BENZODIAZEPINES AS ORAL PREMEDICANTS

J. KANTO

SUMMARY

The advantages of the benzodiazepines as oral premedicants are: clear anxiolytic and sedative effect; less clear amnesic action which may prevent the recall of the time spent lying on an uncomfortable theatre trolley, but not necessarily recall of the journey to the operating theatre, or induction of anaesthesia; convenient route of administration; long duration of action of 5—8 h which simplifies timing of drug administration; adverse autonomic, hormonal and circulatory system reactions seem to be prevented, thus preventing the stress reaction even before induction of anaesthesia; anticonvulsant and muscle-relaxing actions may be of value in patients receiving local anaesthesia, or in preventing the side-effects of depolarizing muscle relaxants; nausea before and after operation may be decreased; reduced frequency of side-effects before and after operation.

Objects of premedication

The aim of premedication is to establish mental and emotional relaxation, reduce sensory input and metabolic rate and antagonize adverse reactions of the autonomic nervous system (Collins, 1976). The use of morphine before anaesthesia was suggested by Lorenzo Bruno in 1850 (Collins, 1976) and since then, narcotics have been used extensively (Collins, 1976). However, potent analgesics should only be given to patients with pain since, otherwise, a state of dysphoria may result (Cohen and Beecher, 1951; Collins, 1976). The routine use of anticholinergics has also been questioned (Mirakhur, Dundee and Connolly, 1979) especially in the elderly (Roberts, 1976). Since 1965 there has been an increased use of oral premedicants, especially benzodiazepines (Dundee and Haslett, 1970) and it has been suggested that oral administration might be more satisfactory than i.m. (McCaughey and Dundee, 1972; Dundee, Lilburn et al., 1977; Lindgren, Saarnivaara and Himberg, 1980). The high frequency of venous sequelae after i.v. administration favours the oral route of administration (Dundee, 1979). Benzodiazepines are useful premedicants since they can reduce apprehension, excitement and autonomic nervous system reactions before anaesthesia and surgery (Dundee and Haslett, 1970).

The preoperative visit by the anaesthetist has been shown to reduce anxiety (Leigh, Walker and Janaganathan, 1977), but for optimum effect the visit should be combined with medication (Norris and Baird, 1967). Psychological benefits may last up to 18 h after the visit (Egbert et al., 1963) and the anaesthetist should not underestimate the value of this procedure (Eckenhoff and Helrich, 1958). No reduction in anxiety was found when the sole addition to atropine was a barbiturate (Cohen and Beecher, 1951; Eckenhoff and Helrich, 1958). It has even been stated by patients that anaesthetists are clever doctors who lack emotional impact (Sheffer and Greifenstein, 1960).

Since potent induction agents are now available the primary aims of premedication and the preoperative visit are to reduce patient's fears and to prevent stress reactions beginning even before induction of anaesthesia. The use of benzodiazepine derivatives as oral premedicants is reviewed here with special reference to their anti-anxiety property.

Oral v. other routes of administration

At physiological pH, all benzodiazepines are highly lipid-soluble and fairly rapidly and almost completely absorbed after oral ingestion (Bellantuono et al., 1980). After i.m. injection, absorption of diazepam (Kanto, 1975) and chloridiazepoxide (Greenblatt, Shaler et al., 1978) is slow and erratic, possibly because of crystallization at the injection site. In contrast, lorazepam (Elliot, 1976), flunitrazepam (Clarke et al., 1980), and clorazepate (Rey et al., 1979) are absorbed more rapidly following i.m. than after oral administration. Following i.v. injection, a rapid and
reliable sedative effect has been found after diazepam, chlordiazepoxide and flunitrazepam, but subjects to whom lorazepam was given orally appeared to be as sedated as those to whom it had been administered i.m. or i.v. (Elliot, 1976). The reason for the slow onset of action of lorazepam appears to be its slow penetration of the blood–brain barrier (Aaltonen, Kanto and Salo, 1980) and similarly, its placental transfer is retarded compared with diazepam (Kanto, Aaltonen et al., 1980).

