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Flumazenil in Benzodiazepine Antagonism
Actions and Clinical Use in Intoxications and Anaesthesiology

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Summary

In anaesthesia and in the intensive care unit, benzodiazepines have proven safe and effective agents for the induction and maintenance of sedation for a variety of therapeutic goals. However, in these contexts, or in benzodiazepine overdose, it is often desirable to

be able to terminate or interrupt sedation without waiting for the effect of the benzodiazepine to become dissipated by normal metabolism and excretion.

Flumazenil, a 1,4-imidazobenzodiazepine, is a highly effective, specific benzodiazepine antagonist which is indicated for use when the effect of a benzodiazepine must be attenuated or terminated at short notice. It acts by displacing other benzodiazepines from the receptor site by competitive inhibition. The onset of effect after intravenous administration occurs within 1 to 3 minutes. The optimal dosage is determined for each patient by a dose titration procedure and lies in the range 0.2 to 1.0mg in anaesthesiology, and 0.1 to 2.0mg in intensive care use. Despite its short elimination half-life of around 1 hour, after general anaesthesia or conscious to moderate sedation for short procedures, a single dose of flumazenil is usually sufficient to attain and maintain the desired level of consciousness. After intoxication with high benzodiazepine doses, the duration of effect of a single dose of flumazenil is not expected to exceed 1 hour. In such cases, the period of wakefulness can be prolonged as necessary by repeated low intravenous doses of flumazenil or by infusion (0.1 mg/hour).

Flumazenil is well tolerated both systemically and locally. The only adverse events seen with greater frequency after flumazenil compared with placebo were nausea and/or vomiting after general anaesthesia, although the incidence of actual vomiting was not significantly different between the 2 groups. Since these effects were virtually absent in studies of intensive care patients and after sedation for short procedures, and were not seen in tolerability studies in healthy volunteers receiving intravenous bolus doses of up to 100mg, there may be a link between these symptoms and the other agents used in general anaesthesia, some of which have well-known emetic properties.

Thus, flumazenil provides a safe and effective means of attenuating or reversing the CNS-depressant effects of benzodiazepines whenever indicated, e.g. following benzodiazepine-induced general anaesthesia, conscious sedation, or after benzodiazepine overdose, either alone or in combination with other agents. Its reliability of effect, lack of influence on vital functions, and specificity for benzodiazepines also allow its use for diagnostic purposes, e.g. to exclude benzodiazepine intoxication in patients with consciousness impairment of unknown origin.

Benzodiazepines are among the most widely used drugs in the world. In anaesthesia and in the intensive care unit they have proved safe and effective agents for the induction of sedation for a variety of therapeutic goals: in the induction and maintenance of general anaesthesia, for conscious sedation in shorter diagnostic and therapeutic procedures, for sedation of patients requiring mechanical ventilation, for the treatment of status epilepticus, and for the sedation of critically ill patients in anxiety-provoking situations. However, in these contexts, or in benzodiazepine overdose, it is often desirable to be able to terminate or interrupt sedation without waiting for the effect of the benzodiazepine to become dissipated by normal metabolism and excretion. This constitutes the basic rationale for the application of benzodiazepine antagonism in clinical practice.

This review describes the role of a specific benzodiazepine antagonist in reversing benzodiazepine sedation in clinical practice and in overdosed patients.

1. Applications of Benzodiazepine Antagonism in Clinical Practice

1.1 Benzodiazepine Antagonism in Anaesthesiology

Benzodiazepines are commonly used as premedication sedatives and for the induction of anaesthesia or sedation in surgical procedures. However, as a result of the individual variability in response, some patients become or remain somewhat more heavily sedated than others receiving the same doses under similar conditions. Moreover, the hypnogenic and CNS-depressant effects

of benzodiazepines may be enhanced by other drugs administered during surgery. Depending on the dosage of benzodiazepine required, the depth of anaesthesia or sedation maintained until the end of the operation, the other agents administered, and the actual length of the operation, the sedative effects of the benzodiazepine may persist postoperatively for longer than necessary or desirable, thus requiring more intensive monitoring and supervision. Postoperative administration of a specific benzodiazepine antagonist would allow rapid reversal of benzodiazepine-induced sedation when sedation is no longer required.

1.2 Diagnosis and/or Management of Benzodiazepine Intoxication

Coma of indeterminate cause presents a primary question of diagnosis, as this state can be due to a variety of organic or functional disturbances or to intoxication, and might involve a number of time-consuming diagnostic procedures. In the case of coma due to intoxication, most patients admitted to hospital have taken a variety of drugs in high doses with the intention of committing suicide. Benzodiazepines, because of their hypnotic properties and their availability to outpatients, are often a component of such intoxications or may be taken alone in overdose since patients are not aware that the outcome of pure benzodiazepine overdose is almost never lethal. Thus, early detection or exclusion of benzodiazepines in the differential diagnosis of coma of unknown aetiology would be a realistic first-line approach in managing such patients. A safe, specific, rapidly acting benzodiazepine antagonist would allow almost certain exclusion, or detection and management, of benzodiazepine intoxication within a few minutes.

Benzodiazepine overdose may also be induced iatrogenically in patients who require long term administration of high therapeutic doses, in slow metabolisers or patients with impaired metabolic function, in patients who are particularly sensitive to benzodiazepines, or by accident. Although benzodiazepines have proved relatively safe in clinical use, their administration in high doses may constitute a potential secondary risk source, because they can potentiate the ability of other drugs to aggravate or induce respiratory failure, particularly in the elderly or in patients with chronic respiratory insufficiency.

1.3 Interruption or Termination of Long Term Benzodiazepine Sedation

Patients under intensive care may require prolonged anxiolysis and long term sedation for two main reasons: firstly, to reduce fears engendered by the seriousness of their condition and secondly, to lessen the anxiety associated with the impersonal, stressful setting in the intensive care unit itself. Such patients often require mechanical ventilation for a prolonged period, and therefore must be maintained under continuous sedation. The benzodiazepines are among the most widely used drugs for this purpose since they combine the requisite pharmacological properties (sedation, anxiolysis, muscle relaxation, and anterograde amnesia) with dosing flexibility, compatibility with a broad range of other medications, and relative safety. However, when the sedative benzodiazepine medication is stopped (e.g. when the need for sedation is past, when patients are to be awoken from sedation for assessment of the status of their disease or on weaning from mechanical ventilation), the effect of the administered benzodiazepine may persist for longer than required as a result of the high doses given and the consequent accumulation. Thus, it would be highly desirable to have at hand a means of interrupting or terminating benzodiazepine sedation on demand. Use of a specific benzodiazepine antagonist would make it possible to produce almost immediate awakening, allowing, in an administration schedule, for either a temporary awakening or continued wakefulness, as dictated by the requirements of the patient.

1.4 Management of Oversedation or Paradoxical Reactions to Benzodiazepines

In some rare cases prolonged coma or paradoxical reactions (e.g. hyperactivity) have been observed after standard therapeutic doses of benzo-

diazepines (Geller, personal communication). In other situations in which benzodiazepine sedation is supplemented with intravenously administered narcotics, as is often the case, the potential for oversedation or respiratory depression may be increased. In both contexts, the availability of a benzodiazepine antagonist would provide the means to counteract the unwanted response.

