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Pharmacology of Dormicum® (midazolam) and Anexate® (flumazenil)

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Midazolam and flumazenil have some characteristics in common which make them suitable partners as benzodiazepine (BZD) agonist and antagonist. After intravenous (i.v.) administration, both drugs are rapidly distributed into similar distribution volumes, from which they are cleared with a comparable short elimination half-life ($t_{1/2}\beta$) in the range of 1 h (flumazenil) to 3 h (midazolam). Both drugs undergo hepatic metabolisation with a relatively high hepatic extraction ratio of around 0.3 for midazolam and 0.6 for flumazenil. The metabolisation of midazolam and flumazenil may equally be affected by considerable loss of active liver cells or by temporarily reduced hepatic blood flow. In such a case, elimination of both drugs may be prolonged in the same way. Flumazenil has only an inactive metabolite. The main active α-hydroxy-metabolite of midazolam does not contribute much to the activity of midazolam after parenteral administration. Its potency is lower than that of midazolam and its shorter elimination half-life (0.8 h) does not prolong the activity of the parent drug. As indicated by the therapeutic index, both drugs have a very high safety margin, which is considerably higher than that of thiopentone or propofol. Only low doses of both drugs are necessary to produce initial effects. Increasing doses intensify the drug activity and a ceiling effect is observed after maximal doses of midazolam and flumazenil. The onset of effect immediately follows the diffusion of the substances into the CNS and can be observed within the first minutes following flumazenil or midazolam administration. The rapid onset of effect allows both drugs to be administered in repeated small bolus doses under close observation of the patient's reaction. This titrated administration allows one to consider the individual requirements of the patient, his age, and physical condition. The titration method not only allows the optimisation of the drug's effect in each patient but also contributes to tolerability and minimisation of adverse events.

Key words: Antagonist; benzodiazepine agonist; flumazenil; midazolam; pharmacology.

For many years diazepam was the most frequently investigated benzodiazepine with a widespread spectrum of practical use. However, the more recent benzodiazepine agonist midazolam (Dormicum, Hypnovel, Versed) of the new class of imidazobenzodiazepines, as well as the first highly specific benzodiazepine antagonist flumazenil (Anexate), have received enormous attention within the fields of clinical and neurological research. The availability of 2650 reports and publications dealing with midazolam 7 years after its introduction and of 2500 papers reporting on flumazenil 2 years after its first introduction reflect the great interest of the research and medical community in these two substances.

Like other benzodiazepines, both drugs have a wide margin of safety and a high therapeutic index. For parenteral administration, both substances are dissolved in an aqueous solution contributing to their good local tolerability. These properties allow both drugs to be administered in an extended field of indications in anaesthesia, intensive care, and with diagnostic procedures. Preclinical and clinical pharmacology data, on midazolam (1–4) and on flumazenil (5–8) can be found in detail in the literature.

In this paper we will try to find out whether the pharmacological prerequisites of both drugs harmonise to a sufficient extent to make them partners for sedation and reversal of sedation with a benzodiazepine agonist and antagonist, respectively.

Like other benzodiazepine agonists, midazolam possesses anxiolytic, sedative, anticonvulsive, and after increased doses, muscle relaxant and anterograde amnesic properties (8). The sedative-hypnotic component of midazolam is of high potency and allows the rapid induction and maintenance of deep sleep stages. The titrated administration of low doses permits the patient to co-operate during conscious sedation adequate for carrying out diagnostic or therapeutic procedures.

Flumazenil, the BZD antagonist, is able to block completely or reverse the behavioural, neurological, and electrophysiological effects of all BZD agonists (9, 10). Doses of 0.3–2.0 mg are sufficient to abolish immediately BZD-induced effects in case of iatrogenic or accidental BZD overdose (11, 12). On the other

hand, flumazenil did not exhibit relevant intrinsic activities when it was administered in doses of below 5 mg i.v. to healthy volunteers.

Both drugs are available as ready-to-inject aqueous solutions and are also manufactured as tablets. In several countries the midazolam tablet is available for sleep disturbances. The flumazenil tablet is not yet marketed.