After i.m. injection, prolonged pain at the injection site has been reported for each compound, sometimes lasting weeks (Kanto, 1975; Greenblatt, Shader et al., 1978a; Dundee et al., 1979; Clarke et al., 1980). Local sequelae following i.v. injection were less with flunitrazepam than with diazepam (Hegarty and Dundee, 1978). Both these side-effects support the oral use of benzodiazepines as premedicants. Rectal administration of diazepam in solution is reliable, but suppositories result in variable plasma concentrations (Kanto, 1975; Knudsen, 1977).

**Interactions**

Antacids reduce the rate (diazepam and chlordiazepoxide) or both the rate and amount (nordiazepam from chlorazepate) of benzodiazepines reaching the systemic circulation (Greenblatt, Shader et al., 1978; Greenblatt, Allen et al., 1978; Bellantuono et al., 1980). However, this effect on the absorption of diazepam seems to depend on the nature of the antacid (Nair et al., 1976).

The addition of morphine, pethidine or atropine to oral diazepam premedication resulted in slower gastrointestinal absorption, while the addition of metoclopramide increased the rate of absorption and resulted in greater plasma diazepam concentrations (Gamble et al., 1976). Oral administration of ethanol and diazepam was associated with greater plasma diazepam concentrations and a smaller volume of distribution than after diazepam alone and the pharmacological effects of diazepam were potentiated (MacLeod et al., 1977). Cimetidine also potentiated the sedative effect of diazepam (Klotz and Reimann, 1980), while disulfiram decreased the clearance of diazepam and chlordiazepoxide, but not that of oxazepam (MacLeod et al., 1978).

In general, all benzodiazepines increase the central depressant effect of other sedatives, hypnotics, antipsychotic drugs and tricyclic antidepressants, especially at the start of treatment (Burrows, 1976).

**Effect of age and disease**

In full-term and, especially, in premature infants, capacity for metabolizing benzodiazepines is limited and long-lasting sequelae are possible (Morselli, 1976; Kanto, 1980). Similarly, an increased frequency of side-effects has been reported in the elderly (Bellantuono et al., 1980).

Oxazepam and lorazepam do not need oxidative metabolism before glucuronidation and there may be no change in their distribution and elimination with increasing age or in disease (Shull et al., 1976; Verbeeck et al., 1976; Odar-Cederlöf et al., 1977; Kraus et al., 1978; MacLeod et al., 1978). In contrast, both age and disease cause marked changes in the pharmacokinetics of diazepam, chlordiazepoxide, nitrazepam and chlorazepate (Klotz et al., 1975; Kangas et al., 1976, 1979; Greenblatt, Shader et al., 1978; Kanto, Mäenpää et al., 1979; Klotz and Müller-Seydlitz, 1979; Ochs et al., 1979) resulting in an increased drug effect. In addition to kinetic changes, there is apparently an increased sensitivity to sedatives in old age and benzodiazepines should be used in reduced doses (Bellantuono et al., 1980).

Curiously, the rate of absorption of diazepam from the gastrointestinal tract has been found to be faster in subjects with a high neuroticism score than in those with a low score (Nakano, Ogawa and Kawazu, 1980). This may have clinical significance because the rapidity of increase in concentration, rather than the absolute value, seems to determine the subjective drug effect of the benzodiazepines (Bliding, 1974).

**Anxiolysis**

Anaesthesia and surgery constitute great psychic stress in any patient. The effectiveness of drugs given before operation on this transient anxiety and on autonomic nervous system reactions can be evaluated and compared, because the primary goal is to free the patient from fear, restlessness and autonomic reactions (Forrest, Brown and Brown, 1977; Kanto, Kangas and Mansikka, 1979). The overall frequency of anxiety before anaesthesia is 40–60% (Norris and Baird, 1967). Using an extensive psychological questionnaire, as many as 80% of patients were anxious (Corman et al., 1958). A greater frequency has been found in females than in males, in females less...
than 70 kg more often than in females over this weight and in patients receiving sedative drug therapy (Norris and Baird, 1967). In orthopaedic patients, anxiety remained greater for several days after surgery, but women undergoing elective gynaecological operations were more anxious on the day before admission to hospital than on the day before surgery (Johnston, 1980). Thus, in selected cases, the anxiety-relieving efforts should last longer than is generally the case.