2. *Agents Possessing Benzodiazepine Receptor Binding Properties*

Three different substance classes are known to interact with the benzodiazepine receptor:

1. Benzodiazepine agonists, e.g. diazepam. These substances bind specifically to the benzodiazepine receptor and produce the classical benzodiazepine effects, i.e. anxiolysis, sedation, muscle relaxation and anticonvulsant activity.

2. Inverse benzodiazepine agonists, e.g. β-carbolines. These substances bind specifically to the benzodiazepine receptor and produce effects that are diametrically opposed to those of benzodiazepines, e.g. anxiogenesis, stimulation, convulsant activity, increase in muscle tone.

3. Benzodiazepine antagonists, e.g. flumazenil. These substances have a high affinity to the binding site on the benzodiazepine receptor, but have no direct action on their own.

3. *Mechanism of Action of Specific Benzodiazepine Antagonists*

At present, the commercially available drugs that are used to counteract benzodiazepine effects are physostigmine (a centrally active cholinesterase inhibitor), naloxone (an antagonist of endogenous opioid peptides), methylxanthines (purine receptor blockers), and other analeptics. However, these compounds act by mechanisms other than competitive displacement at the benzodiazepine receptor, and counteract benzodiazepine effects by exerting an intrinsic positive effect. Their capacity to neutralise specific benzodiazepine effects is therefore mostly marginal and unpredictable in nature (Geller et al., in press 1987).

However, a specific benzodiazepine antagonist, flumazenil (Ro 15-1788), is currently undergoing clinical evaluation and registration world wide. Flumazenil, a member of the chemical group of 1,4-imidazobenzodiazepines, is the first specifically acting benzodiazepine antagonist to be subjected to clinical investigation. It has been shown to reduce or totally suppress in a dose-dependent manner the central effects of benzodiazepines by competitively displacing other benzodiazepines from the receptor (fig. 1). Currently, flumazenil has been registered as a benzodiazepine antagonist in Switzerland, France and New Zealand. Registration is expected to follow in other countries shortly.

4. *Clinical Pharmacology of Flumazenil*

The chemical structure of flumazenil (fig. 2) is similar to that of midazolam or triazolam (Hunkeler et al. 1981). However, it differs fundamentally from them in its pharmacological and clinical properties (Bonetti et al. 1982; Darragh et al. 1981; Hunkeler et al. 1981; Polc et al. 1981). Flumazenil has a particularly high binding affinity to the benzodiazepine receptor (fig. 1) [Möhler et al. 1981] but, unlike classical benzodiazepines in clinical use, it does not exert intrinsic effects when administered alone in low doses, either in pharmacological studies or under clinical conditions of use. On the contrary, in animals flumazenil has been shown to block all the typical benzodiazepine effects, such as the anticonvulsant, anticonflict, muscle relaxant, and amnesic effects (Bonetti et al. 1982). For most of these effects in animals the potency of flumazenil as a specific benzodiazepine antagonist was similar to that of diazepam as an agonist. Figure 3 compares and contrasts the agonist/antagonist profile of flumazenil and 2 benzodiazepine agonists in a series of animal models.

4.1 Pharmacodynamics in Humans

4.1.1 Benzodiazepine Antagonist Effects

Flumazenil has been shown to fully block the CNS effects of other benzodiazepines in healthy volunteers in a number of experimental settings. When administered after a benzodiazepine it re-

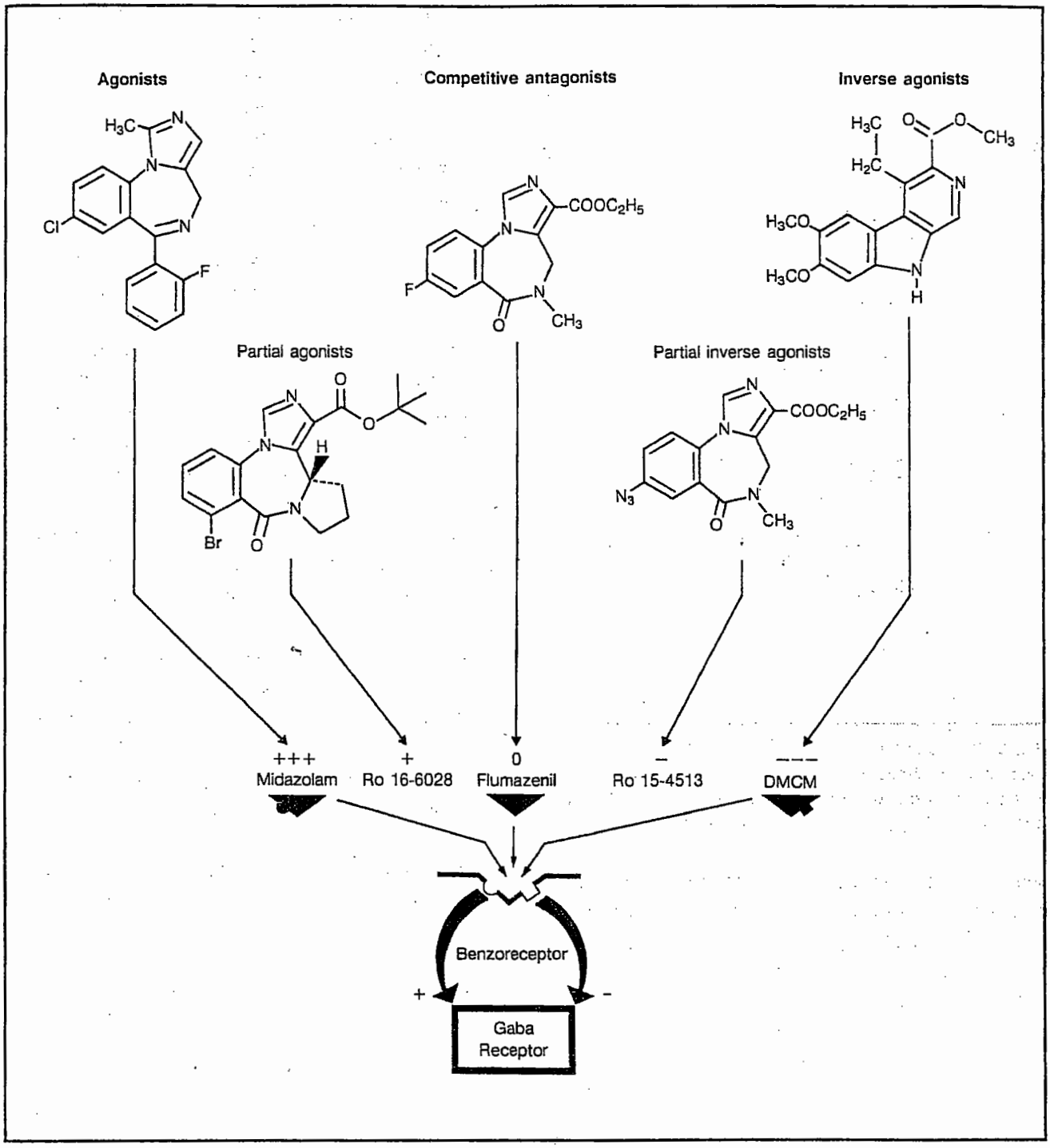

Fig. 1. Schematic representation of the different modes of interaction of 3 basic types of benzodiazepine receptor ligands (DMCM = dimethoxy-β-carbolin-methylester), from strongly agonist (+++) to neutral (0) to strongly inversely agonist (– – –) [from Richards et al. (1986)].

sults in a return to baseline values for parameters of CNS effect, e.g. vigilance, response time, performance, and memory.

