Midazolam and Other Benzodiazepines

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Abstract The actions of benzodiazepines are due to the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA). Practically all effects of the benzodiazepines result from their actions on the ionotropic $GABA_A$ receptors in the central nervous system. Benzodiazepines do not activate $GABA_A$ receptors directly but they require GABA. The main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated

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J. Schüttler and H. Schwilden (eds.) *Modern Anesthetics.*
Handbook of Experimental Pharmacology 182.

muscle relaxation and anti-convulsant activity. In addition to their action on the central nervous system, benzodiazepines have a dose-dependent ventilatory depressant effect and they also cause a modest reduction in arterial blood pressure and an increase in heart rate as a result of a decrease of systemic vascular resistance. The four benzodiazepines, widely used in clinical anaesthesia, are the agonists midazolam, diazepam and lorazepam and the antagonist flumazenil. Midazolam, diazepam and flumazenil are metabolized by cytochrome P450 (CYP) enzymes and by glucuronide conjugation whereas lorazepam directly undergoes glucuronide conjugation. CYP3A4 is important in the biotransformation of both midazolam and diazepam. CYP2C19 is important in the biotransformation of diazepam. Liver and renal dysfunction have only a minor effect on the pharmacokinetics of lorazepam but they slow down the elimination of the other benzodiazepines used in clinical anaesthesia. The duration of action of all benzodiazepines is strongly dependent on the duration of their administration. Based on clinical studies and computer simulations, midazolam has the shortest recovery profile followed by lorazepam and diazepam. Being metabolized by CYP enzymes, midazolam and diazepam have many clinically significant interactions with inhibitors and inducers of CYP3A4 and 2C19. In addition to pharmacokinetic interactions, benzodiazepines have synergistic interactions with other hypnotics and opioids. Midazolam, diazepam and lorazepam are widely used for sedation and to some extent also for induction and maintenance of anaesthesia. Flumazenil is very useful in reversing benzodiazepine-induced sedation as well as to diagnose or treat benzodiazepine overdose.

1 Introduction

The first benzodiazepines were synthesized already in the 1950s (Greenblatt and Shader 1974) but the intravenous use of benzodiazepines did not begin until 1960s when intravenous diazepam was used for induction of anaesthesia (Stovner and Endresen 1965). To date, thousands of different benzodiazepines have been synthesized and about 30 are in clinical use in various parts of the world. However, only four benzodiazepines, the agonists midazolam, diazepam and lorazepam and the antagonist flumazenil are widely used in clinical anaesthesia. This chapter will focus on the basic and clinical pharmacology of these four benzodiazepines. In addition, the chapter will review the pharmacology of the new benzodiazepine agonist Ro 48-6791 which was developed for anaesthesia but which so far has not been registered for clinical use (Dingemanse et al. 1997a, b).

2 Chemical Structure and Physicochemical Characteristics

The four benzodiazepines commonly used in clinical anaesthesia are rather small molecules with molecular weights ranging from 284.7 to 325.8 daltons. Their structures and the structure of Ro 48-6791 are shown in Fig. 1.

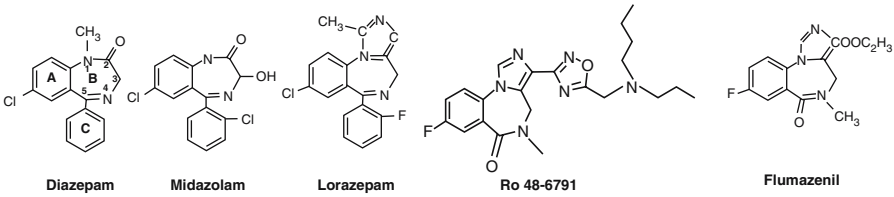

Fig. 1 The structure of Ro 48-6791 and the four benzodiazepines used in clinical anaesthesia. They are all composed of a benzene ring (*A*) fused to a seven-membered 1,4-diazepine ring (*B*). Anaesthesiologically relevant benzodiazepine agonists also contain a 5-aryl substituent (ring *C*), which enhances the pharmacological potency. However, the benzodiazepine antagonist flumazenil has two important structural differences as compared to the above agonists. Flumazenil has a keto function at position *5* instead of ring *C* and a methyl substituent at position *4*

Table 1 Physicochemical characteristics of four benzodiazepines used in clinical anaesthesia

	Molecular weight (daltons)	pK_a	Water solubility	Lipid solubility
Midazolam	325.8 (hydrochloride 392.3)	6.2	Good at pH<4	Good at pH>4
Diazepam	284.7	3.2	Poor	Good
Lorazepam	321.2	1.3, 11.5	Poor	Moderate
Flumazenil	303.3	1.7	Moderate	Poor

Data from Dollery (1991)

The physicochemical characteristics of midazolam, diazepam, lorazepam and flumazenil are summarized in Table 1. Unlike the other benzodiazepines, midazolam is used clinically as a hydrochloride salt which is essential for the physicochemical characteristics desirable in clinical anaesthesia. Interestingly, midazolam hydrochloride displays pH-dependent solubility. The pH of the commercial midazolam hydrochloride preparation is adjusted to 3 with hydrochloride acid and sodium hydroxide. As midazolam is injected into patients, pH is increased and the seven-membered 1,4-diazepine ring is closed thus increasing the lipid solubility (Gerecke 1983).

3 Pharmacology

3.1 Pharmacological Action at Receptor Level

Practically all effects of the benzodiazepines result from their actions on the central nervous system. Compared to other intravenous anaesthetics, the mechanism of action of benzodiazepines is rather well understood (Möhler et al. 2002). The main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated muscle relaxation and anti-convulsant activity. The current view is that the actions of benzodiazepines are due to the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA). GABA receptors are membrane-bound proteins which can be divided into

two subtypes. Ionotropic $GABA_A$ receptors are put together from five subunits forming an integral chloride channel. It is the $GABA_A$ receptors which are mainly responsible for inhibitory neurotransmission in the central nervous system. $GABA_B$ receptors are metabotropic receptors made up of single peptides. Their signal transduction mechanism is based on coupling with the G proteins. Recent studies have identified several subtypes of $GABA_A$ receptors. Sedation, anterograde amnesia and anti-convulsant activity are mediated through α_1 receptors whereas anxiolysis and muscle relaxation seem to be mediated by the α_2 $GABA_A$ receptor (Möhler et al. 2002).

Benzodiazepines exert their action by binding to a specific site that is distinct from that of GABA binding on the $GABA_A$ receptors. Benzodiazepines do not act at $GABA_B$ receptors. The chemical structure of the each benzodiazepine is closely linked to its receptor binding properties and also pharmacokinetics. The order of receptor affinity of the three agonists is lorazepam > midazolam > diazepam. Thus, midazolam is more potent than diazepam and lorazepam is more potent than midazolam (Mould et al. 1995). Benzodiazepines do not activate $GABA_A$ receptors directly but they require GABA. The ligands binding to the benzodiazepine-receptor have different effects depending on the ligand in question. They can act as agonists, antagonists or inverse agonists. Agonists increase the $GABA_A$-produced chloride current at the benzodiazepine receptor while the antagonists have an opposite effect. Thus, benzodiazepine agonists shift the GABA concentration-response curve to the left. Inverse agonists shift the curve to the right. The actions of both agonists and inverse agonists can be inhibited by benzodiazepine antagonists which themselves do not affect the function of $GABA_A$ receptors.