A positive correlation between anxiolysis and ease of induction of anaesthesia has been reported (Lindgren, Saarnivaara and Himberg, 1980), which supports the importance of the anxiolytic component of premedication. Relief of apprehension may reduce excessive hormonal and circulatory response to anaesthesia and may reduce the minimum effective dose of anaesthetic agents (Male et al., 1980).

In comparison with placebo or no premedication, oral flunitrazepam 1-2 mg (Kanto, Kangas and Mansikka, 1979; Male et al., 1980), nitrazepam 5 mg (Kangas, Kanto and Mansikka, 1977), lorazepam 2.5-5 mg (Male et al., 1980) and chlordiazepoxide 25-50 mg (Brandt, Lui and Briggs, 1962) have produced significantly greater anxiolysis. Oral medazepam 10 mg (Assaf, Dundee and Bali, 1975; Herbert, Bourke and Rose, 1979), diazepam 10-20 mg (Assaf, Dundee and Bali, 1975; Male et al., 1980) and oxazepam 30 mg (Mansikka et al., 1979) have failed to alleviate fear in some studies. The high placebo response resulting from frequent visits to patients has been thought to affect these results (Assaf, Dundee and Bali, 1975). However, in patients undergoing conservative dentistry, medazepam was effective in allaying apprehension (Hailey and Baird, 1979).

Better anxiolysis can be induced in children aged less than 5 yr with drugs other than benzodiazepines such as trimeprazine or triclofos. However, in older children benzodiazepines are useful (Haq and Dundee, 1968; Boyd and Manford, 1973; Lindgren, Saarnivaara and Himberg, 1980) and better than oral premedicants such as phenobarbitone and trimeprazine (Gordon and Turner, 1969). In anxious children, the significance of preoperative crying and tachycardia in increasing bleeding after adenotonsillectomy has been established (Haq and Dundee, 1968). In contrast, it has been reported that the behaviour of unsedated children in the anaesthetic room was comparable to that of children given sedative premedication. Therefore, unsedated children should be included in premedication studies (Beeby and Hughes, 1980).

The anxiolytic effect of oral diazepam 10 mg was comparable to that of oxazepam 30 mg (Kanto, Iisalo et al., 1979), lorazepam 2 mg (Paymaster, 1973) and pentobarbitone 100 mg (Hovi-Viander, Kangas and Kanto, 1980) and there were no great differences in the effects of these agents as oral premedicants. Similarly, there was no difference between diazepam 5 mg and pentobarbitone 60 mg as rectal premedicants in small children (Kanto, Iisalo et al., 1980). However, in another study, both oral lorazepam 3 mg and diazepam 10 mg caused significantly fewer preoperative side-effects than heptabarbitone 400 mg (Wilson and Ellis, 1973). Generally, the anxiolytic property of benzodiazepines has been considered to be superior to that of barbiturates (Zimmermann-Tansella, Tansella and Lader, 1979).

We found no difference in anxiolytic response between flunitrazepam 2 mg and lorazepam 2.5 mg (Mansikka, Kangas and Kanto, 1980) and flunitrazepam 1 mg and oxazepam 30 mg (Pakkanen, Kangas and Kanto, 1981). In contrast, the frequency of restlessness and apprehension has been found to be less with flunitrazepam 1-2 mg than with lorazepam 2.5-5 mg or fosazepam 40, 60 or 80 mg (Dundee, Johnston et al., 1977). The author's opinion is that the clinically important property of flunitrazepam is its anxiolytic effect (Kanto, Kangas and Mansikka, 1979). Similarly, in a placebo-controlled study we found tofizopam to be a highly anxiolytic agent, but there was no significant difference between nitrazepam and placebo (Pakkanen et al., 1980).