In a series of studies (Doenicke 1984; Doenicke et al. 1982, 1984; Forster et al. 1983; Ziegler & Schalch 1983) flumazenil was administered intra-

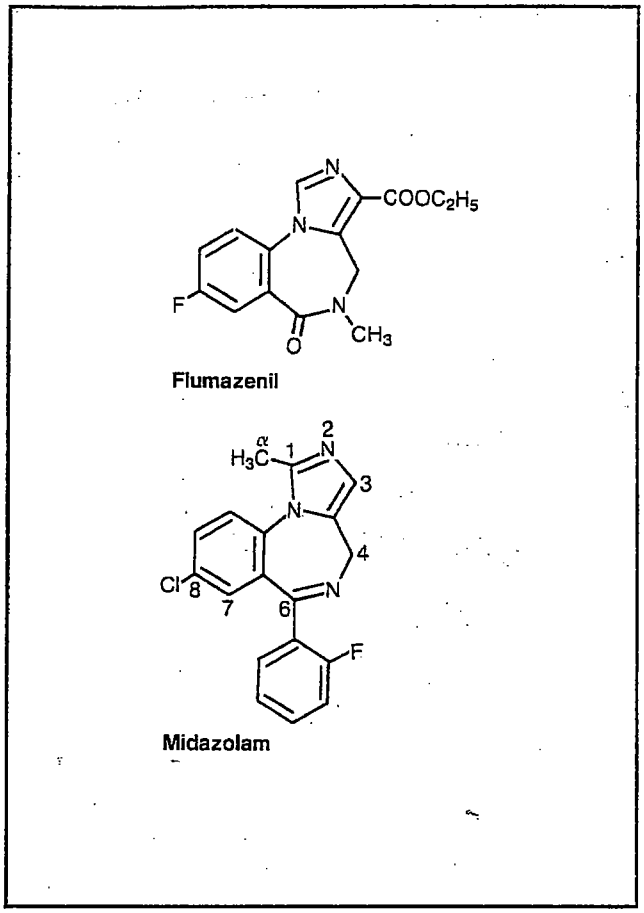

Fig. 2. Structural formulae of flumazenil (ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo [1,5-a] [1,4] benzodiazepine-3-carboxylate) and of midazolam (8-chlor-6-(2-fluorphenyl)-1-methyl-4H-imidazo [1,5-a] [1,4] benzodiazepine).

venously 5 to 60 minutes after an intravenous dose of a standard benzodiazepine sedative (flunitrazepam or midazolam). At the time of flumazenil administration the subjects were in a state of deep sedation with muscle relaxation, amnesia, and loss of lid reflex. Within approximately 60 seconds of flumazenil administration, all subjects were awake and oriented. The duration of their wakefulness depended on both the dose of flumazenil administered and the dose of the benzodiazepine.

In studies by Ziegler (personal communication), Lauven et al. (1982, 1985) and Schwilden et al. (1982), flumazenil was administered to subjects during continuous midazolam infusion after attainment of a pharmacokinetic and pharmacodynamic steady-state, at which the subjects were deeply asleep, as confirmed by the investigators' assessment of their psychometric test performance and the degree of sedation. In the study by Ziegler, midazolam was administered in a loading dose of 0.1 to 0.15 mg/kg followed by continuous intravenous infusion of 0.06 mg/kg/h for 5 hours. After attainment of the steady-state at 2 hours, the subjects received a single intravenous dose of flumazenil (0.125 to 1mg in 6 subjects; 0.1 mg/kg in 5 subjects). Within approximately 60 seconds the subjects showed a dose-dependent response to flumazenil, ranging from a slight weakening of midazolam effect after the lowest flumazenil dose (0.125mg intravenously) to full antagonism of the midazolam effect after doses of 0.375mg or more, with return to baseline levels of vigilance and orientation within 1 minute. Under continuing midazolam infusion, the duration of flumazenil effect was 2 to 3 hours, after which the sedative effect of the benzodiazepine gradually returned. In the study by Lauven a higher midazolam dose was used, i.e. a short infusion of 60mg over 10 minutes followed by a maintenance infusion of 16 mg/h. Steady-state levels of midazolam were attained at 1 hour, at which time the subjects were heavily sedated, with reduced β- and δ-activity in the EEG. After an intravenous injection of 10mg flumazenil the subjects awoke spontaneously within 28 to 48 seconds (fig. 4). The EEG returned to baseline status within, at most, 5 minutes, while performance scores at 15 and 30 minutes were the same as at baseline. Within a median period of 100 minutes the subjects became drowsy again, and were deeply asleep again within a median time of 145 minutes.

In other studies, flumazenil was administered either before or simultaneously with another benzodiazepine. When administered intravenously 10 minutes before midazolam, flumazenil 5mg prevented the appearance of CNS effects of intravenous doses up to 6mg, while intravenous midazolam doses higher than 6mg were shown by the EEG to override the antagonist effect of 5mg flumazenil (Gath et al. 1984).

Thus, the antagonist effects of flumazenil can be summarised as follows:

1. The effect of intravenously administered flu-

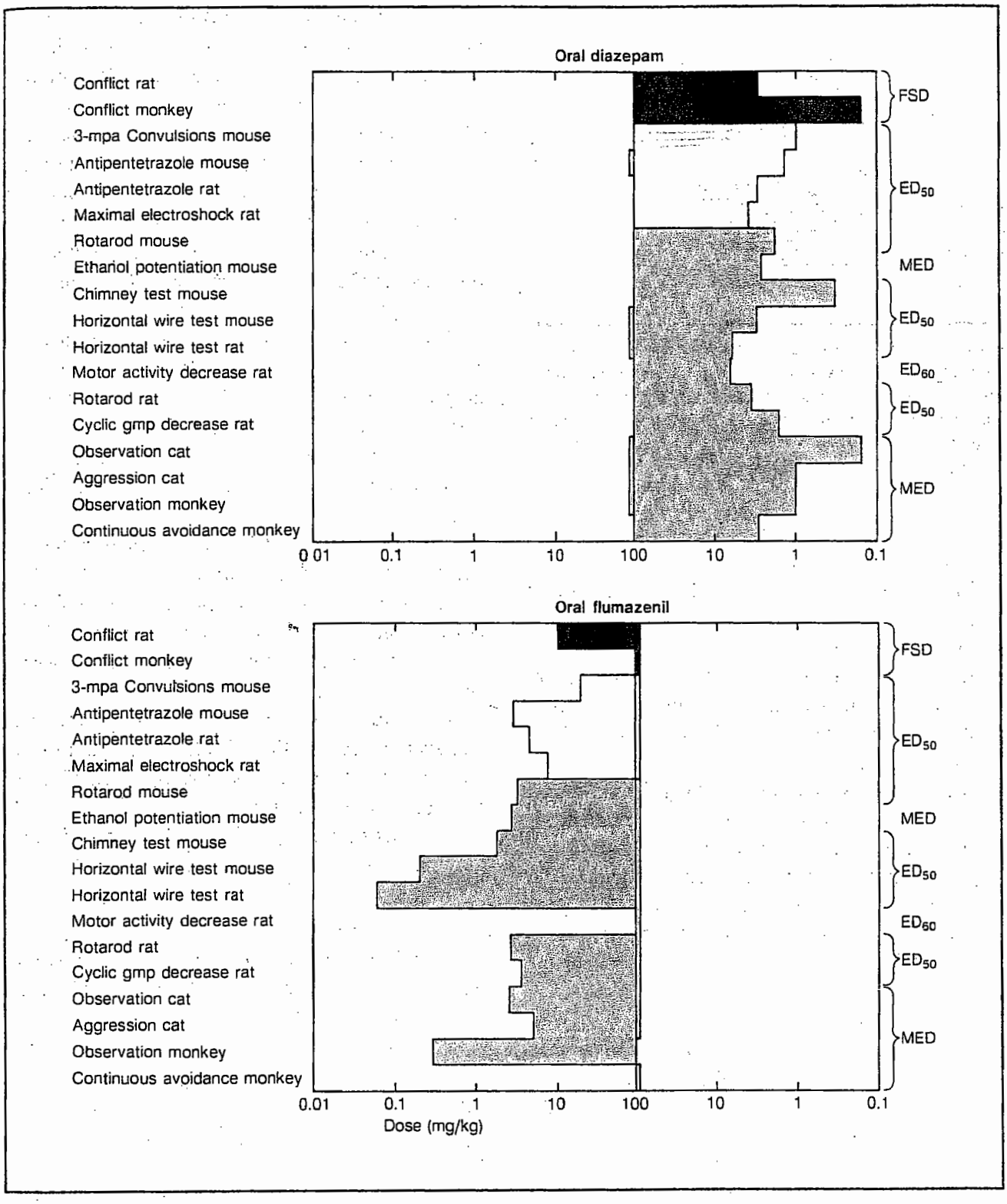

Fig. 3. Comparison of the pharmacological profiles of (a) the benzodiazepine agonist diazepam and (b) the benzodiazepine antagonist flumazenil after oral administration in various animal experiments [from Pieri (1986)].
Key: FSD = first significant dose; ED_{50} = effective dose 50%; MED = minimum effective dose 50%; ED_{60} = effective dose 60%; ■ = anxiolytic; □ = anticonvulsant; ▨ = central depressant. That part of graph to the left of 100 mg/kg dose indicates an antagonist effect of drug, to the right of 100 mg/kg dose shows an agonist effect.

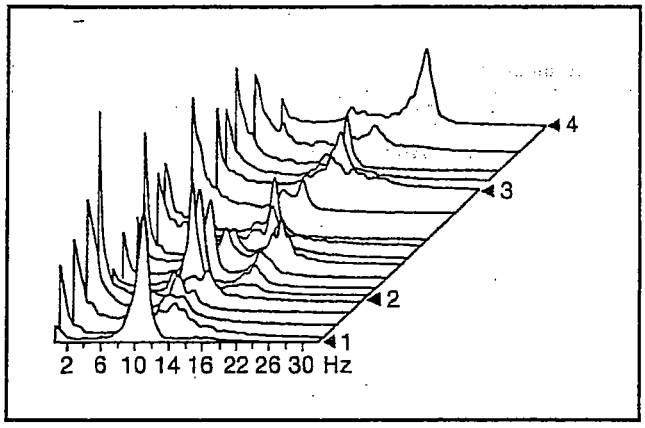

Fig. 4. EEG profile: power spectra following an intravenous bolus injection of 10mg flumazenil in a healthy subject during continuous midazolam infusion after attainment of midazolam steady-state (timepoint 1 = start of midazolam infusion; 2 = intravenous bolus of flumazenil; 3 = end of midazolam infusion; 4 = awake) [Schwilden et al. 1982].

mazenil is rapid in onset, generally within approximately 1 minute.

2. The degree and duration of effect of flumazenil depend on the dose of the benzodiazepine and the dose of the antagonist.
3. An intravenous dose of 0.25 to 0.5mg flumazenil is sufficient to antagonise a medium strength dose of a previously administered benzodiazepine.
4. A single intravenous dose of 5mg flumazenil inhibits the CNS effects of up to 6mg midazolam administered 10 minutes later; conversely, in the same study, intravenous administration of 6mg or more midazolam counteracted the antagonistic effect of the previously administered dose of 5mg flumazenil.

4.1.2 Intrinsic Effects

Animal studies have pointed to the existence of weak anticonvulsant effects of flumazenil (Albertson 1982; Cowen 1982; Grecksch et al. 1983; Jensen et al. 1983; Kaijima et al. 1983; Nutt & Cowen 1982; Robertson 1983; Robertson & Riwes 1983; Robertson et al. 1984; Vellucci & Webster 1983, 1984). These anticonvulsant effects are far less pronounced than those of diazepam and clonazepam, and depend on both the experimental conditions and the dose of flumazenil. Attempts to reproduce these findings in humans, however, have produced only a weak activity, which is probably of limited clinical relevance. Most studies in healthy human volunteers have shown little or no intrinsic effect of flumazenil administered alone. Those that have been observed consisted mainly of mild, nonspecific effects (e.g. increased alertness and improved performance after sleep deprivation) occurring at doses 10 times those administered for benzodiazepine antagonism in a clinical setting, i.e. after 10 to 100mg intravenously or 200mg orally.

Placebo-controlled EEG studies (Laurian et al. 1983, 1984; Schöpf et al. 1984) showed decreased amplitude of auditory evoked potentials, and decreased α- and θ-power after 5mg administered intravenously (Laurian et al. 1983; Schöpf et al. 1984) and 30 to 300mg administered orally (Laurian et al. 1984).

Sleep laboratory EEG recordings (Gaillard & Blois 1983) showed no significant changes in sleep parameters compared with placebo, apart from a slight reduction of phase 4 sleep duration. No effect of flumazenil on rapid eye movement (REM) sleep was observed.

After oral doses greater than 100mg, some benzodiazepine agonist-like effects (mild sedation) as well as subjective feelings were reported (Ziegler, personal communication).

In epileptic patients, flumazenil showed some anticonvulsant effects (Scollo-Lavizzari 1984).

4.1.3 Tolerability

Flumazenil exhibits benzodiazepine antagonist effects in humans under clinical conditions in doses as low as 0.3 to 1.0mg. Because it has restricted water solubility at low pH, it was possible to produce a water solution free of organic solubilisers, containing 1mg flumazenil in 10ml. This formulation permits administration of doses of up to about 5mg. At this dosage level, flumazenil is both locally and systemically well tolerated. Higher intravenous doses of up to 100mg flumazenil were studied using a different formulation containing propylene glycol and polyethylene glycol as organic solubilisers. Even in these high doses flumazenil

was well tolerated. The most frequently reported adverse event in human pharmacology studies involving approximately 300 subjects was dizziness, which was seen in 25 subjects at intravenous flumazenil doses in the range 5 to 10mg (Darragh et al. 1983, and unpublished data; Forster et al. 1983; Schöpf et al. 1984; Ziegler, unpublished data). The other most common events were facial erythema or flushing (Darragh, unpublished data; Laurian et al. 1983; Ziegler, unpublished data) in 20 subjects (dose range 5 to 60mg intravenously), anxiety (Schöpf et al. 1983) in 9 subjects (5 to 10mg intravenously), and headache (unpublished data) in 5 cases (20 to 30mg intravenously). All events were mild and short-lasting, usually disappearing within a few minutes. Most events were noted in subjects receiving intravenous bolus doses greater than 5mg.

No signs of benzodiazepine withdrawal effects were seen in any of the studies in healthy subjects, even when flumazenil was used in high doses to antagonise very high doses of benzodiazepines.

