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Tofisopam and midazolam: differences in clinical effects and in changes of CSF monoamine metabolites

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The effect of two repeated oral doses of 100 mg tofisopam 15 mg midazolam and placebo on the concentrations of monoamine metabolites (MHPG, 5-HIAA, HVA) in lumbar CSF were studied in general surgical patients operated on under spinal analgesia ($n = 12$ in each group). Midazolam, but not tofisopam, improved the quality of sleep the night before surgery. Both active agents reduced preoperative anxiety of the patients, but tofisopam was without subjective sedative action. In the placebo group, in contrast to the active drug groups, there was a slight positive correlation between the MHPG concentration and degree of anxiety before surgery. The only significant difference in the monoamine metabolites in lumbar CSF was found in the concentrations of HVA between tofisopam and placebo treated patients. The lower HVA concentrations suggest that the curious 3, 4-benzodiazepine derivative, tofisopam, modifies central dopaminergic activity.

Keywords tofisopam midazolam monoamine metabolites in CSF clinical study

Introduction

There is some evidence that the 3,4-benzodiazepine derivative, tofisopam, differs pharmacologically from the usual 1,4-benzodiazepines, like diazepam, oxazepam and nitrazepam (Petőcz & Kosoczky, 1975). Clinical studies suggest that it reduces symptoms of anxiety without sedative, anticonvulsant and muscle-relaxing properties (Varady *et al.*, 1975; Goldberg & Finnerty, 1979; Pakkanen *et al.*, 1980; Seppälä *et al.*, 1980 Kanto *et al.*, 1982). In fact, it may have a mild stimulant action (Varady *et al.*, 1975; Pakkanen *et al.*, 1980; Kanto *et al.*, 1982). Typically, the interindividual variability in its clinical response is wide, probably due to active metabolites produced by an individually variable metabolism or a slow accumulation of the parent drug into the central nervous system (Kanto *et al.*, 1982). In addition, tofisopam or its metabolites do not bind to central benzodiazepine receptors *in vitro* or *in vivo* (Aaltonen *et al.*, 1979; Saano *et al.*, 1981; Aaltonen & Lammintausta, unpublished results), but the parent drug increases the binding of [^{3}H]-flunitrazepam to specific binding sites in rat brain (Saano *et al.*, 1981). Thus the mechanism of action of this novel anxiolytic agent is still unclear. In this work we have evaluated its effect on central monoamine metabolites and compared the results with those produced with placebo and midazolam. The latter is a typical 1,4-benzodiazepine derivative with a pharmacological profile similar to that of diazepam (Pieri *et al.*, 1981).

Methods

The present work was done with three comparable patient groups undergoing general surgical operations under spinal analgesia

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Table 1 Some patient characteristics of the study (mean ± s.d.).

	n	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Heart rate (beats min^{-1})*	*Systolic blood pressure (mm Hg)*	*Diastolic blood pressure (mm Hg)*
Group 1 (tofisopam)	15	61.4 ± 6.0	72.9 ± 8.4	172.1 ± 8.2	72.1 ± 10.3	146 ± 29	88 ± 13
Group 2 (midazolam)	15	57.8 ± 7.6	70.0 ± 9.6	168.1 ± 8.3	73.2 ± 10.9	167 ± 23	86 ± 14
Group 3 (placebo)	15	60.8 ± 7.4	73.1 ± 7.3	170.8 ± 9.7	93.2 ± 15.2	177 ± 27	94 ± 16
	Hyper-tension	*Cardiac insufficiency*	*Bronchial asthma*	*Chronic bronchitis*	*Diabetes*	*Coronary artery disease*	*Prostatic cancer*
Group 1	$n = 3$	$n = 1$	$n = 1$	$n = 0$	$n = 0$	$n = 0$	$n = 0$
Group 2	$n = 2$	$n = 0$	$n = 1$	$n = 0$	$n = 1$	$n = 0$	$n = 1$
Group 3	$n = 0$	$n = 3$	$n = 0$	$n = 1$	$n = 0$	$n = 2$	$n = 0$

(L_4-L_5) (Table 1). In a double-blind study the patients received in random order either 100 mg tofisopam (group 1), 15 mg midazolam (group 2) or a placebo (group 3) at 21.00 h on the night before surgery and on the following morning before operation. According to our previous studies (Pakkanen *et al.*, 1980; Kanto *et al.*, 1982), a single 100 mg dose of tofisopam was considered to be equipotent as an anxiolytic with a 15 mg dose of midazolam. No other premedication was used. The time interval between the second dose and the assessments of drug effects was 61.5 ± 13.2 (s.d.) min in group 1, 52.9 ± 15.1 min in group 2, and 57.6 ± 14.4 min in group 3 (differences not significant). The subjective and objective assessments were recorded just before the lumbar puncture in the operating room, as suggested by Dundee *et al.* (1962) with minor modifications (Pakkanen *et al.*, 1980; Kanto, 1981; Kanto *et al.*, 1982). The patients subjectively estimated the quality of sleep the night before operation (good, moderately good, fair, poor), and preoperatively the degree of sedation (marked, moderate, slight, nil), apprehension and excitement, dizziness, dysphoric effect, headache (nil, slight, moderate, marked), and emetic effect (nil, slight nausea, severe nausea, vomiting). The anaesthetist measured systolic and diastolic blood pressures and heart rate and estimated the ease of installation of i.v. infusion (easy, fairly easy, moderately easy, difficult). The lumbar puncture was performed in supine position between 08.00 h and 10.00 h and the volume of CSF collected was about 2 ml (Nordin *et al.*, 1982). The concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG, metabolite of noradrenaline), 5-hydroxyindole-acetic acid (5-HIAA, metabolite of 5-hydroxytryptamine), and homovanillic acid (HVA, metabolite of dopamine) in lumbar cerebrospinal fluid (CSF) were measured with a high-performance liquid chromatographic method with electrochemical detection (Scheinin *et al.*, 1983). The precision of this method is high (within-run and between-run coefficients of variation = 2–6% and less than 10%, respectively), and the lower limit of sensitivity sufficient for human studies (using a 100 μl injection volume = 8 nM for MHPG, 10 nM for 5-HIAA and 20 nM for HVA). The statistical analyses of the results were carried out using Student's *t*-test (non-paired data), χ^2-test and regression analysis.