In general, oral benzodiazepines seem to be effective in reducing anxiety before anaesthesia and surgery. This is important because less anxiety means safer surgery (Johnston, 1980).

Sedation

Sedation is by no means synonymous with lack of anxiety. However, it has been considered a useful property of premedicant drugs (Collins, 1976). Generally, it is easy to differentiate the sedative effect of the oral benzodiazepines from that of placebo (Assaf, Dundee and Bali, 1975; Kanto, Kangas and Mansikka, 1979; Mansikka et al., 1979; Male et al., 1980; Pakkanen et al., 1980).

In an uncontrolled study, chlordiazepoxide 50 mg orally alleviated apprehension effectively.
and caused evident sedation without alteration in arterial pressure or respiration. A dose of 25 mg was less good (Coppolino and Wallace, 1961). As a sedative, diazepam 10 mg is equivalent to lorazepam 2–2.5 mg (Paymaster, 1973; Dundee et al., 1979) or 3 mg (Wilson and Ellis, 1973) and to 30 mg of oxazepam (Kanto, Iisalo et al., 1979). It is, however, superior to 10 mg of medazepam (Assaf, Dundee and Bali, 1975). Similarly, diazepam 10 mg and lorazepam 3 mg were comparable to pentobarbitone 100 mg (Hovi-Viander, Kangas and Kanto, 1980) and heptobarbitone 400 mg (Wilson and Ellis, 1973). In children, diazepam 5 mg was as sedative as oxazepam 15 mg (Kanto, Iisalo et al., 1979).

Nitrazepam 5 mg caused markedly more sedation than placebo, but there was no difference between tofizopam 100 mg and placebo in this respect (Pakkanen et al., 1980). The degree of sedation obtained after two different doses of nitrazepam (5 and 10 mg) was comparable to that after one tablet of Mandrax (methaqualone 250 mg + diphenhydramine 25 mg) but postoperative emetic sequelae were greater with the larger dose of nitrazepam in comparison with the two other premedicants (Norris and Telfer, 1969).

Oral lorazepam 2 mg was comparable to nitrazepam 5 mg, while lorazepam 4 mg was similar to nitrazepam 10 mg (Norris and Wallace, 1971). Lorazepam 2 and 4 mg, while showing an increase in sedative effect with increasing dose, did not show a significant difference in comparison with one tablet of Mandrax. Similarly, doubling the dose of diazepam (from 10 to 20 mg) lorazepam (from 2.5 to 5 mg) and flunitrazepam (from 1 to 2 mg) increased the sedative effect to some extent, but failed to relieve apprehension any further (Male et al., 1980).

| Table I. The quality of sleep the night before operation based upon subjective assessment by patients. n.s. = not significant |
|---------------------------------|--------------|---------------------|---------------------|
| Pakkanen, Kangas and Kanto, 1980: | Nitrazepam 1 mg | 79% | 18% | 3% |
| Flunitrazepam 1 mg | n.s. | Oxazepam 30 mg | 89% | 9% | 2% |
| Mansikka, Kangas and Kanto, 1980: | Nitrazepam 2 mg | 84% | 8% | 8% |
| Flunitrazepam 2 mg | n.s. | Lorazepam 2.5 mg | 84% | 14% | 2% |
| Kanto, Kangas and Mansikka, 1979: | Nitrazepam 2 mg | P < 0.001 | Placebo | 22% | 24% | 54% |
| Flunitrazepam 2 mg | 93% | 5% | 2% |
| Kangas, Kanto and Mansikka, 1977: | Nitrazepam 5 mg | P < 0.05 | No drug | 50% | 35% | 15% |
| Nitrazepam 5 mg | 74% | 20% | 6% |
| Mansikka and others, 1979: | Nitrazepam 5 mg | P < 0.01 | Placebo | 74% | 18% | 8% |
| Tofizopam 100 mg | 36% | 36% | 26% |
| Mansikka and others, 1979: | Oxazepam 25 mg | P < 0.05 | Placebo | 50% | 30% | 20% |
| Oxazepam 25 mg | 84% | 16% | 0% |
Flunitrazepam 1 mg had a greater sedative effect than oxazepam 30 mg (Pakkanen, Kangas and Kanto, 1981), and flunitrazepam 2 mg differed similarly from lorazepam 2.5 mg (Mansikka, Kangas and Kanto, 1980). Flunitrazepam 1 and 1.5 mg produced significantly better sedation than diazepam 10 mg or lorazepam 2.5 mg (McGowan et al., 1980). Flunitrazepam 1 mg has been shown, in particular, to offer advantages over placebo, diazepam 10 mg and lorazepam 2.5 mg for routine premedication (Male et al., 1980). In children, oral flunitrazepam 1, 1.5, and 2 mg, was associated with greater preoperative sedation than oral diazepam 10, 15, and 20 mg (Richardson and Manford, 1979).