4.2 Pharmacokinetic Properties

Flumazenil is extensively distributed into tissues in humans, moderately bound to plasma proteins, and about equally distributed between plasma and blood cells (table I).

Because of a high hepatic blood clearance approaching hepatic blood flow, flumazenil is rapidly cleared from the body by metabolism, with an elimination half-life of around 1 hour. In urine, flumazenil is excreted only in the form of inactive metabolites.

The basic pharmacokinetic parameters, volume of distribution and clearance, were found to be independent of the dose tested over the extremely broad dose range of 2 to 100mg intravenously. Little intraindividual (fig. 5) or interindividual (fig. 6) variability was observed in the plasma concentration-time profiles.

The good predictability of the pharmacokinetic behaviour of flumazenil in the body and the fact that no interactions with benzodiazepines frequently used in anaesthesia (Klotz et al. 1985a,b; O'Boyle et al. 1982, 1983) have been observed provide the pharmacokinetic prerequisites for a favourable safety profile.

Mass balance studies confirm that flumazenil and its metabolites are rapidly and completely removed from the body. After hepatic metabolism as much as 60 to 70% of the dose is excreted as metabolites in the urine within 2 hours of administration. A radioactive dose was completely eliminated from the human body within 48 to 72 hours. The carboxylic acid derivative and its glucuronide conjugate were the only quantitatively important metabolites found in the urine. These two metabolites have no benzodiazepine antagonist effect.

4.3 *In Vivo* Binding of Flumazenil in Human Brain Investigated by PET

Positron emission tomography (PET) is a new, non-invasive technique which can be used to investigate binding characteristics of benzodiazepine at the benzodiazepine receptor '*in vivo*' in brain. Since 1983 the technique has been used to perform quantitative autoradiographic measurements of the

Table I. Pharmacokinetic parameters following intravenous administration of flumazenil to healthy volunteers (from Roncari et al. 1986)

Dose (mg)	No. subjects	Vd_{ss} (L/kg)	Vd_{β} (L/kg)	CL_p (L/h)	$t_{½\beta}$ (h)
20	6	1.23	1.38	72.12	0.96
40	6	1.11	1.27	72.48	0.82

Abbreviations: Vd_{ss} = volume of distribution at steady-state; Vd_{β} = volume of distribution during terminal elimination phase; CL_p = total plasma clearance; $t_{½\beta}$ = elimination half-life.

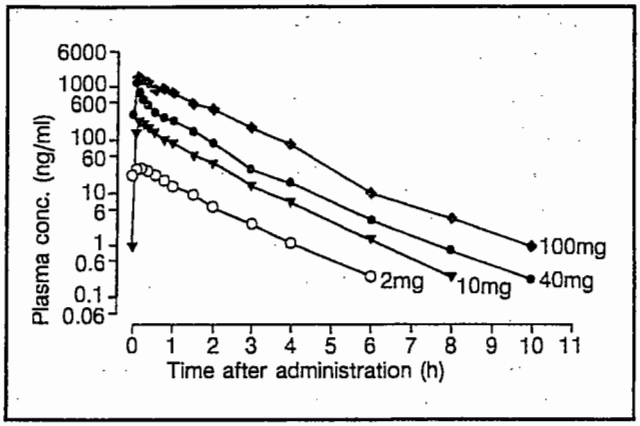

Fig. 5. Plasma concentration-time profiles of unchanged flumazenil following single intravenous doses of 2mg, 10mg, 40mg and 100mg flumazenil to a healthy subject.

binding of flumazenil to benzodiazepine binding sites.

Studies in humans (Mindus et al. 1986; Persson et al. 1985; Samson et al. 1985) have shown that flumazenil is bound with high affinity in cerebral regions known to be well endowed with benzodiazepine receptor sites, and that this concentration at the site of action attains and persists at a higher level than that in the blood. This is in keeping with the pharmacokinetic profile of flumazenil, which shows a large volume of distribution.

5. Clinical Experience in Anaesthesiology

Flumazenil has been administered to over 2000 patients, in all phases of clinical investigation, for the purpose of reversing benzodiazepine sedation administered to induce general anaesthesia or conscious sedation in a variety of contexts, e.g. in short therapeutic or diagnostic procedures. The benzodiazepines used were the standard compounds employed in clinical practice. Depending on the type and length of the operation, the patient received benzodiazepine for premedication, for induction of anaesthesia and for maintenance, midazolam being used for short procedures and flunitrazepam or diazepam for longer operations.

Overall analysis of these double-blind studies in both general anaesthesia and conscious sedation (table II) show that the effects of benzodiazepine-induced sedation were reversed within 5 minutes in 79 to 98% of patients who received flumazenil, compared with 25% of the patients who received placebo, regardless of procedure, benzodiazepine or anaesthetic used. Differences between flumazenil and placebo were usually sustained at a statistically significant level for up to 60 minutes after trial drug administration, by which time a lessening of the effect of the benzodiazepine and spontaneous awakening are usually to be expected. The clinical picture may, however, also be affected by other CNS depressants administered during anaesthesia, resulting in a slightly delayed response or only partial awakening.

5.1 General Anaesthesia

The overall results are illustrated by a double-blind, placebo-controlled study by Jensen et al. (1985) conducted in 40 patients who had undergone flunitrazepam-induced general anaesthesia for surgical resection of a slipped disc. A median dose of flumazenil 0.4mg (range 0.3 to 0.7mg) awoke all patients within 5 minutes. In contrast, only 35% of the placebo-treated patients (median dose 1.0mg equivalent) were awake at this time. The difference between the two treatments was statistically significant ($p < 0.001$, in favour of flumazenil) for up to 2 hours after trial drug administration for the parameters sedation, orientation and amnesia. There was also a significantly higher PaO_2 and significantly lower $PaCO_2$ in the active drug group compared with placebo in the immediate postoperative period.

Other authors have reported similar results in flunitrazepam-induced general anaesthesia. Tolksdorf et al. (1986) assessed the efficacy of flumazenil in a double-blind, placebo controlled study in 60 surgical patients. Five minutes after administration they found the flumazenil-treated patients to be significantly less sedated than those receiving placebo ($p \leq 0.01$), a difference which was maintained for up to 60 minutes. The flumazenil-treated patients were also better oriented at 15 minutes and showed less anterograde amnesia than the placebo group. At around 2 hours the sedative effect of flu-

