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Oral flunitrazepam in the prevention of local anaesthetic- induced convulsions in mice

The present study determined whether oral flunitrazepam was effective reducing CNS toxicity of lidocaine and bupivacaine. Pretreatment of mice with flunitrazepam, 0.065–0.25 mg·kg⁻¹, significantly reduced or prevented convulsions and mortality induced by lidocaine 106 and 209 mg·kg⁻¹ or bupivacaine 58 and 90 mg·kg⁻¹ injected intraperitoneally. The doses of flunitrazepam used did not cause measurable sedation in mice. The efficacy of oral flunitrazepam in preventing local anaesthetic-induced convulsions is similar to that previously reported by intraperitoneal or intramuscular injections in mice.

Flunitrazepam could be useful for oral premedication of patients before regional anaesthesia.

Key words

HYPNOTICS, BENZODIAZEPINES: flunitrazepam;
ANAESTHETICS, local: lidocaine, bupivacaine;
COMPLICATIONS: local anaesthetic toxicity, convulsions.

It was recently shown that the central nervous system is the primary target for the toxic effects of local anaesthetics, because convulsions are produced in doses three to seven times less than those required to provoke irreversible cardiovascular depression.¹ The increasing use of regional anaesthesia makes it important to improve the safety of this procedure by reducing the toxicity of local anaesthetics.

Benzodiazepine derivatives have been found to be very useful in preventing or minimizing convulsions and other manifestations of CNS toxicity induced by local anaesthetics.^{2–5} Flunitrazepam has greater affinity than diazepam for the benzodiazepine receptors, a fact which is believed to result in its superior sedative, anti-anxiety and amnesic effects.^{6–8} Recently we have shown that flunitrazepam given by intraperitoneal or intramuscular injection in mice was more effective than diazepam in preventing convulsions induced by local anaesthetics.^{9,10}

The present study was undertaken to determine whether the oral administration of flunitrazepam to mice would also be effective in reducing the CNS toxicity of two commonly used local anaesthetics, lidocaine and bupivacaine.

Methods

Male mice (Hebrew University Sabra strain) weighing 25–30 gm were pretreated orally with different doses of flunitrazepam (0.065, 0.125 and 0.25 mg·kg⁻¹) 45 min before the intraperitoneal injection of either lidocaine (160 mg·kg⁻¹ (20 mice) or 209 mg·kg⁻¹ (50 mice) or bupivacaine (58 mg·kg⁻¹ (20 mice) or 90 mg·kg⁻¹ (50 mice)). Eighty other mice were pretreated orally with saline before the injection of one of each of the four doses of local

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TABLE I Effect of flunitrazepam on locomotor activity

Pretreatment drug	Mean locomotor score $\pm$ SE
Saline n = 20	14.3 $\pm$ 2.4
Flunitrazepam 0.065 mg·kg ⁻¹ n = 20	15.3 $\pm$ 5.5
Flunitrazepam 0.125 mg·kg ⁻¹ n = 20	21.9 $\pm$ 6.0
Flunitrazepam 0.25 mg·kg ⁻¹ n = 20	10.4 $\pm$ 2.8

anaesthetics as indicated above. The doses of lidocaine and bupivacaine used had previously been found to produce convulsions in 50 and 95 per cent of the mice for each drug respectively.^{9,10}

During the 45-minute period between oral feeding with flunitrazepam and intraperitoneal injection of local anaesthetics, the effect of oral flunitrazepam or saline on spontaneous locomotor activity of the mice was assessed by recording the number of squares crossed during five minutes in an "open field" marked into 5 $\times$ 4 squares, measuring 5 $\times$ 5 cm each. After the intraperitoneal injection of local anaesthetics the incidence of convulsions and mortality in mice was studied. Results were analysed by analysis of variance, Student's *t* test or chi-square test where appropriate, and significance assigned to *p* values less than 0.05.

Results

Flunitrazepam in doses of 0.065–0.25 mg·kg⁻¹ caused no significant reduction of locomotor activity compared to that in mice given saline (Table I).

However, 0.065 mg·kg⁻¹ of flunitrazepam markedly reduced or completely prevented the convulsions caused by either lidocaine or bupivacaine (Table II). Flunitrazepam (0.065 mg·kg⁻¹) also significantly reduced the mortality after both doses of lidocaine and the lower dose of bupivacaine.