The sedative effect of the benzodiazepine derivatives as oral premedicants seems to be clinically comparable to that of drugs which have been in use longer, such as barbiturates, antihistamines and chloral derivatives. Our results on the quality of sleep on the night before operation are presented in table I.

Amnesia

The benzodiazepines have a specific amnesia-producing property especially when administered i.v. (George and Dundee, 1977). Amnesia for unpleasant aspects of the perioperative period is a useful property of premedication, but lack of recall of picture cards or other such items does not necessarily mean that the patient will not remember such events as journey to the operating theatre or induction of anaesthesia.

The amnesic action of oral diazepam 10 mg has been assessed as superior to that of placebo (McKay, Dundee and George, 1978), similar to that of heptabarbitone (Wilson and Ellis, 1973) and inferior to that of trimetrazine (Haq and Dundee, 1968). The more potent soporific effect of trimetrazine may explain this difference although the anterograde amnesic action of benzodiazepines is not wholly dependent on sedation. However, significant failure to identify cards seems to require appreciable sedation at the time of card presentation (Dundee et al., 1979).

The amnesic action of oral diazepam 10 and 20 mg has been assessed as superior to that of placebo (McKay, Dundee and George, 1978), similar to that of heptabarbitone (Wilson and Ellis, 1973) and inferior to that of trimetrazine (Haq and Dundee, 1968). The more potent soporific effect of trimetrazine may explain this difference although the anterograde amnesic action of benzodiazepines is not wholly dependent on sedation. However, significant failure to identify cards seems to require appreciable sedation at the time of card presentation (Dundee et al., 1979).

The amnesic action of oral diazepam 10 and 20 mg is dose-dependent: after 10 mg, amnesia lasts for 120 min (i.v. route 15–20 min) while after 20 mg as many as 50% of patients had poor recall of events during the day of operation (Brandt and Oakes, 1965; Baird and Hailey, 1972). In contrast, Harry and Richards (1971) showed a negligible difference between diazepam 10 and 20 mg and that neither dose was as potent as oral lorazepam 2 or 4 mg.

Lorazepam is capable of producing dose-dependent, prolonged amnesia with slower onset of action than other benzodiazepines (George and Dundee, 1977). A 1-mg oral dose does not appear to affect memory (Dundee et al., 1979) while increasing the oral dose from 4 to 5 mg does not increase the frequency of anterograde amnesia (Dundee, Lilburn et al., 1977). Almost half the patients receiving lorazepam 4 mg had complete amnesia for events occurring 60–90 min after drug administration irrespective of the route of administration (p.o., i.m.; Dundee, Lilburn et al., 1977). In general, lorazepam has been considered to be the most potent benzodiazepine derivative in causing long-lasting (up to 8 h or more) amnesia which is pleasant for patients (Wilson and Ellis, 1973; George and Dundee, 1977; Dundee, Lilburn et al., 1977). However, the slow onset of action of lorazepam must be taken into consideration when timing premedication. It is an effective oral premedicant when rapid recovery is not essential (Dundee, Lilburn et al., 1977). In contrast to diazepam and flunitrazepam, its amnesic action is paralleled by its sedative effect (George and Dundee, 1977).