3.2 Central Nervous System

Compared to barbiturates, propofol and inhalational anaesthetics, the benzodiazepines are not able to produce the same degree of neuronal depression. At low doses the benzodiazepines have anxiolytic and anti-convulsive effects. As the dose increases, the benzodiazepines produce sedation, amnesia and finally sleep. The effect of the benzodiazepines is clearly dose-related but there seems to be a ceiling effect where increasing the dose does not increase the effect (Hall et al. 1988). Benzodiazepines reduce cerebral metabolism ($CMRO_2$) and cerebral blood flow (CBF) without disturbing the normal $CBF/CMRO_2$ ratio (Forster et al. 1982). Although the benzodiazepines may be used as hypnotics during the intravenous induction of anaesthesia, they are not optimally suited for this purpose. Induction of sleep requires relatively high doses, meaning that recovery from all the effects of benzodiazepines takes a long time because, for instance, amnesia and sedation are produced at much lower concentrations than the hypnotic effects. If benzodiazepines are used also for the maintenance of anaesthesia, the recovery is even slower because during and after long-lasting infusions, it is the elimination of the

drug from the body which is of vital importance for the recovery. Following bolus injection of benzodiazepines, recovery from anaesthesia is enhanced by the redistribution of the drug within the body from the receptors to non-specific sites of action. Thus, it is understandable that the postoperative period of sedation can be rather long (Fig. 2).

The development of tolerance to benzodiazepines seems to be a controversial issue. While some authors have observed tolerance to benzodiazepines, others have been unable to confirm these findings (Coldwell et al. 1998; Fiset et al. 1995; Greenblatt and Shader 1978; Ihmsen et al. 2004; Shafer 1998; Shelly et al. 1991; Somma et al. 1998). Additionally, different mechanisms for tolerance have been suggested. A popular explanation for tolerance is the downregulation of the benzodiazepine-$GABA_A$ receptor complex (Miller 1991). However, Tietz et al. (1989) suggested that the prolonged exposure to benzodiazepines results in an altered effect of the benzodiazepine agonists on the GABA concentration-response relationship.

There is some evidence in experimental animals that benzodiazepines would have a neuroprotective effect in brain (de Jong and Bonin 1981; Ito et al. 1999). Furthermore, midazolam, diazepam and lorazepam also decrease the local anaesthetic-induced mortality in mice (de Jong and Bonin 1981). Unfortunately, studies in other animals have not been able to confirm the usefulness of benzodiazepines in neuroprotection (Hall et al. 1998). There is no evidence that benzodiazepines would have neuroprotective effects in man.

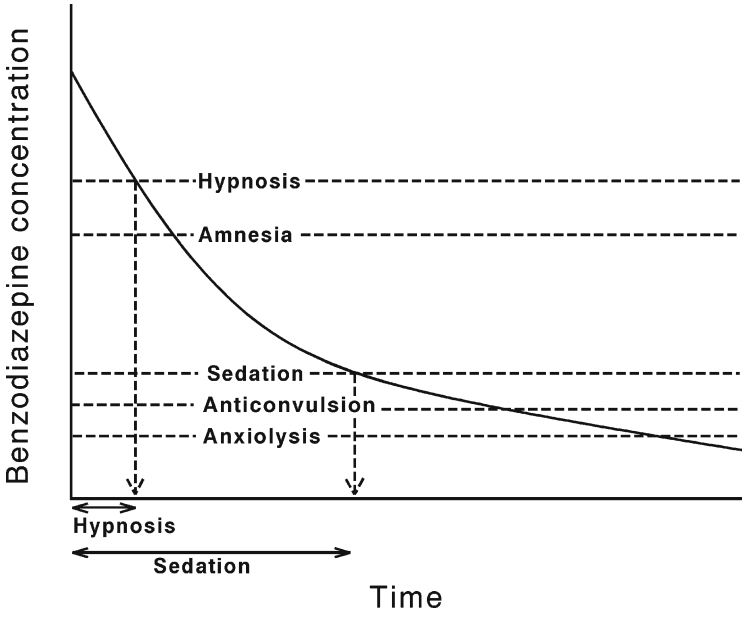

Fig. 2 Schematic presentation on the relationship between benzodiazepine concentration and clinical effect

3.3 Respiration

Normal oral hypnotic doses of benzodiazepines have essentially no effect on respiration in normal subjects. At higher doses, the benzodiazepines do influence respiration. The benzodiazepines affect respiration in two different ways. First, they have an effect on the muscular tone leading to an increased risk of upper airway obstruction (Norton et al. 2006). Thus, benzodiazepines are not recommended and are considered even contraindicated in patients suffering from obstructive sleep apnoea. Second, they also affect the ventilatory response curve to carbon dioxide by flattening the response (Fig. 3). However, unlike opioids, benzodiazepines do not shift the curve to the right (Sunzel et al. 1988). A typical reaction to benzodiazepines is a decrease in tidal volume. If the patient is given benzodiazepine together with an opioid, the risk of clinically significant ventilatory depression is increased markedly (Tverskoy et al. 1989). An important factor contributing to the ventilatory depressant effect of benzodiazepines is their ability to depress the reaction to hypoxia under hypercapnic conditions (Alexander and Gross 1988). Especially patients suffering from chronic obstructive pulmonary disease should be closely monitored.

3.4 Cardiovascular System

The intravenous administration of sedative or anaesthetic doses of the benzodiazepines cause a modest reduction in arterial blood pressure and increase in heart rate. These changes are mainly due to a decrease in systemic vascular resistance. In

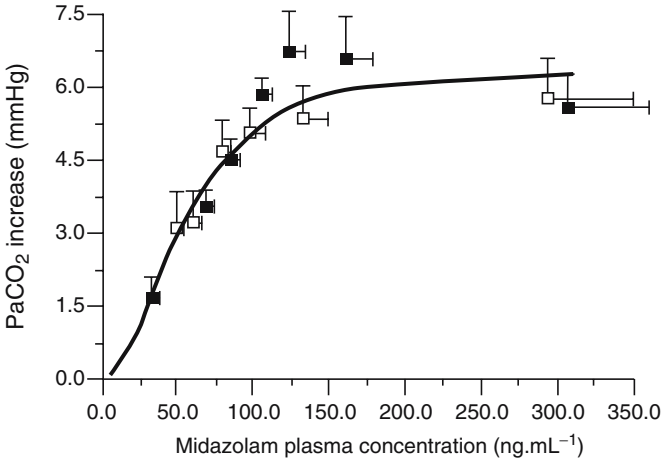

Fig. 3 Increase in $PaCO_2$ from baseline versus the midazolam plasma concentration after three intravenous bolus doses of midazolam (0.05 mg/kg) given at 20-min intervals. Mean values ± standard error of mean (SEM) are given. (Modified with permission from Sunzel et al. 1988)

addition, they induce a minor reduction of cardiac output (Samuelson et al. 1981; Ruff and Reves 1990). Midazolam and diazepam have also been shown to depress the baroreflex. This occurrence means that both midazolam and diazepam induce a limited ability to compensate for haemodynamic alterations related to hypovolemia (Marty et al. 1986).