CHEMISTRY

Midazolam (13) (Fig. 1) and flumazenil (14) (Fig. 2) are both BZDs. They belong to the same BZD ring system (the imidazo [1,5-a][1,4] benzodiazepines), the imidazole ring being fused in the 1,2 position with the diazepine ring. Despite the similar basic structure, there are several differences between the two compounds:

a) The phenyl group of midazolam is replaced by a carbonyl group in flumazenil.
b) Midazolam is very lipophilic and at neutral and alkaline pH it is very sparingly soluble in water. The nitrogen in position 2 of the imidazole ring, however, renders midazolam a basicity which allows the preparation of salts. From these salts purely aqueous injectable solutions can be prepared. The solubility in water is highly dependent on pH, which is about 3.3 in the commercial ampoules of midazolam hydrochloride.
c. Flumazenil is less lipophilic than midazolam. As a weak base its water solubility is lower as compared with midazolam but still sufficient to prepare an injectable aqueous solution of 0.1 mg·ml^{-1} for practical use. The commercial ampoules have a pH of about 4.

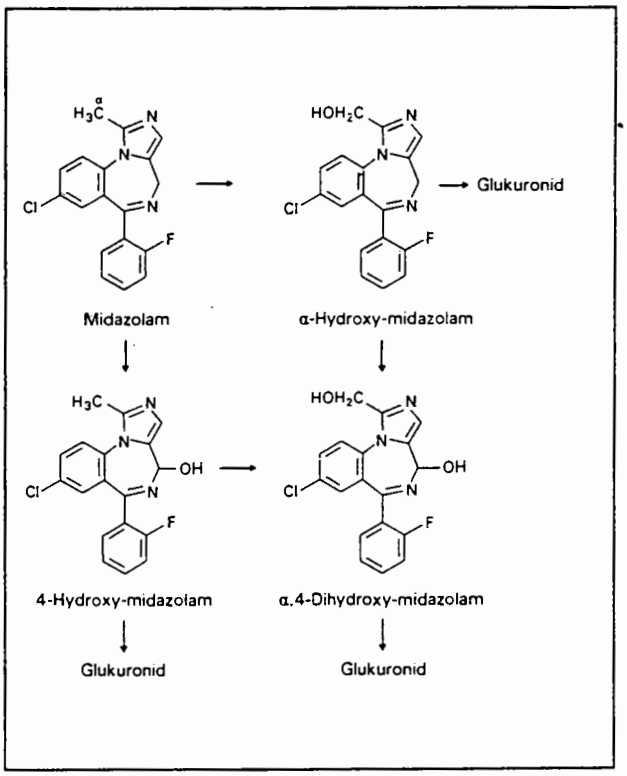

Fig. 1. Biotransformation of midazolam (8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo [1,5-a] [1,4] benzodiazepine) into clearly less active α-hydroxy- and 4-hydroxymidazolam and inactive α,4 dihydroxymidazolam.

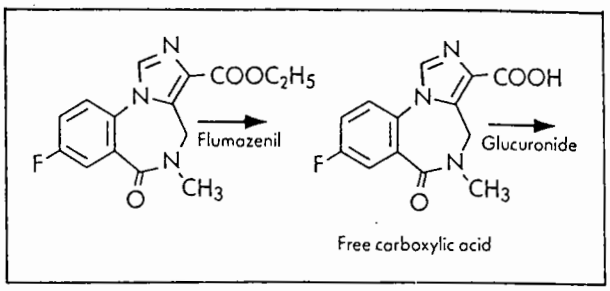

Fig. 2. Flumazenil (ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4 H-imidazo [1,5-a] [1,4] benzodiazepine-3-carboxylate) is metabolised to the inactive free carboxylic acid.

In spite of a different basicity and lipophilicity, both compounds diffuse rapidly across the capillary wall into the central nervous system. Both substances can be mixed with infusion solutions like NaCl 0.9%, glucose 5%, or glucose 2.5% solution. Infusion mixtures with midazolam or flumazenil are physically and chemically stable for 24 h at room temperature. There is no absorption into the infusion bag. Both ampoule formulations can be kept at room temperature.

BIOTRANSFORMATION

Both drugs are completely and rapidly metabolised by hepatic microsomal oxidative mechanisms. Flumazenil is completely metabolised to the inactive free carboxylic acid Ro 15-3890 and the corresponding glucuronide (14). Of the administered dose of midazolam, 60–80% is excreted as α-hydroxy-midazolam (13, 15) in the urine. This main metabolite has an intensity of effect somewhat less pronounced than the parent substance (16). Because of a shorter own elimination half-life ($t_{1/2}\beta$) of 0.8 h, it contributes only to a low extent (which cannot yet be defined exactly) to the total activity of midazolam. Two other metabolites, 4 hydroxy-midazolam and α, 4-dihydroxy-midazolam (inactive) are formed in parallel but in small amounts (3% and 1% respectively) (15, 17). Ninety percent of the administered midazolam is excreted via the urine within 24 h in the form of glucuronide conjugated

metabolites (Fig. 1). The amount of unchanged substance excreted in the urine is about or below 1% for both drugs.