The relative amnesic action and duration of effect of flunitrazepam seem to be greater than those of diazepam (George and Dundee, 1977a). A dose-dependent effect was found 1 h after premedication when the amnesic property of diazepam 10 and 20 mg, lorazepam 2.5 and 5 mg, flunitrazepam 1 and 2 mg, and placebo were compared. The results were almost similar with flunitrazepam and lorazepam and superior to those with diazepam (Male et al., 1980). In children also, oral flunitrazepam 1, 1.5, and 2 mg caused a greater frequency of amnesia than oral diazepam 10, 15, and 20 mg (Richardson and Manford, 1979).

The amnesic actions of lorazepam and flunitrazepam seem to be superior to that of diazepam. Oral premedication with lorazepam, in particular, provides significant anterograde amnesia with good sedation and some postoperative basal narcosis (Wilson, 1973).

Other actions

In the doses used for oral premedication, benzodiazepines appear to have little effect on the cardiovascular or respiratory systems. They are
less likely to cause postoperative nausea and vomiting than are the strong analgesics and their effect seems to be at least as good as that of opiates, with fewer side-effects (Norris and Telfer, 1969; Wilson, 1973). Oral flunitrazepam and nitrazepam significantly decreased heart rate in comparison with placebo or no premedication (Kangas, Kanto and Mansikka, 1977; Kanto, Kangas and Mansikka, 1979) and flunitrazepam prevented increase in systolic arterial pressure more effectively than oxazepam (Pakkanen, Kangas and Kanto, 1981). Furthermore, flunitrazepam was associated with less postoperative vomiting than diazepam (Richardson and Manford, 1979). The antiemetic action of benzodiazepines has, however, not been proved in all studies (Kangas, Kanto and Mansikka, 1977; Kanto, Kangas and Mansikka, 1979; Mansikka et al., 1979; Pakkanen et al., 1980). In addition, the antisynergic effect of the benzodiazepines is poor, especially in children (Haq and Dundee, 1968; Boyd and Manford, 1973; Lindgren, Saarnivaara and Himberg, 1980) and in patients undergoing e.n.t. procedures (Pakkanen, Kangas and Kanto, 1981). Theoretically, the anti-convulsant and muscle-relaxing actions of benzodiazepines could be of value in patients receiving local anaesthesia, but the clinical significance of this is unknown (Wesseling, 1973). Prolonged neuromuscular blockade in conjunction with tubocurarine has been observed (Feldman and Crawley, 1970a,b) but, again, the clinical significance of this observation remains to be elucidated. In children, flunitrazepam has been shown to prevent fasciculations caused by suxamethonium more effectively than diazepam or triclofos (Lindgren, Saarnivaara and Himberg, 1980). Lorazepam has caused a relatively high frequency (9%) of adverse reactions in some studies (Mansikka, Kangas and Kanto, 1980) apparently caused by marked muscle relaxation.

The benzodiazepines have no analgesic action, but mothers receiving them during labour appear to require smaller doses of analgesics (Dundee, 1979; Kanto, 1981).

Following nitrazepam (Kangas, Kanto and Mansikka, 1977) and diazepam (Paymaster, 1973) premedication, an increased frequency of headache has been recorded but, in contrast, flunitrazepam seems to protect from this sensation (Kanto, Kangas and Mansikka, 1979). The benzodiazepines often cause dizziness (Paymaster, 1973; Kanto, Kangas and Mansikka, 1979; Clarke et al., 1980). Lorazepam 4 mg orally has been shown to prevent central sequelae after ketamine more effectively than other compounds, which has made ketamine acceptable to patients as an induction agent (Dundee et al., 1979).

The insertion of an i.v. cannula has been significantly more difficult after placebo premedication compared with oxazepam (Mansikka et al., 1979). The difference also almost reached significance between flunitrazepam and placebo (Kanto, Kangas and Mansikka, 1979). However, in neither study did the temperature of the forefinger before, during or after the anaesthesia vary significantly between the two groups. Measurement of cutaneous temperature of the finger as an indication of sympathetic reaction to anaesthesia and surgery therefore seems of little use.

