mg) through its central effect on nociception potentiates any opioid; in addition, it adds to the sedative effects of κ -stimulating opioids, e.g. nalbuphin. The surprise of a sudden emergency gives anxiety a dominant place in generation of pain, explaining the success of this combination exactly prehospitally beyond a general synergism with the opioid.

The need for prehospital *sedation* without intubation is a problem of its own. It generally obliges continued monitoring during transport where the physician might have been ready for another mission. Not always successful is the use in psychotic and violently aggressive patients, who are therefore initially given nalbuphine 20–40 mg and, when everything has failed, ketamine thereafter. The experiences from pediatric premedication may in a few cases be adopted for facilitating an IV line in children 5–10 min after IM application.

Particularly prehospitally, midazolam may be used as an adjunct for *ketamine anaesthesia* [36]. Although intubation is generally called for in prehospital anaesthesia, a few cases, predominantly children, may not need ventilation.

An alternative principle for *prehospital anaesthesia* involves the use of midazolam only after successful intubation [37]. It is recommended to carry out the intubation exclusively with etomidate and a suitable adjunct, e.g. nalbuphine. With the opioid already given (and/or possibly added later), midazolam is then titrated according to the demand. This demand is signified by movements or wakeful appearances, a primitive principle for primitive surroundings and thus highly effective.

A personal testimonial for the success of this technique may be worth considering: the author's preferred intubation technique (blind nasotracheal) was dependent upon persistent breathing, excluding midazolam and most opioids along with etomidate. Possibly facilitated through the route of intubation (an orotracheal tube produces a persistent noxious reflex stimulation), it was probably easier to keep the patients sedated.

The dosage used varies according to the general and haemodynamic condition. Patients in shock need much less and comatose trauma patients more than the average requirements. The dosages of midazolam are shown in Table 3.

Primary indication for endotracheal intubation	n	Midazolam, mg (average)
Comatose, trauma	53	12.4
Comatose, non-trauma	37	8.1
Shock, trauma	26	7.7
Shock, non-trauma	26	2.8
No shock, all	110	10.8
No of Pat.s (n)/average	162	9.1

Table 3: Dosage of midazolam after intubation until admission of 162 consecutive patients.

Taking all indications together, midazolam became the most frequently used drug in the author's prehospital emergency kit.

The benzodiazepine-antagonist

Flumazenil is the first and so far only clinically available BZD-antagonist, acting by a strong affinity and negligible intrinsic action at the benzodiazepine receptor. It does, however, produce weak anticonvulsive properties [38], which may help explain why convulsions are extremely rare after reversal of benzodiazepine sedation with this drug. Other agonistic activities of flumazenil (all weak and clinically irrelevant) include anxiolytic activity in stimulated stress [39]. The elimination half-life of 53 min is shorter than any benzodiazepine agonists, making rebound sedation a possibility after long-acting BZD. Like midazolam, it is a water-soluble imidazo-benzodiazepine and can therefore be administered IM or mixed in an infusion. In order to avoid sudden withdrawal, the drug is titrated with 0.1 mg each min until desirable effect or a maximum 1.0 mg is reached. It is recommended to add any excess to the infusion solution in order to provide an increased duration of action. It may produce some awakening effect in alcohol intoxication [40] and hepatic coma [41] but complete awakening can be regarded as a diagnostic (and therapeutic!) proof of BZD overdose.

I have used flumazenil quite a number of times, also prehospitally [42], but very seldom towards midazolam. Still, I consider the mere availability of this antagonist also of importance for midazolam, since it enables the reversal of any excess (undesirable) sedation or respiratory depression in unexpected synergism [43] or presence of other disease conditions resulting in awkward effects of the drug. Thereby, flumazenil adds substantially to the *safety of midazolam* - provided it is available among your drugs.

A less complete and unspecific reversal of midazolam sedation is achieved with *physostigmine* [44] and *aminophylline* [45].