MODE OF ACTION

All known BZDs exert their activity at the BZD receptor within the central nervous system. The BZD receptor is an integral part of the gamma-amino-butyric acid (GABA) receptor complex (18, 19) (Fig. 3). GABA is the major inhibitory neurotransmitter within the brain. The release of GABA into the synaptic cleft triggers the chloride channel in the postsynaptic membrane. The opening of the channel and the concomitant influx of chloride ions into the postsynaptic cell hyperpolarise its cell membrane, thereby impeding or preventing an impulse conduction and reaction of the respective effector organ.

The BZD receptor is a positive modulatory subunit of the GABA receptor (18). A ligand bound to the BZD receptor enhances the effect of GABA on the chloride channel by increasing its opening frequency (20). No influence of flumazenil on chloride channel activity was found. Chloride uptake by cultured neurons following midazolam was found to be dose-dependent. Chloride flux rates reached the maximum at 5 min after incubation of chick neuronal cells with midazolam (21). This experimental observation coincides with the clinical experience of the onset of action after i.v. midazolam and the recommendation to observe the patient's reaction during the 2–3 min before an incremental dose is administered.

However, for a BZD to be effective, a minimum amount of GABA has to be present at the GABA receptor. In case of a total lack of GABA, a BZD receptor ligand (like midazolam) is not able to exert any effect (21, 22). The therapeutic value of a BZD therefore is to enforce the effects of suboptimally available amounts of GABA at the postsynaptic site in the respective brain area in a specific patient situation.

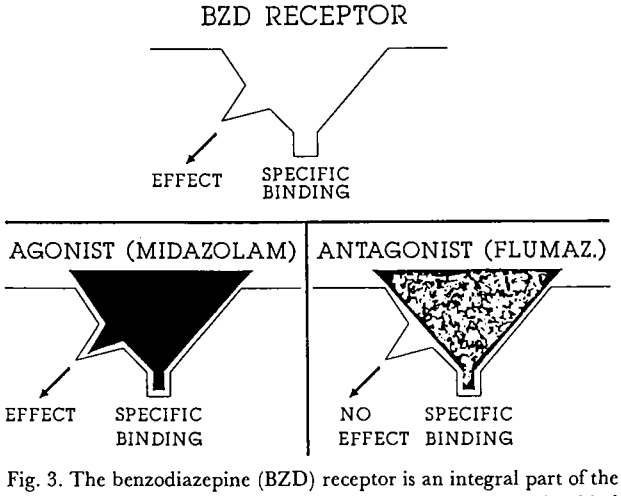

Fig. 3. The benzodiazepine (BZD) receptor is an integral part of the GABA receptor complex. BZD agonists as well as antagonists bind specifically to the BZD receptor, but only BZDs with agonistic properties are able to trigger an effect.

Table 1

The different effects of BZDs became apparent at different occupancies of BZD receptors.

Effect	Postulated receptor occupancies
Anticonvulsive	20–25%
Anxiolytic	20–30%
Sedative	25–50%
Hypnotic	60–90%

The ideal therapeutic dose of a BZD therefore depends on external and internal factors. These may be the intensity and nature of external stimuli, the uptake and neuronal processing of a stimulus, and the amount of GABA available and necessary to cope with the stimulus. Although diagnostic and surgical procedures are to a great extent standardised within each hospital unit, and when dealing with a patient attempts are made to protect him from exciting stimuli, each patient's perception of what happens around him, or may happen to him is different. As a result, patients may react differently to equal doses of a given BZD or *vice versa* different doses may be needed to achieve the same effect in different patients. The different dose requirements of individual patients can be met by the quality of the GABA-ergic and BZD receptor system to exert different activities with a different BZD receptor occupancy. These limitations have to be kept in mind when one tries to explain the effect of a BZD by the degree of receptor occupancy (Table 1).