A large oral dose of nitrazepam (40 mg) as a premedicant has been shown to decrease plasma cortisol concentrations compared with control (James and Fisher, 1970). Nitrazepam decreased the induction dose of thiopentone which indicates its marked sedative effect, but tofizopam did not do so (Pakkanen et al., 1980). The benzodiazepines have provided adequate preoperative sedation over a period of 5–8 h with minimum side-effects before or after operation (fig. 1) (Norris and Wallace, 1971; Wilson and Ellis, 1973; Kanto, Kangas and Mansikka, 1979; Dundee et al., 1979). However, after nitrazepam (Bond and Lader, 1972), flunitrazepam (Bond and Lader, 1975) and flurazepam (Bond and Lader, 1973) easily detectable residual effects have been determined the day after drug administration. In inpatients this may be desirable but not, of course, in the outpatient. The author's personal view of the difference between benzodiazepine derivatives as oral premedicants is shown in table II.

Relationship between plasma concentration and effect

When used as oral premedicants, no obvious relationship has been found between the plasma concentrations and clinical effects of diazepam (Kanto, Isalos et al., 1979; Richardson and Manford, 1979; Hon-Viander, Kangas and Kanto, 1980), oxazepam (Kanto, Isalos et al., 1979; Mansikka et al., 1979), nitrazepam (Kangas, Kanto and Mansikka, 1977) or flunitrazepam (Kanto, Kangas and Mansikka, 1979; Richardson and Manford, 1979). It would appear, therefore, that a
BENZODIAZEPINES AS ORAL PREMEDICANTS

1. Total concentration of flunitrazepam (F) + its N-demethylated metabolite (NF) in plasma after the second 2-mg oral morning dose of flunitrazepam. No correlation between the plasma concentration and clinical effect was found. Mean apprehension decreased (increase in points scored) although mean sedation remained unaltered in the flunitrazepam group (individual results + mean score). In the placebo group (mean score only), no significant change was found in apprehension or sedation during the study. The beneficial effects of flunitrazepam lasted for at least up to 8 h after the second dose (Kanto, Kanagas and Mansikka, 1979).

**Table II.** The author's personal view of the differences between benzodiazepine derivatives estimated in the operating theatre just before induction of anaesthesia. Assessment were made after two oral doses (the night before, and morning of, operation) using the method of Dundee, Moore and Nicholl (1962), with minor alterations (diazepam 10 + 10 mg, nitrazepam 5 + 5 mg, flunitrazepam 1 + 1 mg or 2 + 2 mg, oxazepam 25 + 25 mg or 30 + 30 mg, lorazepam 2.5 + 2.5 mg, tofizopam 100 + 100 mg).

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Flunitrazepam &gt; lorazepam = oxazepam = diazepam = nitrazepam &gt; tofizopam = placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apprehension + excitement (anxiolysis)</td>
<td>Flunitrazepam = (?) tofizopam &gt; placebo &lt; diazepam = oxazepam = lorazepam = nitrazepam</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Flunitrazepam &gt; placebo = tofizopam &lt; nitrazepam = lorazepam = oxazepam = diazepam</td>
</tr>
<tr>
<td>Headache</td>
<td>Nitrazepam &gt; placebo = diazepam = oxazepam = lorazepam = tofizopam &gt; flunitrazepam</td>
</tr>
<tr>
<td>Cardiovascular changes</td>
<td>Flunitrazepam &lt; placebo = diazepam = oxazepam = nitrazepam = lorazepam = tofizopam</td>
</tr>
<tr>
<td></td>
<td>Nitrazepam &lt; no premedication</td>
</tr>
</tbody>
</table>

plasma concentrations were significantly greater in those with amnesia for the induction period. Similarly, there was a tendency to greater benzodiazepine concentrations in those children who did not vomit after operation (Richardson and Manford, 1979).