Synopsis: Indications and Dosages

Indication	Dosage and Application
Premedication	
Children	Rectal, p.o., nasal, IM (See table 2)
Adults	7.5 mg p.o. or 3-5 mg IM
Regional anaesthesia	
	1-2 mg initially + 0.5-1.0 mg IV Titr. (max. 5 mg)
Analgesedation	Opioid, then midazolam Titr. as above
Strong sedation	Nalbuphine 20 mg first, then IV Titr. as above
Sedation for endoscopy	
	7.5 mg p.o. or 5 mg IM + 1-2 mg IV + Titr.
General anaesthesia	
	5 mg 1 min IV before hypnotic in reduced dosage or 0.15-0.2 mg/kg with opioid agonist (0.3 mg/kg without premedication)
Intensive care	
Anxiolysis & hypnosis	04-22 h: 0.2-1 mg/h 22-04 h: 1-2 mg/h 22 h: 2.5 mg + Titr.
Sedation by ventilatory support	2-5 mg/h + opioid by infusion
Convulsive status	2.5 - 15 mg IV Titr. , followed by 10-15 mg/h
Emergency medicine	
Analgesedation	Nalbuphine 20 mg first, then 2.5 mg IV + Titr. or opioid agonist first, then 2.5 mg IV + Titr.
Seizures, therapy	5 mg IM + Titr. IV
Seizures, prophylaxis (infants)	0.2 mg/kg IM or 0.3 mg/kg sublingual
Hyperventilation	2.5-5mg IM/IV
„Anaesthesia“ after intubation	2.5-5 mg IV + Titr. (see guidance in Tab. 3)
Antagonism	
	Flumazenil 0.2-0.5 mg Titr.

Table 4: Synopsis of the text. **Titr.:** repetitive titrated intravenous doses of 0.5-1.0 mg midazolam until desired effect (or a maximum of 5 mg) is obtained. IV application if not specified.

Comments
Therapeutic option: cooperation and anxiolysis, not sedation (degree of sedation inversely proportional to age)
Option: anxiolysis, amnesia may occur (unpredictable)
Music on headphones
The opioid should be given first, midazolam then titrated
When strong <i>sedation</i> , not analgesia is dominant demand
Cautious use for outpatients (no driving home afterwards)
Co-induction, bringing anxiolysis into general anaesthesia Patients more sedated postoperatively
Plus organizational measures, preferably with sedation monitoring
Possible alternative: propofol (then better call it anaesthesia)
Ventilatory support should prevail at such doses
Nalbuphine is not useful for titration purposes
Ventilatory monitoring (oxymetry) mandatory
IV line after success from IM dose (avoiding IV line after febrile convulsions)
Higher dose in hospital
Caution in shock and hypovolaemia
Good to have just in case...

Caution is required for the use of midazolam

- with chronic respiratory failure
- in old age
- with hypovolaemia or shock
- by interaction in particular with anticholinergics and neuroleptics (PR)
- by interaction with other sedatives
- by interaction with opioids

Table 5: Conditions where adverse effects are prone to occur.

Abbreviations:

BZD	Benzodiazepine
ICU	Intensive Care Unit
IM	Intramuscular
IV	Intravenous
p.o.	Peroral (by mouth)
PR	Paradoxical Reaction
Tit.	Titrated, i.e.: repetitive small IV doses until desired effect

Conclusion

With midazolam, not just another BZD was introduced into clinical use. The drug is better titrated than any other BZD and its short duration of action turned out to be important for its use in anaesthesia and related fields. The principles for premedication, both paediatric and adult, were changed as a consequence of its introduction (it may now be difficult for younger anaesthetists to imagine what premedication was like before). No other BZD had been used the way, midazolam now gained introduction into anaesthesia, intensive care and emergency medicine.

Along with the use, also the options for the expected BZD-effects changed. It was realized that a cautious and small dosage was often effective in removing anxiety without necessarily demonstrating sedation. Should it not suffice, you could add a mg or two, whereas you could hardly draw back 5 mg that had already been injected. Even as it became possible to antagonise the drug with flumazenil, you would certainly prefer to avoid any excess effect, leaving the antagonist a potential rescue medication "better not used".

We can now look back at 20 years of clinical use of Midazolam - surprising adverse effects of major importance are not apt to occur. Still, some interactions, indicated in this description, deserve studies. Uncritical use is, of course, not to be advocated, but for anaesthetists, intensive care and emergency physicians, it has become a drug worthy of being known by heart. It remains an important resource in the clinical areas here described.