The occupancy of BZD receptors directly depends on the free BZD concentrations (C) around the receptor (18). It is further determined by the affinity of the BZD to the receptor (K_c) and the number of receptors occupied by the BZD according to the mass action law (23).

The receptor occupancy (R) which finally determines the degree of efficacy of a BZD agonist like midazolam is represented by the equation:

$$R = \frac{C}{C + K_c} \qquad (1)$$

After injection of the BZD antagonist flumazenil, the agonist will be displaced competitively from the receptor. The displacement mainly depends on the same criteria as the occupancy by the agonist, namely the free concentration near the receptor (C_i) and the affinity constant of the antagonist (K_i) to the receptor.

The reversible receptor occupancy (R) by a BZD agonist and antagonist can be described by the equation:

$$R = \frac{C}{C + K_c(1 + C_i/K_i)} \quad (2)$$

It can be shown in an *in vitro* assay, using the radioligand binding technique, that midazolam and flumazenil are among the BZDs with the highest affinity for the receptor (affinity constant about 1 nM compared with 9 nM for diazepam).

With regard to a situation when a patient should be aroused from deep sedation following 15 mg midazolam, the remaining receptor occupancy (by midazolam) after reversal of sedation by 0.3 mg flumazenil can be calculated. The free plasma concentration 30 min after midazolam administration is estimated to be 10 $ng \cdot ml^{-1}$ with an assumed free fraction of 4% for midazolam. According to equation (1), this concentration suffices to occupy 91% of the BZD receptors in the brain, which is equivalent to deep sedation.

Using equation (2), an estimated distribution volume V_1 of 3.0 l, a blood plasma concentration coefficient of 0.88 for flumazenil, and a dose of 0.3 mg flumazenil the remaining receptor occupancy by midazolam is calculated to be 18% after flumazenil injection. The practical implication of this result is that a dose of 0.3 mg flumazenil is able to arouse a patient after 15 mg midazolam. However, the remaining 18% receptor occupancy is sufficient for a still resting anxiolytic effect of midazolam. This result has been confirmed by numerous clinical studies when midazolam sedated patients became fully awake and remained peaceful and relaxed without signs of anxiety after the titrated administration of flumazenil.

In consequence, a parenterally given potent BZD should not be administered in a single high bolus dose but in repeated low doses titrated to the condition and the reaction of the patient. Since the onset of effect with midazolam and flumazenil is immediate, this dose titration can be done easily with these two drugs.

TOLERABILITY

Midazolam and flumazenil have an extremely low toxicity. In intravenous studies in animals, acute toxicities of midazolam (24) and flumazenil were compared with thiopentone sodium (25) (Table 2).

The drugs were injected at different doses in rats and mice and the animals were observed for up to 14 days. The highest non-lethal intravenous dose (maximum tolerated dose, MT) is taken here as an estimate of the acute intravenous toxicity of these drugs. A ratio relating the MT in rodents to the clinical dose (CD) in man is considered as a therapeutic index ThI = MT/CD. For flumazenil this therapeutic or safety index is more than ten times that of midazolam, which in turn is almost 30 times greater than that of thiopentone or propofol (26).

Table 2

Therapeutic index (ThI = MT/CD) calculated from the highest non-lethal (maximum tolerated, MT) i.v. dose in rodents and the clinical dose (CD) in man.

Drug	Mean MT ($mg \cdot kg^{-1}$) Rodents	CD≥$mg \cdot kg^{-1}$ Man	ThI Man
Midazolam maleate	53.5	0.2	267.5
Flumazenil	64.25	0.02	3212.5
Thiopentone sodium	37.5	3.5	10.7
Propofol	25	2.5	10.0

PHARMACOLOGY

The neuropsychopharmacological profile of activity of midazolam in different animal species is that of an agonist at the benzodiazepine receptor (8). In preclinical pharmacological investigations where BZDs exert their characteristic effects, midazolam showed a pharmacological profile of activity comparable to diazepam. In lower doses anxiolytic and anticonvulsant properties of midazolam became obvious, whereas in higher doses the hypnotic action was predominant and twice as potent as diazepam in rats. In tests for muscle tone and coordination in mice, midazolam was shown to be four times more potent than diazepam (8). According to the total voltage increase in the EEG midazolam appeared to be five times more potent than diazepam in human volunteers (27). However, this result does not imply that midazolam is five times more potent than diazepam in the clinical situation.