4 Pharmacokinetics and Biotransformation

The pharmacokinetic variables of intravenous benzodiazepines are summarized in Table 2. The two principal pathways of the benzodiazepine biotransformation involve hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) and glucuronide conjugation (Fig. 4). Microsomal oxidation reactions are catalysed by cytochrome P450 (CYP) isoenzymes 3A4/3A5 and 2C19. Unlike glucuronide conjugation, oxidation may be affected, e.g. by age, disease states and concurrent

Table 2 Pharmacokinetic variables of midazolam, diazepam, lorazepam, Ro 48–6971, and flumazenil

	Elimination half–life (h)	Clearance (ml/kg/min)	V_{ss} (l/kg)	Plasma protein binding (%)	Reference(s)
Midazolam	1.7–2.6	5.8–9.0	1.1–1.7	96	Dundee et al. 1984a
Diazepam	20–50	0.2–0.5	0.7–1.7	98	Greenblatt et al. 1980
Lorazepam	11–22	0.8–1.8	0.8–1.3	90	Greenblatt et al. 1979
Ro 48–6791	3.8	18–44	1.5–3.4		Dingemanse et al. 1997a, b
Flumazenil	0.7–1.3	13–17	0.9–1.1	40	Klotz and Kanto 1988; Breimer et al. 1991

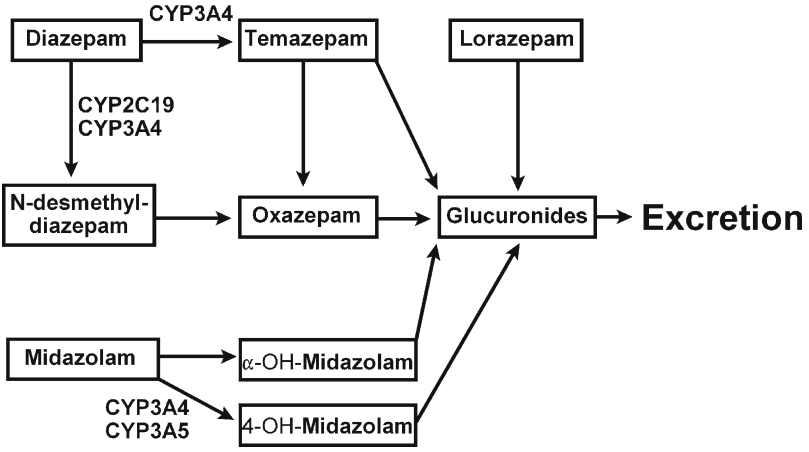

Fig. 4 Metabolic pathways of midazolam, diazepam and lorazepam

intake of other drugs (Elliott 1976; Klotz and Reimann 1980; Heizmann et al. 1983; Inaba et al. 1988; Park et al. 1989; Wandel et al. 1994).

4.1 Midazolam

The first step in the metabolism of midazolam is hydroxylation by CYP3A4 and CYP3A5 (Wandel et al. 1994). The two metabolites formed are α-hydroxymidazolam and 4-hydroxymidazolam, which both are pharmacologically active (Heizmann et al. 1983; Ziegler et al. 1983). The α-hydroxymidazolam is as potent as the parent compound and may contribute significantly to the effects of the parent drug when present in sufficiently high concentrations. 4-Hydroxymidazolam is quantitatively unimportant (Mandema et al. 1992). Both metabolites are rapidly conjugated by glucuronic acid to form products which have been considered to be pharmacologically inactive (Heizmann et al. 1983).

Following intravenous administration, midazolam is rapidly distributed and the distribution half-time is 6–15 min (Allonen et al. 1981). The fused imidazole ring of midazolam is oxidized much more rapidly than the methylene group of the diazepine ring of other benzodiazepines, which accounts for the greater plasma clearance of midazolam ranging from 5.8 to 9.0 ml/kg per minute as compared with diazepam, 0.2–0.5 ml/kg per minute and lorazepam, 0.8–1.8 ml/kg per minute (Greenblatt et al. 1979, 1980; Dundee et al. 1984a; Bailey et al. 1994). In elderly men, the clearance of midazolam is reduced and the elimination half-time is prolonged as compared to young males. Between elderly and young women, however, no significant differences were detected in the clearance or the elimination half-time of midazolam (Greenblatt et al. 1984).

Midazolam is extensively bound to plasma proteins (94%–98%). Small changes in its plasma protein binding will produce large changes in the amount of free drug available, which may have consequences in clinical practice (Dundee et al. 1984b). The high lipophilicity of midazolam accounts for the relatively large volume of distribution at steady-state, i.e. 0.8–1.7 l/kg (Heizmann et al. 1983). Older age does not increase the volume of distribution significantly (Greenblatt et al. 1984; Harper et al. 1985). However, in obese patients, the volume of distribution is increased and the elimination half-time is prolonged while the clearance remains unchanged (Greenblatt et al. 1984). The elimination half-time of α-hydroxymidazolam is about 70 min (Mandema et al. 1992).

The plasma disappearance curve of midazolam can be fitted to a 2- or 3-compartment model with an elimination half-time ranging from 1.7 to 3.5 h (Allonen et al. 1981; Heizmann et al. 1983; Greenblatt et al. 1984). The elimination half-time is independent of the route of administration of midazolam. Major operations seem to increase the volume of distribution and prolong the elimination half-time (Harper et al. 1985). In a small proportion of the population, the elimination half-time of midazolam has been reported to be prolonged to more than 7 h (Dundee 1987; Kassai et al. 1988). In five out of 90 subjects (46 healthy volunteers, 17 surgical patients, and

12 patients with stabilized cirrhosis), the volume of distribution was clearly increased without a change in clearance. Thus, the prolonged elimination half-time was secondary to an increase in the volume of distribution (Wills et al. 1990).

In addition to the liver, midazolam is also metabolized at extrahepatic sites. This has been demonstrated by the discovery of metabolites following intravenous injection of midazolam during the anhepatic period of liver transplantation (Park et al. 1989). In patients with advanced cirrhosis of the liver, the plasma clearance is reduced and the elimination half-time is prolonged as compared to healthy volunteers, while the volume of distribution remains unchanged (Pentikäinen et al. 1989).