References

- 1 Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiol Scand* 1990;92(Suppl.):6-15.
- 2 Gross JB, Blouin RT, Zandsberg S, Conard PF, Haussler J. Effect of flumazenil on ventilatory drive during sedation with midazolam and alfentanil. *Anesthesiology* 1996;85:713-20.
- 3 Mohler H, Okada T. Benzodiazepine receptor: demonstration in the central nervous system. *Science* 1977;198:849-51.
- 4 Squires RF, Braestrup C. Benzodiazepine receptors in rat brain. *Nature* 1977;266:732-4.
- 5 Schou J, Atanassov P. Prämedikation mit Midazolam in der Kinderanästhesie. *Kinderarzt* 1986;17:326-9.
- 6 McErlean M, Bartfield JM, Karunakar TA, Whitman MC, Turley DM. Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. *J Pediatr* 2003;142:429-30.
- 7 Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth* 2002;12:685-9.
- 8 Arya V, Ramji S. Midazolam sedation in mechanically ventilated newborns: a double blind randomized placebo controlled trial. *Indian Pediatr.* 2001;38:967-72.
- 9 Tolksdorf W, Berlin J, Bathke U, Nieder G. Psychische und somatische Auswirkungen der Prämedikation mit Rohypnol, Thalamonal und Placebo in Kombination mit Atropin. *Anästh Intensivther Notfallmed* 1981;16:1-4.
- 10 Seibert W. Thalamonal-Prämedikation als Auslöser extremer Angst und die post-operativen Folgen. *Anästhesist* 1987;36:662-3.
- 11 Heine GH, Weindler J, Gabriel HH, Kindermann W, Ruprecht KW. Oral premedication with low dose midazolam modifies the immunological stress reaction after the setting of retrobulbar anaesthesia. *Br J Ophthalmol* 2003;87:1020-4.
- 12 Knaack-Steinegger R, Schou J. Therapie und Prophylaxe der paradoxen Reaktion nach Midazolam zur Regionalanästhesie, *Anaesthesist* 1987;36:143-6.

-
- 13 Ruprecht J, Dworacek B. Central anticholinergic syndrome in anaesthetic practice. *Acta Anaesth Belg* 1976;27:45-60.
 - 14 Schou J. *Prehospital Emergency Medicine - Challenges and Options in Rescue Services*, 2nd Edition. Harwood Academic Publ., Amsterdam B.V., 448 pp, 1997.
 - 15 Bonta PI, Kok MF, Bergman JJ, Van den Brink GR, Lemkes JS, Tytgat GN, Fockens P. Conscious sedation for EUS of the esophagus and stomach: a double-blind, randomized, controlled trial comparing midazolam with placebo. *Gastrointest Endosc* 2003;57:842-7.
 - 16 Murphy PJ, Erskine R, Langton JA. The effect of intravenously administered diazepam, midazolam and flumazenil on the sensitivity of upper airway reflexes. *Anaesthesia* 1994;49:105-10.
 - 17 D'Honneur G, Rimaniol JM, el Sayed A, Lambert Y, Duvaldestin P. Midazolam/propofol but not propofol alone reversibly depress the swallowing reflex. *Acta Anaesthesiol Scand* 1994;38:244-7
 - 18 Paspatis GA, Manolaraki M, Xirouchakis G, Papanikolaou N, Chlouverakis G, Gritzali A. Synergistic sedation with midazolam and propofol versus midazolam and pethidine in colonoscopies: a prospective, randomized study. *Am J Gastroenterol* 2002;97:1963-7.
 - 19 Schou J. *A Philosophical Approach to Anaesthesia*. Alix Publ., 104 pp, 1994.
 - 20 Adachi YU, Watanabe K, Higuchi H, Satoh T. A small dose of midazolam decreases the time to achieve hypnosis without delaying emergence during short-term propofol anesthesia. *J Clin Anesth* 2001;13:277-80.
 - 21 Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia. *Anaesthesia* 1984;59:439-2.
 - 22 Toft P, Romer U. Comparative evaluation of midazolam and diazepam to supplement total intravenous anaesthesia with ketamine vor endoscopy. *Can J Anaesth* 1987;34:466-9.
 - 23 Wilson L. Intensive care delirium. *Arch Intern Med* 1972;130:225-6.
 - 24 Hemmingsen R, Kramp P, Rafaelsen OJ. Delirium tremens and related clinical states. *Acta Psychiatr Scand* 1979; 59:337-69.
 - 25 Schou J, Kübler J, Scherb M. Induktives Monitoring zur Beurteilung und Propylaxe psychischer Störungen auf der Intensivstation. *Intensivmed* 1992;29(Suppl):67-71.