Flumazenil in the same preclinical testing did not produce any relevant activity on its own, although a weak anticonvulsant effect was observed (28). The highest antagonistic potency (in rodents) was found against motor incoordination and muscle relaxation induced by diazepam. The least potency was seen in a test indicative of anxiolytic activity after diazepam (29). The animal findings are in good correlation with patient observations when flumazenil in low doses first antagonises hypnosis and sedation, but only at high doses does it antagonise the anticonvulsant and anxiolytic properties of the BZD agonists.

Time response analysis indicated that, unlike BZDs like lorazepam or oxazepam (30), midazolam exhibited a quick onset and a short duration of action. Effects

of midazolam and flumazenil can be observed within 1–3 min after i.v. administration.

In human pharmacological studies a transient sedative effect was observed after 0.025 mg midazolam kg^{-1} body weight, which was enhanced to lasting sleep stages after 0.1 $mg \cdot kg^{-1}$ (31).

Following 0.15 $mg \cdot kg^{-1}$, a sigmoidal relationship between the logarithm of the plasma concentration and the number of errors in a tracing test was obvious (32). When 7.5 mg, 15 mg, or 25 mg midazolam were infused to volunteers (27) 7.5 mg already caused unresponsiveness to verbal stimuli. The EEG recording showed increased total voltage with increased doses of midazolam compared to the baseline. A peak of total voltage was reached within 1–2 min, similar at different doses. Increasing doses of midazolam prolonged the duration of effect. With 5–10 mg i.v. midazolam the level of consciousness is gradually reduced over 2–3 min (4); subjects fall asleep but generally remain arousable.

In some subjects 10 mg midazolam i.v. led to the loss of the palpebral reflex. After the administration of 12.5 mg midazolam, psychometric tests (reaction time, tracing test) tended to return to normal within 2 h after the injection and were completely normalised within 4 h (33).

EEG variations are found as early as 50 s after intravenous administration of 15 mg midazolam, indicating a sleep stage sufficiently deep for induction of anaesthesia. With 15 mg i.v. midazolam given over 20 min, subjects became drowsy after 10 min and arousable only by voice after 20 min (34). The latency of effect indicates that the speed of injection influences the onset of effect. The shorter the time of injection, the more quickly the stage of deep sleep is reached (3), but fall in blood pressure and apnoea is then more frequent.

The maximum clinical effect after intravenous injection of midazolam is reached in about 3 min. After i.m. administration, the first effects are recorded within 5 min and the maximum effects are observed within 20–30 min (35).

In clinical studies in older or susceptible patients, as little as 2.5 mg midazolam i.v. have been shown to be sufficient to induce sedation before dental treatment (36). A sedative and anxiolytic effect is evident after 5 mg midazolam i.v. (16) and anterograde amnesia for events after the intramuscular administration of midazolam is found with 7.5 mg (37). In intensive care, midazolam is used as an infusion at doses of 1–15 $mg \cdot h^{-1}$ for the sedation of critically ill patients who need to be mechanically ventilated (38).

Flumazenil reverses the benzodiazepine properties opposite to their appearance and reciprocal to the dose. Low doses of midazolam are necessary to induce anxiolysis but high doses of flumazenil are needed to reverse these anxiolytic effects. On the other hand, high midazolam doses are necessary for a deep hypnotic state and low doses of flumazenil already restore the patient's vigilance considerably (Table 3).

Flumazenil exerts its antagonistic effects independent of whether it is given before, together with, or after the benzodiazepine (25). In clinical practice it completely and permanently reversed the effects of BZDs given in therapeutic doses and at different times before flumazenil administration (39, 40).

In pharmacological investigations in volunteers, 200 mg flumazenil given orally blocked the expected sedative effects of 8–20 mg of the potent BZD meclonazepam for at least 2.5 h. Two hundred mg flumazenil (oral) in combination with 20 or 40 mg diazepam prevented cognitive and motor impairment for 6 h (41, 42). When flumazenil 10 mg i.v. was given during a running infusion of approximately 100 mg midazolam (after steady state was reached), the deeply sedated subjects were fully awake and oriented within 1 min (43). In a similar study approach (44), the same antagonistic effect was observed after only 2.5 mg flumazenil.