Glucuronidated α-hydroxymidazolam, the main metabolite of midazolam, has a substantial pharmacological effect and can penetrate the intact blood–brain barrier. It can accumulate in patients with renal failure (Fig. 5). Furthermore, in vitro binding studies show that the affinity of glucuronidated α-hydroxymidazolam to the cerebral benzodiazepine receptor is only about ten times weaker than that of midazolam or unconjugated α-hydroxymidazolam (Bauer et al. 1995).

4.2 Diazepam

Diazepam is metabolized in the liver with only traces of the unchanged drug being excreted in urine. The two major pathways of diazepam metabolism, the formation of *N*-desmethyldiazepam and temazepam, are catalysed by different CYP isoforms (Inaba et al. 1988). The third potential metabolite, 4-hydroxydiazepam,

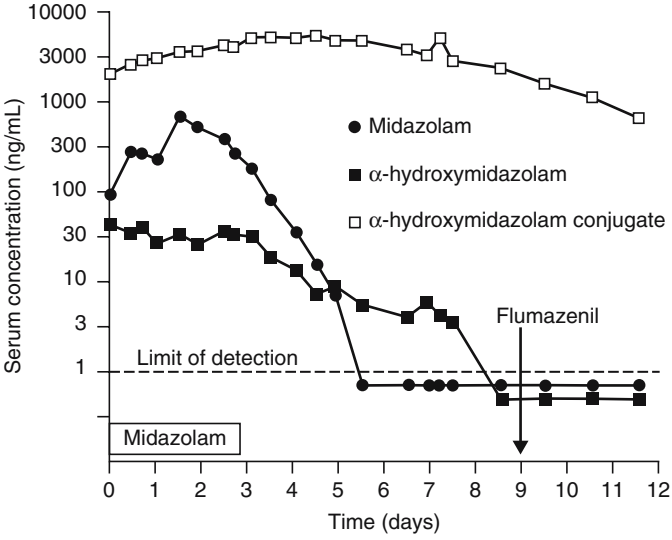

Fig. 5 Serum concentration time profile of midazolam and its metabolites in a patient with renal failure. (Modified with permission from Bauer et al. 1995)

seems to be less important. Studies with a series of CYP isoform-selective inhibitors and an inhibitory anti-CYP2C antibody indicate that temazepam formation is carried out mainly by CYP3A isoforms, whereas the formation of *N*-desmethyldiazepam is mediated by both CYP3A isoenzymes and *S*-mephenytoin hydroxylase, CYP2C19 (Andersson et al. 1994; Kato and Yamazoe 1994). *N*-Desmethyldiazepam has a similar pharmacodynamic profile to diazepam but its elimination half-time is longer. *N*-Desmethyldiazepam is hydroxylated to oxazepam, which is also active. Oxazepam has a shorter elimination half-time and it is conjugated with glucuronic acid (Greenblatt 1981). Temazepam and oxazepam do not appear to contribute much to the effects of diazepam since they have shorter half-times than the parent drug.

Due to the redistribution of diazepam, the concentrations considerably decrease during the first 2–3 h after administration. Thereafter the rate of disappearance from plasma slows down (Greenblatt et al. 1989). The distribution half-time of diazepam, 30–66 min (Mandelli et al. 1978; Greenblatt et al. 1980), is significantly longer than that of midazolam or lorazepam. In healthy volunteers, the clearance of diazepam ranges from 0.2 to 0.5 ml/kg per minute (Greenblatt et al. 1979) but older age tends to reduce the clearance (MacLeod et al. 1979). The formation of *N*-desmethyldiazepam accounts for 50%–60% of total diazepam clearance. The mean elimination half-time of diazepam is 30 h with a range of 20–100 h while that of *N*-desmethyldiazepam is even longer with a range of 30–200 h (Mandelli et al. 1978). During the elimination phase following single or multiple doses, the plasma concentration of *N*-desmethyldiazepam can be higher than that of diazepam. Plasma protein binding of diazepam averages 98% and the volume of distribution is 0.7–1.7 l/kg (Dasberg 1975; Jack and Colburn 1983; Greenblatt et al. 1988). In obese patients, the volume of distribution of diazepam is increased and the elimination half-time prolonged (Abernethy et al. 1983).

In patients with liver cirrhosis, the plasma clearance of orally administered diazepam is reduced and the plasma concentrations of diazepam and *N*-desmethyldiazepam are higher than in healthy controls, which results in increased sedation (Ochs et al. 1983). After intravenous administration, however, the serum concentrations of diazepam are lower than in healthy controls. In spite of the lower concentrations, diazepam causes heavier sedation in patients with liver disease, suggesting that the permeability of the blood–brain barrier is increased and diazepam has a higher affinity to benzodiazepine receptors (Bozkurt et al. 1996).

In patients with end-stage renal failure, the mean unbound fraction of diazepam is greatly increased while the volume of distribution of the unbound drug is reduced. However, the plasma clearance of unbound diazepam remains essentially unchanged (Ochs et al. 1981).

4.3 Lorazepam

Lorazepam is biotransformed by direct conjugation to glucuronic acid, yielding a water-soluble metabolite that is excreted in urine. No active metabolites have

been identified. The mean elimination half-time is 15 h with a range of 8–25 h (Greenblatt et al. 1979). The plasma protein binding of lorazepam is about 90%. The clearance varies from 0.8 to 1.8 ml/kg per minute and the volume of distribution from 0.8 to 1.3 l/kg (Greenblatt 1981).

The elimination half-time of lorazepam is increased in patients with alcoholic cirrhosis as compared to healthy controls but the systemic plasma clearance remains unchanged. Acute viral hepatitis has no effect on the disposition kinetics of lorazepam with the exception of a modest decrease in plasma protein binding (Kraus et al. 1978). In renal impairment, the elimination half-time and the volume of distribution of lorazepam are increased but the clearance does not differ significantly from that in healthy controls (Morrison et al. 1984).

4.4 Ro 48-6791

Ro 48-6791 was developed in the search for a benzodiazepine with a faster recovery profile than that of midazolam, while retaining the favourable physicochemical and pharmacodynamic properties of the latter (Dingemanse et al. 1997a, b). Ro 48-6791, 3-(5-dipropylaminomethyl-1, 2,4-oxadiazol-3-yl)-8-fluoro-5-methyl-5, 6-dihydro-4H-imidazo [1, 5-a] [1,4] benzodiazepin-6-one, is a water-soluble full agonist at the benzodiazepine receptor. In two studies with healthy volunteers, the pharmacokinetics of Ro 48-6791 was described with a 2- or 3-compartment model (Dingemanse et al. 1997a, b). The volume of distribution at steady-state and plasma clearance were four- to fivefold higher for Ro 48-6791 than for midazolam. The distribution and the elimination half-times of Ro 48-6791 and midazolam were similar, because both the volume of distribution and the clearance changed in the same direction (Dingemanse et al. 1997a).