Results

Midazolam 15 mg ($P < 0.05$), but not tofisopam 100 mg, improved the quality of sleep during the night before surgery in comparison with placebo. Just before the lumbar puncture, midazolam caused significantly more sedation than tofisopam ($P < 0.01$) or placebo ($P < 0.05$). Again, between placebo and tofisopam there was no difference. When the results of the 'anxiolytic' effect (apprehension and excitement) were compared between the three groups, the difference between group 1 (tofisopam) and group 3 (placebo) was significant ($P < 0.05$), and similarly between group 2 (midazolam) and group 3 ($P < 0.01$). The active drug groups did not differ in this respect. There were no significant differences between the three groups in the incidence of dizziness, emetic effect, dysphoric effect, headache or in the ease of installation of an i.v. infusion. Both tofisopam and midazolam inhibited heart rate elevation in comparison with placebo, but midazolam inhibited systolic blood pressure increase in comparison with both placebo and tofisopam (Table 1). No significant differences were found in diastolic blood pressures.

The concentrations of MHPG, 5-HIAA and HVA in CSF can be seen in Table 2. The only significant difference was found in the concentrations of HVA between groups 1 and 3. In the placebo group, a slight positive correlation was observed between the degree of apprehension and excitement and the level of MHPG in CSF (Figure 1). No other correlations were found between the measured CSF metabolite levels and subjective or objective assessments of drug effects.

Table 2 The concentrations (nmol l^{-1}, mean ± s.d.) of monoamine metabolites in CSF of general surgical patients operated on under spinal analgesia following two 100 mg oral doses of tofisopam, two 15 mg doses of midazolam or placebo. The only significant difference ($P < 0.05$) was found in HVA levels between patients treated with tofisopam and placebo. $n = 12$ in each group.

	MHPG	*5-HIAA*	*HVA*	
Tofisopam	38 ± 15	84 ± 30	142 ± 54	
Midazolam	37 ± 11	84 ± 33	184 ± 59	$P < 0.05$
Placebo	39 ± 14	123 ± 63	200 ± 79	

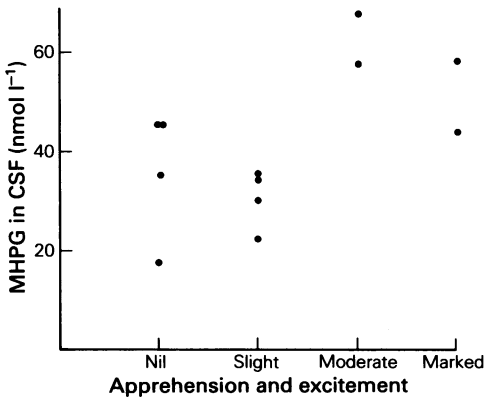

Figure 1 In the placebo group ($n = 12$), a slight positive correlation ($r = 0.531$, $0.05 < P < 0.10$) was observed between the anxiety reported by the patients and the levels of MHPG in CSF.

Discussion

Anaesthesia and surgery constitute great psychic stress in every patient, and the effectiveness of different drugs in reducing this transient anxiety and autonomic nervous system reactions can be evaluated and compared in this special situation (Kanto, 1981). Our results show that tofisopam differs from the water-soluble 1, 4-benzodiazepine, midazolam, both in clinical effects and in its effects on monoamine metabolites in human CSF. Oral midazolam proved to be an effective premedicant with sedative action as stated in earlier studies (Sjövall *et al.*, 1982, 1983, 1984a, b). Similar to our earlier findings, tofisopam had an anxiolytic effect but was without sedative properties (Pakkanen *et al.*, 1980; Kanto *et al.*, 1982). Thus it appears to be suitable for daytime anxiolytic therapy (Varady *et al.*, 1975).

It has been suggested that noradrenergic hyperactivity is a factor in the production of anxiety states (Charney *et al.*, 1983) and, accordingly, a slight positive correlation was found between the degree of anxiety and the level of MHPG in CSF in our placebo treated patients. No such relationship was present in the tofisopam or midazolam groups. Charney *et al.* (1983) reported that oral diazepam 10 mg was ineffective in antagonizing the yohimbine-induced increase in plasma MHPG although it significantly decreased yohimbine-induced anxiety. In the present work, the two benzodiazepines appeared to destroy the slight correlation between anxiety and level of MHPG in CSF. Basically, however, this group of drugs has been thought to act at sites 'downstream' from noradrenergic neurons (Costa & Guidotti, 1979) without affecting plasma or CSF levels of MHPG.

The most interesting finding in the levels of monoamine metabolites in CSF was the significantly lower average HVA concentration in the patients receiving two 100 mg doses of tofisopam. Nordin *et al.* (1981) found a similar response following bromocriptine administration. Thus tofisopam appears to behave like a dopamine agonist in the central nervous system. This gives further support to the uniqueness of tofisopam among the clinically used benzodiazepine derivatives: anxiolytic effect without sedation, no direct binding to benzodiazepine receptors, and a reduction in central dopaminergic activity. The latter property may be mediated through agonistic effects on central dopaminergic autoreceptors or may be due to alterations in dopamine synthesis or catabolism.

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