In a further study (45), flumazenil 5 mg was given i.v. 10 min before incremental doses of midazolam or placebo without alterations in the EEG. First signs of drowsiness as detected by the α/σ power ratio in the EEG power profile appeared only after the administration of 6–10 mg midazolam. On average, 7.3 mg i.v. midazolam counteracted the presence of flumazenil 5 mg. This study shows that with a higher midazolam dose the inhibitory effect of flumazenil can be overcome, a finding which is of practical interest for clinical use of the antagonist (Fig. 4).

In a double-blind placebo-controlled parallel group study in 100 volunteers, the minimum effective dose was flumazenil 0.003 $mg \cdot kg^{-1}$ to antagonise the psychomotor impairment after a maximum dose of diazepam 30 mg i.v. (46). In clinical practice doses of

Table 3

Reciprocal dose-dependent effects of benzodiazepines and flumazenil.

High midazolam doses induce hypnosis but already very low flumazenil doses reduce hypnosis to sedation		
Midazolam Low dose	Anxiolysis Anticonvulsion Slight sedation Reduced attention Amnesia	Flumazenil High dose
↓		↑
High-dose Benzodiazepine Midazolam	Intense sedation Muscle relaxation Hypnosis	Low dose Flumazenil

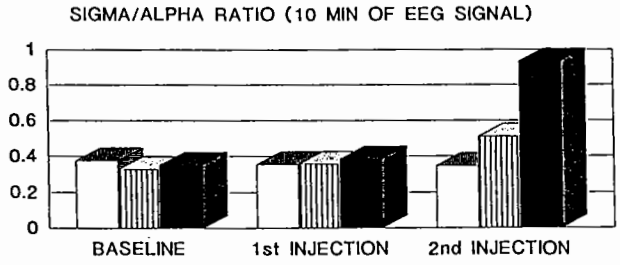

Fig. 4. Gath et al. (45) examined flumazenil in opposing the action of midazolam. After a baseline EEG 5 mg flumazenil or placebo were injected to volunteers without alteration in the EEG signal (1st injection). Ten minutes later, injection of incremental doses of midazolam revealed that at doses of 6 mg and above (average 7.3 ± 1.6 mg) midazolam started to counteract the receptor blocking effects of 5 mg flumazenil (2nd injection). The sigma/alpha ratio was not changed after flumazenil + placebo but was changed, as expected, after placebo followed by midazolam. □ flumazenil + placebo. [||||] flumazenil + midazolam. ■ placebo + midazolam.

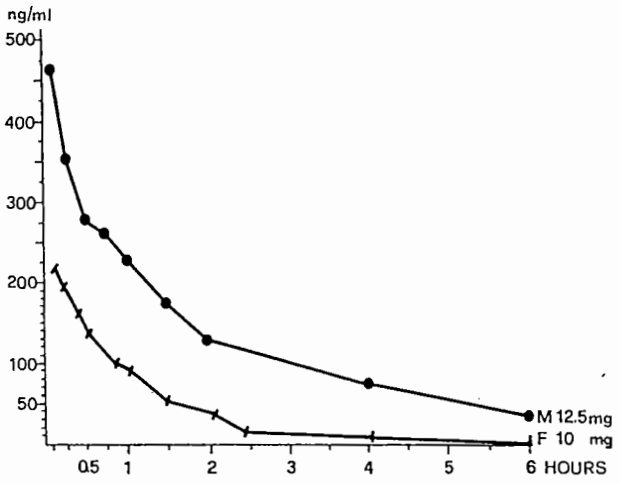

Fig. 5. Plasma concentrations after different doses of flumazenil (F) or midazolam (M) exhibit linear disposition kinetics. An extensive distribution phase, especially evident after midazolam, is followed by a short elimination half-life.

0.2–0.5 mg flumazenil are sufficient to antagonise the effects of BZDs given for basic sedation, induction, or maintenance of anaesthesia. Maximum doses of up to 2 mg may sometimes be needed in case of severe BZD overdose to reverse comatose or hypnotic conditions.

PHARMACOKINETIC ASPECTS

The pharmacokinetics (Table 4) of both drugs are closely related. Primary pharmacokinetic parameters such as mean residence time, plasma clearance, or distribution volume do not vary within the broad tested dose range of 2.5–100 mg (47) of i.v. administered flumazenil and 5–60 mg midazolam (48) in healthy volunteers. Kinetics of midazolam during prolonged infusion over several days are consistent with the single-dose profile (2, 4).