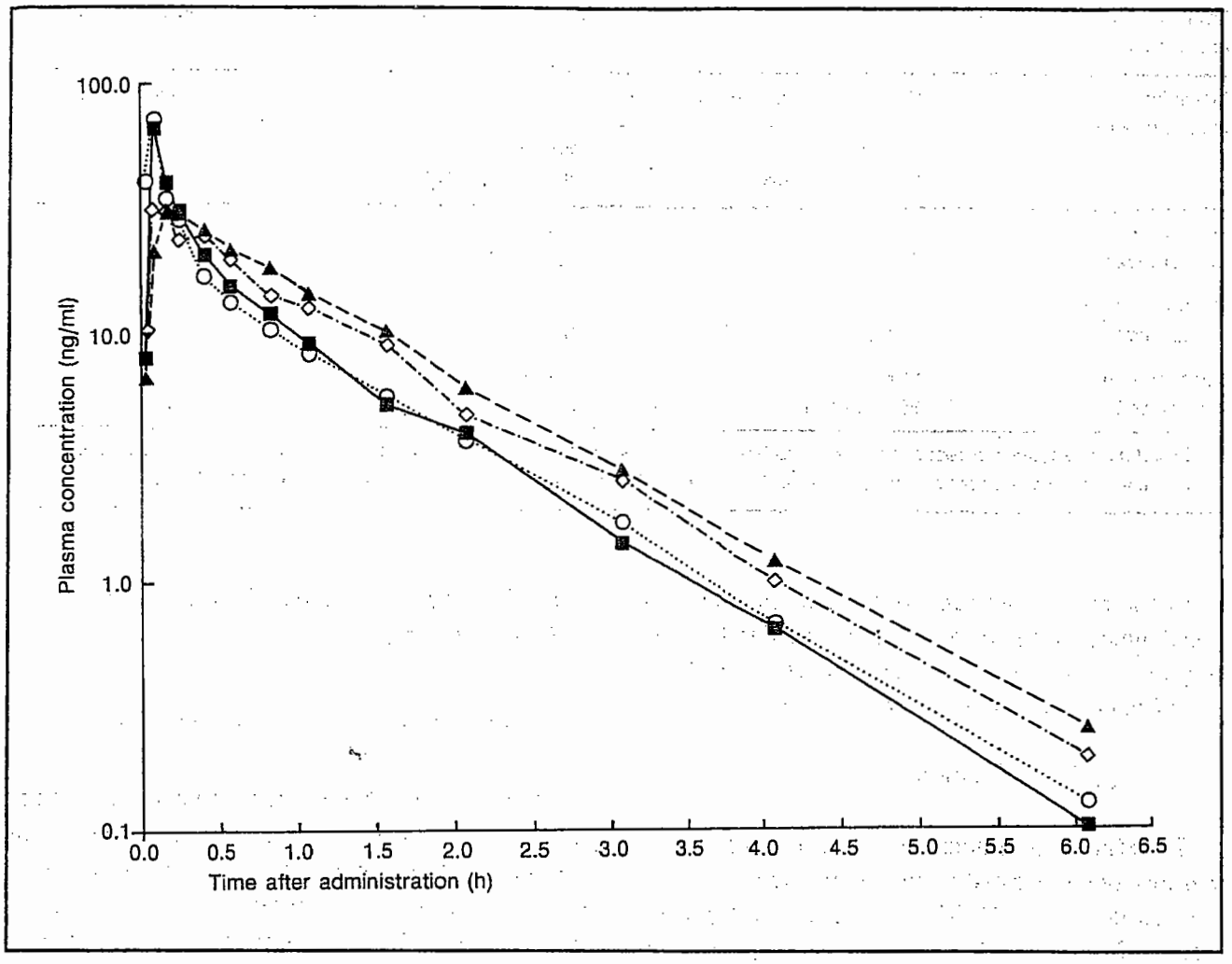

Fig. 6. Plasma concentration-time profiles of unchanged flumazenil following a single intravenous dose of 2mg to 4 healthy subjects.

nitrazepam had largely disappeared in both groups, as was to be expected.

These findings are corroborated by a study of identical design conducted by Ellmauer et al. (1986) in 57 patients undergoing routine vascular or thyroid surgery. A flumazenil dose of 0.1 to 1.0mg significantly reduced the hypnotic/sedative and amnesic effects of flunitrazepam compared with placebo ($p \leq 0.005$) for up to 60 minutes. By 120 minutes there was no longer a significant difference between groups.

A series of double-blind, placebo-controlled studies in midazolam-induced general anaesthesia have yielded an almost identical pattern of response to flumazenil: rapid awakening within 1 to 3 minutes and significant differences compared with placebo for all parameters of efficacy (sedation, cooperation, orientation and anterograde amnesia) [Hennius et al. 1986; Klausen et al. 1986a; Marx et al. 1986; Nicolau 1986; Ravlo et al. 1986; Waldvogel et al. 1986].

Of particular interest is the work reported by Chiolero et al. (1986). In an open study, 18 patients (ASA III) undergoing intracranial surgery for tumour or aneurysm received flumazenil to reverse the CNS effects of midazolam infusion used to induce and maintain general anaesthesia. Two minutes after administration of flumazenil, 14 of the 18 patients opened their eyes, and by 10 minutes 16 patients were extubated and speaking. Glasgow coma scores showed the same pattern for the first 10 minutes but decreased again thereafter. Use of

Table II. Summary of overall percentage of responders in double-blind, placebo-controlled clinical studies using flumazenil in anaesthesiology

Indication (induction agent)	Responders[a] at 5 min post-drug		p Value
	flumazenil median % (range)	placebo median % (range)	
General anaesthesia (flunitrazepam)	(n = 193) 79.0 (64-100)	(n = 199) 24.0 (17-52)	< 0.001
General anaesthesia (midazolam)	(n = 89) 80.0 (79-90)	(n = 89) 13.0 (7-23)	< 0.001
Conscious sedation (midazolam)	(n = 94) 98.0 (93-100)	(n = 97) 36.0 (18-60)	< 0.001

a *Definition of response:* a responder was a patient who, on a sedation rating scale of 0 to 4, was either (a) asleep (score 3-4) at baseline and awake or drowsy (score 0-2) at 5 min, *or* (b) drowsy (score 2) at baseline and awake (score 0-1) at 5 min.

a benzodiazepine antagonist in these patients enabled neurological assessment immediately after surgery, an obvious advantage in patients in whom neurological status may be of concern.

5.2 Conscious Sedation

The efficacy of flumazenil in conscious sedation was also demonstrated in studies by Geller (1986a) and Knudsen et al. (1986). In an open study Geller treated 74 patients following short diagnostic or therapeutic procedures (minor orthopaedic surgery, bronchoscopy, cystoscopy, gastroscopy, cardioversion, intracardiac catheter ablation, cardiac catheterisation) under conscious sedation or local/regional anaesthesia induced with either midazolam or diazepam. Flumazenil was administered in intravenous bolus doses of 0.1mg at 30-second intervals. A dose of between 0.1 and 0.6mg awoke all patients within 1 to 2 minutes.

The double-blind, placebo-controlled study by Knudsen et al. (1986) was conducted in 40 outpatients who had undergone diazepam-induced sedation for gastroscopy. Flumazenil or a matching placebo was given in a dose of 0.2mg at 1-minute intervals. At 5 minutes 80% of the flumazenil-treated patients were awake, compared with 50% in the placebo group, this difference being statistically significant ($p < 0.05$).

6. *Clinical Experience in Intensive Care Patients*

6.1 Benzodiazepine Overdose or Intoxication

Flumazenil has been used to diagnose and manage benzodiazepine intoxication in unconscious patients in intensive care or admitted to the emergency room. Of the 141 patients reported here, 54 were found to be pure benzodiazepine overdose cases, 77 had taken a variety of intoxicants (e.g. alcohol, heroin, tricyclic antidepressants, acetylsalicylic acid), and 10 were unconscious as a result of ingesting agents other than benzodiazepines. Thus, the majority were mixed-drug overdoses, usually taken with suicidal intent. In cases of self-inflicted poisoning it is often difficult to obtain reliable information from the patient or from toxicological tests as to the drugs and doses taken. However, many of the patients in these studies admitted having taken extremely high doses of various compounds, for example, diazepam in a dose range of 100 to 10,000mg (Hofer & Scollo-Lavizzari 1985; Scollo-Lavizzari 1983).