- 26 Treggiari-Venzi M, Borgeat A, Fuchs-Buder T, Gachoud JP, Suter PM. Overnight sedation with midazolam or propofol in the ICU: effects on sleep quality, anxiety and depression. *Intensive Care Med* 1996;22:1186-90.
- 27 Conti G, Merdurio G, Iacobone E, Auricco D, Liberati Q. Sedation in the intensive care unit. *Minerva Anestesiologica* 2002;68:240-4.
- 28 Soliman HM, Mélot C, Vincent J-L. Sedative and analgesic practices in the intensive care unit. *Br J Anaesth* 2001;87:186-92.
- 29 Bolon M, Bouliou R, Flamens C, Paulus S, Bastien O. Sedation par le midazolam en réanimation: aspects pharmacologiques et pharmacocinétiques. *Ann Fr Anesth Reanim* 2002;21:478-92.
- 30 Ulvi H, Yoldas T, Mungen B, Yigiter R. Continuous infusion of midazolam in the treatment of refractory generalized convulsive status epilepticus. *Neurol Sci* 2002;23:177-82.
- 31 Schou J. Midazolam zur Sedierung und Krampfbehandlung in der Notfallmedizin. *Europäischer Anästhesiekongress, Wien 1986, Abstract vol. III, Nr. 862.*
- 32 Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. *Arch Emerg Med* 1987;4:169-72.
- 33 Lahat E, Goldman M, Barr J, Bistrizter T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000;321:83-6.
- 34 Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999;353:623-6.
- 35 Kutlu NO, Dogrul M, Yakinci C, Soylu H. Buccal midazolam for treatment of prolonged seizures in children. *Brain Dev* 2003;25:275-8.
- 36 Bourgoin A, Albanese J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med* 2003;31:711-7.
- 37 Schou J. Three techniques for prehospital emergency anaesthesia. *JEUR* 1994;3:139-45.
- 38 Scollo-Lavizzari G. The anticonvulsant effect of the benzodiazepine antagonist Ro 15-1788. *Eur Neurol* 1984;23:1-6.

-
- 39 Strohle A, Wiedemann K. Flumazenil attenuates the pituitary response to CRH in healthy males. *Eur Neuropsychopharmacol* 1996;6:323-5.
 - 40 Scollo-Lavizzari G, Matthis H. Benzodiazepine antagonist (RO 15-1788) in ethanol intoxication: a pilot study. *Eur Neurol* 1985;24:352-4.
 - 41 Goulenok C, Bernard B, Cadranet JF, Thabut D, Di Martino V, Opolon P, Poynard T. Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. *Aliment Pharmacol Ther* 2002;16:361-72.
 - 42 Schou J, Deklerk J, Scherb M, Kübler J. Antagonism vs. ventilation in drug overdose. *JEUR* 1995;8:136-9.
 - 43 Gross JB, Blouin RT, Zandsberg S, Conard PF, Haussler J. Effect of flumazenil on ventilatory drive during sedation with midazolam and alfentanil. *Anesthesiology* 1996;85:713-20.
 - 44 Ebert U, Oertel R, Kirch W. Physostigmine reversal of midazolam-induced electroencephalographic changes in healthy subjects. *Clin Pharmacol Ther* 2000;67:538-48.
 - 45 Bonfiglio MF, Fisher-Katz LE, Saltis LM, Traeger SM, Martin BR, Nackes NA, Perkins TA. A pilot pharmacokinetic-pharmacodynamic study of benzodiazepine antagonism by flumazenil and aminophylline. *Pharmacotherapy* 1996;16:1166-72.

Midazolam
Midazolam
Midazolam

Alix Publishing

Wallbrunnstr. 106E · D-79539 Loerrach · Germany