Following intravenous administration to man, Ro 48-6791 undergoes rapid biotransformation to form the monopropyl derivate Ro 48-6792. In animals, Ro 48-6792 is at least tenfold less potent a sedative than the parent compound, and the maximum plasma concentration of Ro 48-6792 attained in the study by Dingemanse et al. (1997a) was unlikely to have contributed significantly to the effects of Ro 48-6791. However, the plasma concentrations indicated that the elimination half-time of Ro 48-6792 was markedly longer than that of the parent compound, suggesting that the metabolite could accumulate during prolonged sedation with Ro 48-6791.

4.5 Flumazenil

The plasma protein binding of flumazenil is about 40%, and the elimination half-time is reported to be about 40–80 min. The steady-state volume of distribution is 0.9–1.1 l/kg, and the plasma clearance ranges 13–17 ml/kg per minute. After intravenous administration, flumazenil is extensively metabolized in the liver to the

inactive carboxylic acid form, which is excreted predominantly in the urine (Klotz and Kanto 1988; Breimer et al. 1991).

Licensed drug information states that in patients with hepatic failure, the elimination half-time of flumazenil is prolonged and the systemic clearance is reduced compared with healthy subjects. However, the pharmacokinetics of flumazenil is not significantly affected by renal disease or haemodialysis.

5 Pharmacokinetic-Dynamic Relationship

In a multicompartment pharmacokinetic model, the distribution of the drug between the central and peripheral compartments is a significant contributor to drug disposition in the central compartment. The traditional elimination half-time is inadequate to describe the various drug concentration decrements observed after different dosing schemes (Shafer and Varvel 1991). Computer simulations based on pharmacokinetic models can be used to describe the decay of plasma drug concentrations after discontinuation of drug administration. Specifically, it has been suggested that context-sensitive half-times (Hughes et al. 1992) or other decrement times (Bailey 1995) can be used to describe the decay of drug concentration after discontinuation of drug administration and thus better describe the cessation of drug effect. The context-sensitive half-time (50% decrement time) is the time required for blood or plasma concentrations of a drug to decrease by 50% after stopping the drug administration. Correspondingly, 80% decrement time is the time required for drug concentrations to decrease by 80%. In many cases it is the 50% decrement of the drug concentration that is useful for the prediction of the duration of drug action. However, the duration of drug effect is a function of both pharmacokinetic and pharmacodynamic properties. Other variables include an inconsistent relationship between concentration and response, variable response characteristics for different patients, and the variable effect of concomitantly administered drugs (Keifer and Glass 1999). Figure 6 shows the context-sensitive half-times for commonly used intravenous anaesthetics.

Midazolam has been used as a continuous intravenous infusion with a supplemental volatile agent (Ahonen et al. 1996a) or as the sole hypnotic agent (Theil et al. 1993) in cardiac surgery. More often, continuous infusions of midazolam and lorazepam are administered to intensive care patients for sedation during mechanical ventilation. A recent study shows that midazolam and lorazepam have substantial pharmacokinetic and pharmacodynamic differences when given during intensive care. Barr et al. (2001) have observed that the pharmacodynamic model can predict the depth of sedation for both midazolam and lorazepam with 76% accuracy. The estimated sedative potency of lorazepam is twice that of midazolam and the relative amnestic potency of lorazepam fourfold that of midazolam. The predicted emergence times from sedation after a 72-h benzodiazepine infusion for light and deep sedation in a typical patient are 3.6 and 14.9 h for midazolam infusions and 11.9 and 31.1 h for lorazepam infusions, respectively (Fig. 7). Since both formal modelling

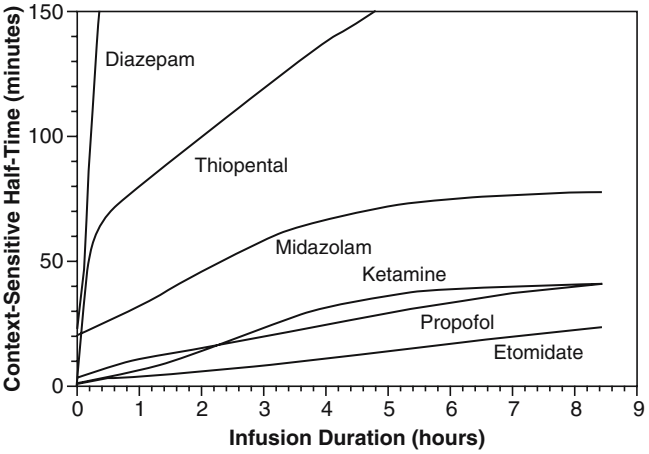

Fig. 6 The context-sensitive half-times for commonly used intravenous anaesthetic drugs. (Modified with permission from Reves et al. 1994)

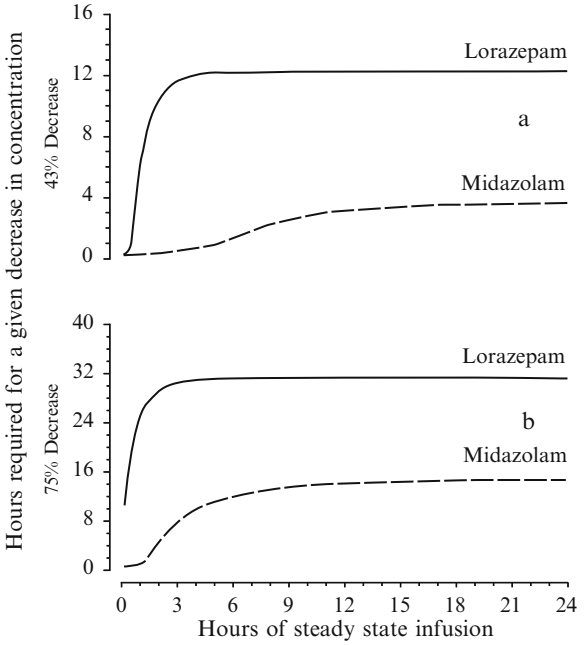

Fig. 7 Predicted time required for (*a*) a 43% decrease and (*b*) a 75% decrease in plasma benzodiazepine concentration as a function of the duration of the benzodiazepine infusion corresponding to the benzodiazepine concentration change required to emerge from light and deep sedation, respectively. (Modified with permission from Barr et al. 2001)

and empirical observations indicate that the relative concentration decrements for midazolam and lorazepam are not markedly different, the differences in emergence times are primarily due to different pharmacokinetics (Barr et al. 2001).

6 Drug Interactions

A drug interaction occurs when two or more drugs are given together. If the resulting pharmacological response is equal to the sum of the effects of the drugs given separately, drug interactions are unlikely to cause problems to clinicians. However, if the response is greater or smaller than the sum of the individual effects, the net result is much more difficult to anticipate. Although the clinical significance of drug interactions has been occasionally exaggerated, drug interactions are in some instances an important cause of drug toxicity. On the other hand, many drug interactions are beneficial and modern anaesthetic techniques depend on the utilization of such drug interactions. A sound combination of drugs helps clinicians to increase the efficacy and safety of drug treatment.