Discussion

The data reported indicate that oral flunitrazepam pretreatment in mice can effectively prevent or reduce local anaesthetic-induced convulsions, even in doses below those producing sedation.^{9,10}

Electrophysiological studies in experimental animals have shown that local anaesthetics produce excitatory effects on the limbic system which are most striking in the amygdaloid nuclear complex.^{11,12} The convulsions produced by local anaesthetics are not due to direct stimulation but to selective depression of inhibitory neurons.^{13,14} Ikeda *et al.*¹⁵ have demonstrated that intraventricular administration of GABA protected rats against convulsions induced by local anaesthetics, and suggested that the γ amino leutyric acid (GABA) system may diminish convulsion induced by local anaesthetics.

Benzodiazepines are known to facilitate γ amino leutyric acid (GABA) synaptic effects.^{6,7} The beneficial effect of small doses of flunitrazepam in this study can be explained by the fact that flunitrazepam particularly has a high affinity for the benzodiazepine receptors.¹⁶ This study supports this hypothesis and further demonstrates the efficacy of flunitrazepam in preventing convulsions induced by local anaesthetics even when given by the oral route.

TABLE II Effect of flunitrazepam on incidence of convulsions and mortality induced by lidocaine and bupivacaine

Dose of oral flunitrazepam mg·kg ⁻¹	Lidocaine				Bupivacaine			
	106 mg·kg ⁻¹		209 mg·kg ⁻¹		58 mg·kg ⁻¹		90 mg·kg ⁻¹	
	Convulsions (%)	Mortality (%)	Convulsions (%)	Mortality (%)	Convulsions (%)	Mortality (%)	Convulsions (%)	Mortality (%)
0.065	5*	10*	5*	10*	0*	10*	10*	60
0.125	0*	10*	0*	10*	0*	10*	0*	70
0.25	0*	10*	0*	10*	0*	20*	0*	70
Saline (control)	50	30	85	45	50	70	94	76

*Significantly different from saline control (χ^2 test) *p* < 0.05.

Although the protocol of this experiment did not include a study of the cardiovascular effect of these drugs in mice, our results are nevertheless in keeping with those obtained by others.^{17,18} Thus, de Jong *et al.*¹⁸ found that bupivacaine in convulsion-producing doses caused severe cardiac arrhythmias in cats but lidocaine did not.

In the present study, a dose of bupivacaine which produced the same incidence of convulsions as that of lidocaine, caused much higher mortality. Diazepam pretreatment has been shown to reduce ventricular irritability induced by local anaesthetics. It is therefore possible that flunitrazepam may also share this property if given in adequate dosage, which would be greater than that used in the present study to protect against the convulsive effects of local anaesthetics.

While one cannot extrapolate directly from doses used in mice to those which could be active in human subjects, we nevertheless would like to suggest that 2 mg of flunitrazepam, which is an effective sedative dose clinically, should also reduce the incidence and severity of convulsions induced by local anaesthetic agents. We are currently investigating whether flunitrazepam can reduce the cardiac toxicity of bupivacaine when given at appropriate dose levels.

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Résumé

Au cours de cette expérience, on a étudié les propriétés anticonvulsivantes du flunitrazépam oral en présence de convulsions provoquées par la lidocaïne et la bupivacaïne chez des souris. Un pré-traitement au flunitrazépam, $0.065\text{--}0.25\text{ mg}\cdot\text{kg}^{-1}$ réduisait de façon significative ou même prévenait les convulsions et la mortalité causées par la lidocaïne $106\text{ mg}\cdot\text{kg}^{-1}$ à $209\text{ mg}\cdot\text{kg}^{-1}$ ou la bupivacaïne $58\text{ mg}\cdot\text{kg}^{-1}$ à $90\text{ mg}\cdot\text{kg}^{-1}$ administrées par voie intrapéritonéale. Ces doses de flunitrazépam n'ont pas occasionné de sédation apparente chez la souris. Donc, pour la prévention de ces convulsions, le flunitrazépam est aussi efficace administré oralement que par voie intrapéritonéale ou intramusculaire chez la souris.

Le flunitrazépam semble donc un agent de prémédication utile chez les malades qui doivent recevoir une anesthésie régionale.