All of the 54 patients who were unconscious as a result of pure benzodiazepine overdose were restored to consciousness within 5 minutes of administration of 0.2 to 1.0mg flumazenil.

6.2 Interruption or Termination of Long Term Benzodiazepine Sedation

6.2.1 Reversal of Long Term Benzodiazepine Sedation

Flumazenil was used to interrupt or terminate benzodiazepine effects in patients in intensive care who had been kept under benzodiazepine sedation for periods ranging from several hours to days.

In one double-blind study in patients recovering from open heart surgery (Louis et al. 1984), 10 of 10 patients in the flumazenil group and none of the 10 in the placebo group awoke within 5 minutes of administration of the trial medication ($p < 0.001$).

In 6 open studies (Geller et al. 1986c, Kleinberger et al. 1985; Ritz 1985, unpublished data), as measured by the degree of sedation, all patients in whom benzodiazepine sedation was the reason for unconsciousness awoke completely after administration of flumazenil. Thus, 84% of the patients studied awoke completely after administration of flumazenil, and there was a clinically significant improvement, but without full awakening, in 4 cases (8%). Four patients (8%) failed to show a clinically significant response. The 8 patients who failed to respond sufficiently were unconscious as a result of severe illness or serious injury (hydrocephalus in one, head injury in five, respiratory failure in two). Furthermore, in 2 of the 4 non-responders in one study, continuous infusion of midazolam was maintained during and after flumazenil administration.

In one study (Geller, personal communication) 3 unconscious patients showed signs of restlessness which the investigator regarded as a possible paradoxical reaction to previously administered benzodiazepines, although other causative factors were also present (brain biopsy in a patient with dementia, drug addiction in one patient). After reversal of sedation by flumazenil these symptoms were absent. Since the origin of these reactions is unclear, their disappearance cannot be attributed with certainty to a direct effect of flumazenil.

6.2.2 Weaning from Mechanical Ventilation

Benzodiazepines are widely used for sedation to enhance acceptance of endotracheal intubation and mechanical ventilation but, in the high doses used in this setting, these drugs diminish both the central respiratory drive and the strength of respiratory muscles, and so make weaning even more difficult (Kleinberger et al. 1985). Two studies, by Kleinberger et al. (1985) and Ritz (1985), specifically addressed the question of using flumazenil to facilitate weaning from the respirator. Benzodiazepine-induced sedation was reversed in all patients. In the study by Kleinberger et al. (1985) all 7 patients began spontaneous breathing after 1 to 7 minutes and were put on continuous positive airway pressure. Weaning failed in 2 cases in whom continuous positive airway pressure was not tolerated. In the Ritz study all 6 patients to whom flumazenil was given to facilitate the return to spontaneous respiration could be weaned from the respirator in a considerably shorter time than usual.

7. Duration of Flumazenil Effect

The duration of action of flumazenil is dictated by several factors, chief of which are the dose of flumazenil, the time elapsed since the benzodiazepine agonist was given, and the dose and elimination half-life of the previously administered benzodiazepine. After administration of an intravenous dose of 10 to 15mg midazolam or 5 to 12mg diazepam for conscious sedation, or of 15 to 25mg midazolam for general anaesthesia, flumazenil doses of the order of 0.5mg or below will reverse sedation and prevent its recurrence. However, after higher doses of flunitrazepam (≥ 2mg) in general anaesthesia, slight sedation was not infrequently seen, although this could be abolished by a second injection of a low dose of flumazenil.

In intensive care, CNS depression may persist for considerably longer because of high short or long term benzodiazepine dosing and involvement of multiple concomitant medications. In the case of intoxication with high doses of benzodiazepines (e.g. 200 to 2000mg diazepam) a single intravenous injection of 1 to 2mg flumazenil is sufficient to

maintain consciousness for 20 to 45 minutes. However, in intensive care use, a temporary awakening is in many cases sufficient for diagnostic or treatment purposes. Nonetheless, should a longer awakening be required, flumazenil may be administered in repeated intravenous bolus doses or as an infusion of 0.1 mg/h (Geller, personal communication; Geller et al. 1985a,b; Kleinberger et al. 1985; Scollo-Lavizzari 1983). The albeit limited experience in this regard suggests that, by this means, the effect of benzodiazepine agonists may be fully counteracted until its spontaneous resolution (Geller, personal communication).

8. *Safety Profile*

The clinical situations in which patients require flumazenil as a benzodiazepine antagonist are, by definition, states of increased risk. Postsurgical patients, injury victims, patients in intensive care, and those with intentional or accidental intoxications may present multiple complicating factors, including instability of vital signs and psychological trauma. Furthermore, an accurate history may not be available for some patients, such as those admitted to the emergency room in a comatose state. In the reference population for the safety overview presented here, which numbered over 1700 closely monitored patients in anaesthesiology or intensive care, flumazenil was exceptionally well tolerated, as outlined in the following more detailed sections.

8.1 Adverse Events

The most frequent individual adverse events in both indications are shown in table III. Flumazenil was generally well tolerated, even by high-risk patients.

In anaesthesiology, adverse events were observed in 21% of patients receiving flumazenil and in 10% of patients receiving placebo in double-blind studies, and in 11% of patients in open studies. The majority of adverse events were of short duration and were rated by the investigators as slight or moderate. Nausea and/or vomiting, either alone or in combination, were the most frequently reported adverse event(s) in both treatment groups, accounting for about 50% of all adverse events reported. Although in general anaesthesia studies the overall incidence of nausea and/or vomiting was greater in flumazenil-treated patients, there was no significant difference between flumazenil and placebo in the number of patients that actually vomited. In the studies in conscious sedation, very few patients reported nausea and/or vomiting, suggesting that the larger number of these events seen in the anaesthesia studies may be related to the type of agents used (e.g. opioid analgesics) or to the surgical procedure.

In intensive care patients adverse events possibly or probably related to flumazenil were seen in 20% of those with pure benzodiazepine overdose (iatrogenic or intentional), 27% of those under long term sedation, 39% of those with multiple intoxications (usually suicide attempts), and 9% of patients in coma not due to benzodiazepine overdose. This distribution reflects (a) the extremely high doses of intoxicants taken by patients with suicidal intent, and (b) possible unmasking of the toxic effects of the other compounds ingested. The single most frequent event was agitation, followed by discomfort (unspecified), tears, cold sensation, and anxiety. Most events were mild to moderate in degree, and did not require remedial measures.

8.2 Benzodiazepine Withdrawal Effects

Since use of flumazenil as a benzodiazepine antagonist presupposes previous administration of a benzodiazepine agonist, the reported adverse events were carefully screened for possible benzodiazepine withdrawal effects. Adverse events that could not be excluded as possible benzodiazepine withdrawal effects were reported in 14 of the 1700 patients surveyed, as follows.