Drugs may interact on a pharmaceutical, pharmacokinetic or pharmacodynamic basis. A number of drugs may also interact simultaneously at several different sites. Many pharmacodynamic interactions are predictable and can be avoided by the use of common sense. However, it is much more difficult to predict the likelihood of pharmacokinetic interactions despite good prior knowledge of the pharmacokinetics of individual drugs. Pharmaceutical interactions normally occur before the drug is given to the patient and they will not be considered here.

6.1 Pharmacokinetic Drug Interactions

The interaction potential of the different benzodiazepines is dictated by their individual pharmacokinetic properties. Accordingly, both diazepam and midazolam undergoing phase I and phase II reactions during their biotransformation are more likely to have metabolic drug interactions. Lorazepam, on the other hand, is a benzodiazepine which is eliminated mainly by direct conjugation at the 3 position with glucuronic acid in the liver (Greenblatt et al. 1976). Therefore, it is less likely to have clinically significant pharmacokinetic drug interactions in man.

6.1.1 Midazolam

Midazolam is metabolized by CYP3A enzymes (Wandel et al. 1994) and it has been shown to have numerous clinically significant interactions with inhibitors and inducers of CYP3A4. It has a rather low oral bioavailability and therefore it is the oral route which is especially susceptible to metabolic drug interactions. However, inhibitors and inducers of CYP3A4 affect also intravenous midazolam. Erythromycin,

fluconazole, itraconazole, saquinavir and voriconazole have been shown to reduce the clearance of intravenous midazolam in healthy volunteers by 50%–70% (Fig. 8). Accordingly, during continuous infusion, the concentrations of midazolam are expected to increase two- to threefold by strong inhibitors of CYP3A4 (Olkkola et al. 1993, 1996; Palkama et al. 1999; Saari et al. 2006). Long-term infusions of midazolam to patients receiving these inhibitors, e.g. during intensive care treatment, may result in undesirably long-lasting hypnotic effects if the dose is not titrated according to the effect. Propofol, an intravenous hypnotic used for the induction and maintenance of anaesthesia, also reduces the clearance of intravenous midazolam by 37% by inhibition of hepatic CYP3A4 (Hamaoka et al. 1999). Correspondingly, fentanyl decreases midazolam clearance by 30% (Hase et al. 1997). These interactions appear to be of minor clinical significance.

The data obtained from healthy volunteers is supported also by data in patients undergoing coronary artery bypass grafting and patients in intensive care (Ahonen et al. 1996a, 1999). Thirty patients undergoing coronary artery bypass grafting were randomly assigned to receive either diltiazem (60 mg orally and an infusion of 0.1 mg/kg per hour for 23 h) or placebo in a double-blind manner. Anaesthesia was induced with midazolam 0.1 mg/kg, alfentanil 50 μg/kg and propofol 20–80 mg and maintained with infusions of 1.0 μg/kg per minute of both midazolam and alfentanil supplemented with isoflurane until skin closure. Diltiazem increased the area under the midazolam concentration-time curve by 25% and that of alfentanil by 40%. Delayed elimination of midazolam and alfentanil was reflected also in pharmacodynamic variables because patients receiving diltiazem were extubated on the average 2.5 h later than those receiving placebo (Fig. 9).

Since the inhibitors change the pharmacokinetics of oral midazolam both by reducing the first-pass metabolism and by reducing elimination, they affect the pharmacokinetics of oral midazolam more than that of intravenous midazolam. Previous studies have shown that the above-mentioned inhibitors may cause up to a tenfold increase in the area under the midazolam concentration-time curve (Olkkola et al.

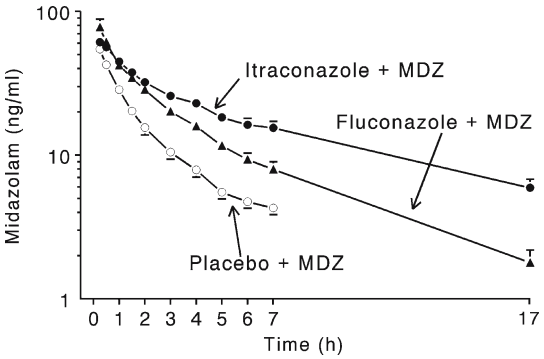

Fig. 8 Concentrations (mean±SEM) of midazolam (*MDZ*) in plasma after an intravenous dose of 0.05 mg/kg after pretreatment with itraconazole (200 mg), fluconazole (400 mg on the first day and then 200 mg), or placebo for 6 days to 12 healthy volunteers. The intravenous dose of midazolam was given on the fourth day of pretreatment. (Modified with permission from Olkkola et al. 1996)

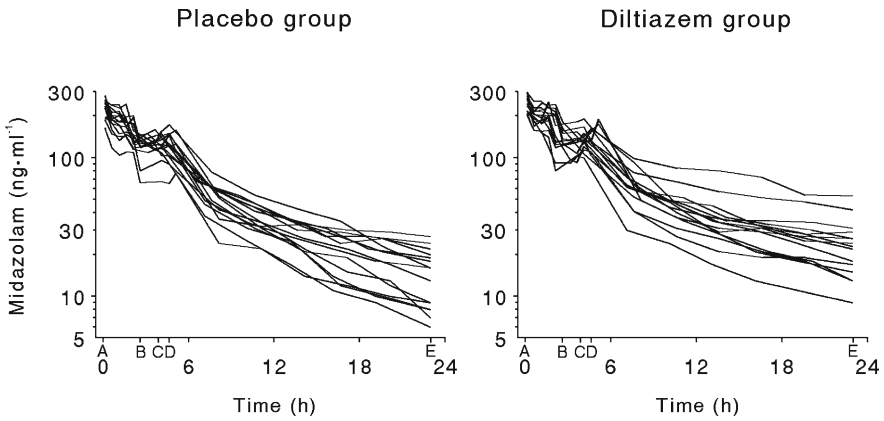

Fig. 9 Midazolam and alfentanil plasma concentrations during and after anaesthesia in 15 coronary artery bypass grafting (CPB) patients receiving diltiazem and in 15 patients receiving placebo. *A*, induction of anaesthesia; *B*, initiation of CPB (average); *C*, end of CPB (average); *D*, end of anaesthesia (average); and *E*, end of diltiazem or placebo infusion. (Modified with permission from Ahonen et al. 1996a)

1993, 1996; Palkama et al. 1999; Saari et al. 2006). The inducers of CYP3A4 cause a profound increase in the elimination midazolam (Backman et al. 1996, 1998). Midazolam is also susceptible to interact with other drugs affecting CYP3A4.

6.1.2 Diazepam

Diazepam is metabolized primarily by CYP2C19 and -3A4 isoenzymes (Bertz and Granneman 1997) and on theoretical basis it is likely to interact with drugs affecting the activity of these isoenzymes. Even strong inhibitors of CYP3A4 appear to have only a minor effect on the pharmacokinetics of diazepam. Erythromycin and itraconazole, both strong inhibitors of CYP3A4, increased the area under the oral diazepam concentration-time curve by 15% (Luurila et al. 1996; Ahonen et al. 1996b). Although these data come from studies with oral diazepam, the results may also be extrapolated to the intravenous route because the oral bioavailability diazepam is essentially 100% (Bailey et al. 1994). Accordingly, the interaction between inhibitors of CYP3A4 does not appear to be clinically significant.