Midazolam and flumazenil undergo an immediate extensive distribution outside the vascular space. This is indicated by the initial decline in the plasma concentration time profile (17, 49) and by a distribution volume of close to 1 $l \cdot kg^{-1}$ for both substances (Fig. 5). The initial distribution phase ($t_{1/2}\alpha$) lasts for less than 5 min after i.v. flumazenil administration. It is longer and more intensive for midazolam but does not exceed 30 min (3). The terminal elimination half-life ($t_{1/2}\beta$) is in the order of 1 h with flumazenil and varies between 1.5–3 h after midazolam in healthy subjects.

Midazolam and flumazenil are eliminated by metabolic processes in the liver. As BZDs both have a relatively high liver extraction ratio, ranging from 0.3 for midazolam to 0.6 for flumazenil. Therefore, elimination of both drugs will not only be sensitive to loss or reduction in the functional liver cell mass but also to changes in hepatic blood flow. If liver perfusion is temporarily reduced, as in high-risk patients with liver impairment or reduced cardiac output, reduced midazolam clearances with drug accumulation during drug infusion and prolonged half-lives may result. In consequence, close monitoring with reduction of the midazolam doses administered is mandatory in these patients.

Prolonged sedation after midazolam infusion was observed in critically ill (49) patients with septic shock (50), low cardiac output (51), renal failure (52), low plasma albumin concentrations, or major surgery (52, 53) (Table 5).

In patients with compensated liver cirrhosis, the elimination half-life was not markedly different from normal in two studies (54, 55), but prolonged sedation was found in two others (56, 57).

Distribution volumes may be increased and the elimination half-life of midazolam may therefore be prolonged in elderly patients compared with younger subjects (53, 58). In pregnant women distribution volume was smaller than in non-pregnant women, and

Table 4
Average pharmacokinetic data for midazolam and flumazenil.

	Midazolam	Flumazenil
Distribution half-life $t_{1/2}\alpha$	25–30 min	≤5 min
Elimination half-life $t_{1/2}\beta$	1.5–3 h	0.7–1.3 h
Volume of distribution V_{ss}	0.7 l kg^{-1}	0.95 l kg^{-1}
Total clearance Cl_{pl}	0.35–0.5 l min^{-1}	0.5–1.3 l min^{-1}
Blood/plasma concentration coeff.	0.53	0.88
Hepatic extraction ratio	0.3–0.5	0.6
Protein binding	96%	50%

midazolam plasma concentrations were higher in patients in labour compared with patients during pregnancy (59).

Flumazenil achieves a relatively higher plasma water concentration than midazolam, with the unbound fraction being around 50% compared with about 4% unbound midazolam. There was no evidence of a genetic polymorphism of midazolam metabolism in a study (60) in 168 surgical patients as a possible cause for prolonged elimination half-life.

The same considerations of liver blood-flow-dependent metabolism of midazolam are valid for flumazenil. Reduced liver blood flow may also lead to a prolonged effect of flumazenil. Since the loss of effect is synchronised for both drugs, the prolongation of efficacy does not become a clinically undesired effect. Furthermore, additional doses of flumazenil are given only under close observation of the pharmacological effect.

With flumazenil, it was observed in subjects and in patients that under practical conditions the duration of action depends on the type (long-acting or short-acting) and the dose of the previously administered benzodiazepine, the dose of flumazenil, and the time elapsed between the administration of the agonist and the antagonist.

PHARMACOKINETIC INTERACTIONS

In volunteer studies (61, 62), it was shown that the concomitant oral administration of H_2 receptor antagonists, cimetidine or ranitidine, increased the bioavailability of oral midazolam by about 30%. However, when a sedative intravenous dose of 5 mg midazolam was given together with cimetidine, no influence on the pharmacokinetic parameters of midazolam could be found (63) (Fig. 6).

Midazolam did not increase histamine release in presurgical patients compared with placebo (64). The calcium channel blocking agent nitrendipine showed no interaction with the pharmacokinetics and the clinical effects of midazolam under steady-state conditions in healthy volunteers (65). Flumazenil is without influence on pharmacokinetic parameters of co-administered BZDs or ethanol (6).

Table 5

Reported mean elimination half-lives ($t_{1/2}\beta$) in hours for midazolam and flumazenil under different conditions. Ref = Reference cited.