In anaesthetic use possible benzodiazepine withdrawal symptoms were observed in 9 patients following the administration of flumazenil. These were generally nonspecific in nature, consisting of symptoms of anxiety, tenseness, fear or confusion in almost all cases. Four occurred in 2 early studies

Table III. Most frequent adverse events in anaesthesiology and intensive care (expressed as number and percentage of flumazenil-treated patients)

Adverse event	Anaesthesiology (n = 1567)		Intensive care (n = 215)	
	[no.]	(%)	[no.]	(%)
Nausea and/or vomiting	170	(10.8)	2	(0.93)
Tremor	10	(0.64)		
Involuntary movements	9	(0.57)		
Dizziness	8	(0.51)	1	(0.46)
Agitation			14	(6.5)
Discomfort			10	(4.6)
Tears	11	(0.7)	9	(4.2)
Anxiety	6	(0.38)	9	(4.2)
Cold sensation	2	(0.13)	7	(3.3)

using a single high dose of flumazenil, a dosage technique that was later superseded by the dose titration procedure described in section 9. In 7 of these cases the symptoms were more probably a result of the patients' waking in anxiety-provoking situations. In the remaining 2 cases, the diagnosis of a benzodiazepine withdrawal effect is questionable because neither patient had been on long term benzodiazepine treatment. These states could be reversed by a low dose of benzodiazepine or, in the case of one chronic alcoholic, a small dose of ethanol.

Amongst the total of 215 patients in intensive care who received flumazenil, one probable (0.5%) and 4 possible (2%) benzodiazepine withdrawal symptoms were reported. These consisted of convulsions (2 cases, both in epileptic patients), myoclonic seizures (1 case in a tracheotomised patient), and agitation (2 cases, both in ventilated patients with head trauma). All occurred after high and/or long term benzodiazepine dosing. Three of these 5 events occurred after high intravenous bolus doses of flumazenil (> 2.5mg) in early studies before the flumazenil administration procedure was revised to provide for more gradual reversal of benzodiazepine effect. This is particularly important in patients who have received high and/or long term benzodiazepine doses and who are therefore at greater risk of experiencing withdrawal symptoms.

Thus, on the basis of these findings, under normal clinical conditions of flumazenil use, benzodiazepine withdrawal effects do not appear to present a problem.

8.3 Other Measures of Safety, and Safety in High-Risk Patients

Other measures of safety (local tolerance signs, laboratory parameters, vital signs) remained uninfluenced by flumazenil, showing only isolated changes not identifiable with an effect of the antagonist. Cardiovascular parameters remained stable even in patients at greater risk, such as those with cardiac or valvular disease undergoing cardiac catheterisation, cardioversion or intracardiac catheter ablation (Geller et al. 1986a,b), in high-risk surgical patients (Urdinovic 1986), and in patients recovering from open heart surgery (Louis et al. 1984) or other types of cardiovascular surgery (Klausen et al. 1986b).

9. Dosage and Administration

As a basic principle, the dosage of flumazenil should be titrated individually to allow achievement of the optimal effect. In studies in anaesthetic and intensive care use, it was found that intravenous flumazenil doses of 0.2 to 0.5mg sufficiently reduced the degree of sedation to yield a level of consciousness deemed appropriate to the individ-

ual patient's state, while an intravenous dose of 0.5 to 1.0mg was usually sufficient to completely abolish the effect of a therapeutic dose of a benzodiazepine. Thus, the reversal of the effects of benzodiazepine may be full or partial, depending on the individual patient. In the emergency room, in patients in whom the reason for unconsciousness is not known, failure to respond to intravenous flumazenil doses above 5mg may indicate the involvement of intoxicants other than benzodiazepines, or signal the presence of functional or organic disorders.

10. Place of Flumazenil in Clinical Practice

Nearly a quarter of all deaths related to anaesthesia occur in the postanaesthetic recovery period. Most of them are related to persisting sedation, which entails the risk of life-threatening complications, such as hypoventilation due to obstruction of the upper or lower airways (Harrison 1978; Hecker & Wartotsch 1979; Special Committee Report 1970). This may occur as a result of bronchial hypersecretion, obstruction of the throat by the tongue, aspiration of vomit by the unconscious patient in the absence of the protective cough reflex, and drug-induced respiratory depression. A return to normal ventilatory function usually occurs concomitantly with the awakening from anaesthesia.

In postsurgical patients or those undergoing other procedures under benzodiazepine sedation, flumazenil induces awakening from benzodiazepine-induced anaesthesia or sedation within 5 minutes, in contrast to the 30 to 120 minutes required for spontaneous awakening by placebo-treated patients. Thus, patients rouse to such an extent that respiratory function normalises, and reflexes and muscular control return, thereby decreasing the risk of complications during the postoperative period.

Patients admitted to intensive care or the emergency room are, by definition, a high-risk group, requiring prompt and usually intensive therapeutic measures. The reasons for their admission are varied, and include intentional or accidental intoxication, severe functional or organic disorders, injury, coma, or major surgery.

In cases of intoxication, first-line treatment entails dealing with life-threatening consequences and reversing sedation with its inherent risk of complications. However, the cause of unconsciousness is often unknown, and the standard treatment measures (gastric lavage, dialysis, activated charcoal) are neither immediate nor specific in effect. Benzodiazepines figure relatively frequently amongst the agents taken in intentional overdose. Since clinical studies have shown 100% efficacy of flumazenil in reversing pure benzodiazepine-induced sedation within 5 minutes, the antagonist may be used as a primary diagnostic tool when benzodiazepine overdose is suspected, with the advantage that benzodiazepine intoxication can be confirmed or excluded almost immediately.

Even when the benzodiazepine is only one component of a mixed intoxication, many patients arouse sufficiently after flumazenil administration to provide details of the intoxicants taken. Once a benzodiazepine intoxication has been identified it can be decided whether it would be safe to allow the patient to relapse into sleep, or whether the risk of complications resulting from the sedation makes it desirable to keep the patient awake or only slightly sedated. Flumazenil may be administered in repeated single doses selected according to the degree of sedation required or given by infusion until the effect of the benzodiazepine has become dissipated by metabolism.

A further practical advantage of clinical benefit to the patient is the fact that, in the conscious patient, gastric lavage may be performed without prior intubation. Furthermore, prolonged intubation and/or mechanical ventilation can be avoided; a point of particular importance in elderly or debilitated patients.

Many patients in intensive care require long term sedation to reduce anxiety connected with their illness or the impersonal setting, or for mechanical ventilation. Benzodiazepines are often used for this purpose. In this context, it is often necessary to interrupt sedation in order to evaluate the patient's condition, or to terminate sedation, such

as when weaning from the respirator. Flumazenil was used for this purpose under standard conditions in the intensive care unit in 7 studies. It was found to be completely effective in reversing benzodiazepine-induced sedation. Moreover, it facilitated weaning of ventilated patients from the respirator, reducing to a few hours a process which can often take days owing to the respiratory-depressant effects of persisting benzodiazepine concentrations.

11. Conclusion

Flumazenil provides a safe and effective means of attenuating or reversing the CNS-depressant effects of benzodiazepines whenever indicated, e.g. following benzodiazepine-induced general anaesthesia, or conscious sedation, or after benzodiazepine overdose, either alone or in combination with other agents. Its reliability of effect and specificity for benzodiazepines also allow its use for diagnostic purposes, e.g. to detect or exclude benzodiazepine intoxication in patients with consciousness impairment of unknown origin. It should be borne in mind, however, that the convenience and relative safety of flumazenil do not free the clinician from the responsibility to exercise clinical judgement in the treatment of each patient, in keeping with good clinical practice.

Experience with flumazenil to date indicates that the antagonist may be used with advantage when a benzodiazepine effect is unexpectedly intense or long lasting, or when it is in the patient's interest to be awoken earlier than originally planned. It is expected that the role of flumazenil will continue to develop as it becomes more widely available and as clinical practice delineates the situations in which its use is of greatest benefit to the patient.

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