It has been shown that the CYP2C19 inhibitor omeprazole and the CYP1A2 and -3A4 inhibitor cimetidine decrease the clearance of intravenous diazepam by 27% and 38%, respectively (Andersson et al. 1990). Fluvoxamine, an inhibitor of CYP1A2, -2C19 and -3A4, reduces the apparent oral clearance of diazepam by 65% and also increases the elimination half-time from 51 to 118 h (Perucca et al. 1994). Thus, the interactions of the strong inhibitors of CYP2C19 and diazepam seem to be clinically significant when diazepam is administered for a longer period. When single bolus doses of intravenous diazepam are used, these interactions are unlikely to be clinically significant.

Interestingly, ciprofloxacin, an inhibitor of CYP1A2, also delays the elimination of intravenous diazepam. Seven-day treatment with ciprofloxacin reduced diazepam clearance by 37% and prolonged the elimination half-time from 37 to 71 h (Kamali et al. 1993). No changes in drug effect were observed. In contrast, rifampicin, an inducer of many cytochromal enzymes increased diazepam clearance by 200%. Thus, the diazepam dose must be increased in patients on rifampicin (Ohnhaus et al. 1987).

6.1.3 Lorazepam

Unlike the other two benzodiazepine agonists, lorazepam is mainly eliminated by direct conjugation with glucuronic acid. It is therefore plausible that it has few pharmacokinetic interactions with other drugs. Probenecid decreases lorazepam clearance by 50% by decreasing the formation clearance of lorazepam-glucuronide (Abernethy et al. 1985). Valproic acid seems to affect the pharmacokinetics of lorazepam with the same mechanism (Samara et al. 1997).

6.1.4 Flumazenil

So far no pharmacokinetic interactions have been reported with flumazenil.

6.2 Pharmacodynamic Drug Interactions

Although pharmacokinetic drug interactions are of academic interest and are also in some cases clinically significant, pharmacodynamic interactions are far more common and have greater significance in anaesthetic practice. Many pharmacodynamic interactions are predictable and can be avoided by the use of common sense and good knowledge of pharmacology. However, in most cases pharmacodynamic drug interactions can be regarded as desirable because a sound combination of drugs having synergistic effects may facilitate the use of smaller and less toxic doses of the individual drugs.

All benzodiazepines act on the central nervous system and they interact with other drugs acting on the central nervous system too. When the interaction between morphine and midazolam is quantified by their sedative effect, the effects of these two drugs are additive (Tverskoy et al. 1989). However, the interactions between the benzodiazepines and opioids are usually considered synergistic. Vinik et al. (1994) studied the hypnotic effects of propofol, midazolam, alfentanil and their binary and triple combinations. The ratios of a single-drug fractional dose (ED_{50}=1.0) to a combined fractional dose (in fractions of single-drug ED_{50} values). thus indicating the degree of supra-additivity (synergism), were: 1.4 for propofol–alfentanil, 1.8 for midazolam–propofol, 2.8 for midazolam–alfentanil, and 2.6 for propofol–midazolam–alfentanil (Fig. 10). Accordingly, the propofol–midazolam–alfentanil

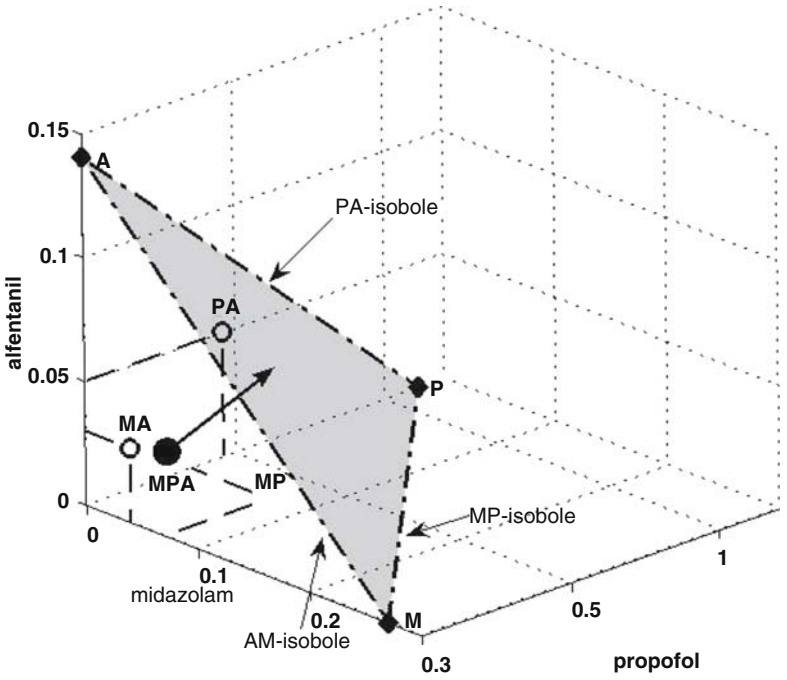

Fig. 10 Binary versus triple synergism: ED_{50} isobolograms for the hypnotic interactions among midazolam (M), alfentanil and propofol (P). The shaded area shows the additive plane passing through three single drug ED_{50} (solid diamonds A,M,P). The boundaries of the plane are binary additive isoboles. The open circles are measured ED_{50} points for the binary combinations (MA, MP, PA) and the solid circle is the measured ED_{50} point for the triple combination (MPA). The ratio (R) of the single-drug dose (ED_{50}=1) to combined fractional dose (in fractions of single-drug ED_{50} values), reflects the degree of synergism. All measured interaction values are significantly different from the additive effect. (Data from Vinik HR, Bradley EL Jr, Kissin I (1994) Triple anesthetic combination: propofolmidazolam-alfentanil. Anesth Analg 78:354-358).

interaction produced a profound hypnotic synergism which is not significantly different from that of the binary midazolam–alfentanil combination.

The interaction between midazolam and ketamine is additive (Hong et al. 1993). The lack of synergism has been regarded as most likely due to the different mechanisms of action of ketamine and midazolam. Ketamine inhibits excitatory transmission by decreasing the depolarization through the blockade of *N*-methyl-d-aspartate (NMDA) receptors. Thiopental, propofol and midazolam exert their general effects by the allosteric modulation of the $GABA_A$ receptors. Thus, the interactions between the hypnotic effects of midazolam and thiopental (Short et al. 1991) and propofol and midazolam are synergistic (McClune et al. 1992).

Xanthines are mainly used for asthma and chronic obstructive pulmonary disease. Besides bronchodilating effects, they also stimulate the central nervous system. Intravenous aminophylline is able to reverse at least partially the sedation from intravenous diazepam (Arvidsson et al. 1982). This interaction appears to be due to the blockade of adenosine receptors by aminophylline (Niemand et al. 1984).