The serum concentrations of both diazepam and flunitrazepam have been observed to be less in children of less than 5 yr than in older children, indicating age-dependent pharmacokinetics in childhood (Lindgren, Saarnivaara and Himberg, 1980).

**References**


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BUSINESS JOURNAL OF ANAESTHESIA

LES BENZODIAZEPINES ADMINISTRES EN TANT QUE MEDICATIONS PREOPERATOIRES BUCCALES

RESUME
Les avantages que presentent les benzodiazepines en tant que medications preoperatoires administrées par voie buccale sont: effet nettement anxiolytique et sedatif; action amnesique moins nette qui peut empécher de se souvenir du temps passé sur un chariot inconfortable de salle d'operations, mais pas nécessairement du temps de transport jusqu'à la salle d'opération, ou de l'induction de l'anesthesie; voie d'administration pratique; longue durée d'action—entre 5 h et 8 h—ce qui simplifie le calcul du temps pour l'administration de la médication; les réactions adverses des systemes autonome, hormonaux et circulatoires semblent pouvoir être évitées, empéchant ainsi la reaction au stress même avant l'induction de l'anesthesie; les actions anticonvulsives et de relaxation musculaire peuvent etre bénéfiques pour les malades recevant une anesthesie locale ou pour eviter les effets secondaires des agents de relaxation musculaire depolarisants; les nausees avant et après l'intervention peuvent être diminuées; une fréquence réduite des effets secondaires avant et après l'intervention chirurgicale.

DIE ANWENDUNG VON BENZODIAZEPINEN ALS PERORALE PRÄMEDIKATION

ZUSAMMENFASSUNG
Die Vorteile der Anwendung von Benzodiazepinen als perorale Prämedikation sind wie folgt: klare angstvermindernde und beruhigende Wirkung; weniger klare amnesische Wirkung, die vielleicht ausreicht, um die Erinnerung an die Zeit zu unterdrücken, die der Patient auf dem unbequemen Rollwagen verbracht hat, aber nicht unbedingt die Erinnerung an den Gang zum Operationsraum oder an die Induktion der Anästhesie; günstige Verabreichungsweise; lange Wirkungsdauer (5–8 Stunden), die die Entscheidung über den Zeitpunkt der Verabreichung vereinfacht; Nachteile autonome, hormonale und krielsuzbezogene Reaktionen werden anscheinend vermieden, sodass die Stress-Reaktion schon vor Induktion der Anästhesie vermieden wird; krankheitsbehandlende und muskelentspannende Aktivität könnte bei Patienten von Nutzen sein, die Lokalanästhesie bekommen, oder zur Vermeidung von den Seitenwirkungen von depolarisierenden Muskelspannungsmittel; Übelkeit vor und nach der Operation könnte abnehmen: Frequenz der Seitenwirkungen vor und nach der Operation reduziert ist.

BENSODIAZEPINAS CUAL PREMEDICAMENTOS ORALES

SUMARIO
Las ventajas de las benzodiazepinas cual premedicamentos orales son: claros efectos de ansiedad y sosiego; una actividad amnésica menos clara que puede impedir que se recuerde el tiempo que se estuvo tumbado en un incómodo carril de teatro de operaciones, pero sin siempre impedir que se recuerde el viaje hasta dicho teatro de operaciones ni la inducción de la anestesia; una ruta de administración conveniente; una actividad de gran duración, de 5 a 8 h, lo que simplifica la temporización de la administración de la droga; parece que se impiden las reacciones adversas del sistema circulatorio, hormonal y autonómico, impidiendo así la tensión incluso antes de la inducción de la anestesia; puede que las actividades de relajación muscular y anticonvulsivas sean de algún valor en aquellos pacientes que reciben anestesia local o para prevenir los efectos secundarios de los relajantes despolarizadores de músculos; las nauseas anteriores y posteriores a la operación pueden disminuirse; frecuencia disminuida de los efectos secundarios antes y después de la operación.