Subjects	Mean $t_{1/2}\beta$ h		Ref
	Midazolam	Flumazenil	
Young volunteers	1.5–3	0.7–1.3	3, 6
Elderly patients	4–6	1.0	53, 58
With renal failure	4.5	(1?)	52
With liver failure	> 10	2.5	56, 57
After cardiac surgery	11		51

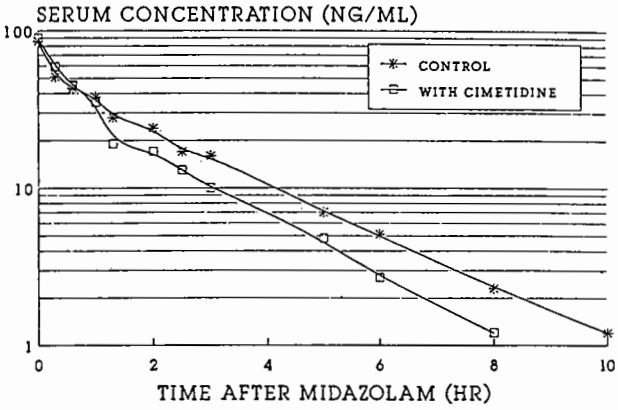

Fig. 6. Serum concentration of midazolam after a single i.v. dose of 5 mg without (*) or with ( ) oral cimetidine (4×300 mg·d^{-1}) before and during midazolam analysis. Data taken from Knüchel et al. (63).

DOSING STRATEGY

The pharmacological properties of both drugs make a dose titration possible and necessary. The patient's reaction to an initial small i.v. dose should be carefully observed. For conscious sedation, as desired for diagnostic procedures, doses as low as 2 mg midazolam may already suffice for the elderly patient. A dose of 7.5 mg, or in some cases even more, is needed in healthy young patients. For the average patient, 5 mg midazolam slowly injected is adequate. Incremental doses can be given after 2–3 min observation.

Anaesthesia can be induced with 0.15–0.20 mg midazolam per kg body weight together with a narcotic in most cases. Under intensive care conditions, sedation can be maintained by a continuous infusion of 0.03–0.2 mg·kg^{-1}, depending on the patient's condition and comedication. In case of reversal of sedation by flumazenil, complete awakening of the patient with full awareness of his situation is not always desirable. A stepwise reversal of BZD effects can be achieved by the titrated administration of low doses of flumazenil. An initial dose of flumazenil 0.2 mg i.v. may suffice to awaken the patient after therapeutic doses of any BZD. Further small doses of 0.1 mg at 1-min intervals and the continuous observation of the patient's reaction allow the interruption of flumazenil administration exactly at the stage of vigilance that is most convenient for the patient. A total dose of 1 mg, and in case of severe BZD overdose, 2 mg, are maximal doses which in general do not need to be exceeded.

INTRINSIC ACTIVITIES OF FLUMAZENIL

Initially flumazenil was described as a benzodiazepine lacking intrinsic action (6). Later some intrinsic effects of flumazenil were reported. An observed anticonvulsant effect in patients with seizure disorders (66) is now the subject of further investigation. Clinical improvement in hepatic encephalopathy after flumazenil (67) will be followed up. Reports on the effect of flumazenil on ethanol overdose are contradictory. In a placebo-controlled study (68), no antagonistic effect of flumazenil on the effects of ethanol was seen.

CONCLUSION

Midazolam and flumazenil are BZDs acting as an agonist and antagonist at the BZD receptor within the central nervous system. Their similar pharmacokinetic properties allow a synchronised pharmacological efficacy. Midazolam administered in therapeutic doses gradually reduces its effect during the time flumazenil occupies the BZD receptors.

Due to its potent sedative-hypnotic effect, midazolam in low doses is suited for anxiolysis and sedation with the patient remaining co-operative. In higher doses anaesthesia can be induced and maintained under comedication with an analgesic narcotic. The short duration of action of midazolam allows one to adapt the degree of sedation in short intervals, following the patient's requirements in the intensive care unit.

The immediate onset of the effect of flumazenil offers the possibility of administering only small doses to increase the patient's vigilance stepwise. Because different receptor occupancy is correlated with a different effect, a low dose of flumazenil reverses deep BZD hypnosis but leaves the patient in a peaceful state of conscious sedation. With a higher dose, the patient can be completely and immediately brought back to full consciousness.

The dosage of both drugs should be administered in repeated small doses taking into consideration the patient's age, physical condition, comedication, and actual need of sedation. From their pharmacological properties, the two drugs supplement each other in a practically ideal form to meet the patient's requirements.

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