7 Clinical Use

7.1 Midazolam

Midazolam is mainly used for sedation in minor investigative or surgical procedures, premedication, induction of general anaesthesia, and sedation in intensive care unit (ICU) patients. Anxiolysis, amnesia, sedation and hypnosis are desirable benzodiazepine properties (de Jong and Bonin 1981; Reves et al. 1985). The ability of midazolam to reduce anxiety and to provide amnesia has been demonstrated reliably over a range of doses administered by various routes (Reinhart et al. 1985; Barker et al. 1986; Forrest et al. 1987). The effects of midazolam and other benzodiazepines on memory are anterograde; the retrograde memory is not affected. It is desirable that the duration of amnesia is not much longer than the duration of the procedure and the period of sedation or anaesthesia. The intensity and duration of amnesia following intravenous administration of midazolam appears to be dose-dependent. After an anaesthetic induction dose the amnestic period is 1–2 h (Langlois et al. 1987; Miller et al. 1989). Typical of benzodiazepines, during sedation the volunteers or the patients seem conscious and coherent, yet they are amnestic for events and procedures (George and Dundee 1977). Compared with intravenously administered midazolam, at identical plasma concentrations of the drug, an oral dose produces more marked effects due to the higher plasma concentrations of the active metabolite alpha-hydroxymidazolam (Crevoisier et al. 1983; Mandema et al. 1992).

A usual total dose for sedation in minor surgical and other procedures in adults varies between 2.5 and 7.5 mg intravenously. An initial dose of 2 mg over 30 s has been suggested supplemented with incremental doses of 0.5–1 mg at intervals of about 2 min if required. The usual dose for induction of anaesthesia is between 0.1 and 0.2 mg/kg in pre-medicated patients and 0.3 mg/kg in patients with no premedication. After intravenous administration, the onset of action of midazolam occurs usually within 30–60 s. The half-time of equilibration between the plasma concentration and the EEG effects is approximately 2–3 min (Breimer et al. 1990). In well pre-medicated patients, an induction dose of 0.2 mg/kg of midazolam given in 5–15 s induced anaesthesia in 28 s, whereas when diazepam at 0.5 mg/kg was also given in 5–15 s induction occurred in 39 s (Samuelson et al. 1981). Due to a synergistic interaction, concurrent administration of other intravenous anaesthetics reduces the induction dose of midazolam and vice versa; even sub-hypnotic doses of midazolam reduce the induction dose of thiopental, for example, by more than 50%. Synergism is strongest in patients who are relatively insensitive to thiopental (Vinik and Kissin 1990; Vinik 1995). Administration of midazolam for premedication and induction of anaesthesia should be undertaken cautiously in the elderly, who are more sensitive to the sedative effects than younger individuals (Gamble et al. 1981; Jacobs et al. 1995).

Emergence from anaesthesia depends on the dose of midazolam and on the administration of adjuvant anaesthetics (Reves et al. 1985). The emergence from a midazolam dose of 0.32 mg/kg supplemented with fentanyl is about 10 min longer

than from a thiopental dose of 4.75 mg/kg supplemented with fentanyl (Reves et al. 1979). Maintenance infusions of midazolam have been used for anaesthesia or sedation (Theil et al. 1993; Barvais et al. 1994; Barr et al. 2001). The termination of action of the benzodiazepines is primarily a result of their redistribution from the central nervous system to other tissues (Greenblatt et al. 1983). After a continuous infusion, however, blood levels of midazolam will decrease more rapidly than those of the other benzodiazepines due to the greater clearance of midazolam. As stated above, the context-sensitive decrement times rather than the elimination half-time can be used to assess the emergence from an infusion anaesthetic (Hughes et al. 1992; Bailey 1995; Keifer and Glass 1999).

7.2 Diazepam

Diazepam is very effective in relieving anxiety before surgery. Diazepam has amnestic properties but it is less effective in this regard than midazolam (Pandit et al. 1971). However, amnesia is more profound when diazepam is combined with other drugs, e.g. with opioids (Dundee and Pandit 1972).

For sedation in minor investigative or surgical procedures, an intravenous dose of 0.1–0.2 mg/kg of diazepam is recommended. At equal plasma levels of diazepam, elderly patients are more sensitive to the depressant effects of diazepam than younger individuals (Reidenberg et al. 1978). The effects of various doses of intravenous diazepam and midazolam on clinical sedation and psychomotor performance have been studied in healthy volunteers. The maximal effects seen after 0.3 mg/kg of diazepam do not reach those of 0.1 mg/kg of midazolam. The effects of midazolam, however, disappear sooner than those of diazepam (Nuotto et al. 1992). After intravenous administration of 0.15 mg/kg of diazepam in healthy volunteers, the duration of diazepam effect, based on a statistically significant difference over the predrug baseline EEG values, is 5–6 h compared with 2.5 h after administration of 0.1 mg/kg of midazolam. When the effect of benzodiazepines is quantified by EEG, diazepam has an EC_{50} value of 269 ng/ml and midazolam 35 ng/ml, respectively (Greenblatt et al. 1989). This difference indicates a greater potency of midazolam compared with diazepam, which is in good agreement with the results of different pharmacodynamic tests (Nuotto et al. 1992). Due to the extremely long context-sensitive half-time of diazepam, it is not suitable to be administered by continuous infusion for the maintenance of anaesthesia or sedation (Reves et al. 1994).

7.3 Lorazepam

Lorazepam has been shown to be an effective anxiolytic and amnestic agent (Fragen and Caldwell 1976). A dose of 2–3 mg may be useful for anxious patients given the night before the operation followed by a smaller dose before the procedure.

Alternatively, 2–4 mg may be given about 2 h before surgery. A dose of 0.05 mg/kg may be administered 30–45 min before the operation if given intravenously. With doses of 4 mg, amnesia persists for 4 h (Pandit et al. 1976). Due to the long-lasting amnestic effect of lorazepam, it is widely used for oral premedication and as an intravenous anaesthetic adjuvant in coronary artery bypass graft surgery. In intensive care, continuous infusions of lorazepam are used for sedation during mechanical ventilation (Barr et al. 2001). Using a target-controlled infusion pump, the initial target plasma concentration of 50 ng/ml has been used. Subsequently, the infusion is titrated according to the level of sedation sought (Barr et al. 2001).

7.4 Flumazenil

A slow intravenous injection of flumazenil can be used to reverse the benzodiazepine-induced sedation as well as to diagnose or treat benzodiazepine overdose. The initial dose for the reversal of benzodiazepine-induced sedation is 0.2 mg, followed by further doses of 0.1–0.2 mg at intervals of 60 s if needed. The total dose should be not more than 1 mg or occasionally 2 mg. If drowsiness recurs, an intravenous infusion of 0.1–0.4 mg per hour may be used (Brogden and Goa 1991).

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