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A study of the potentiation of morphine antinociception by hydroxyzine in the rat

R. MORICHI & G. PEPEU

Department of Pharmacology, University of Florence, Viale Morgagni 65, 50134 Florence, Italy

Hydroxyzine, a minor tranquillizer with antiemetic, antihistaminic and antispasmodic actions, has been shown in man to possess analgesic properties and to potentiate morphine (Beaver & Feise, 1976) and meperidine analgesia without altering its pharmacokinetic and metabolism (Stambaugh & Weiner, 1976). However these findings were not confirmed by Kantor & Steinberg (1976). In this study we investigated the antinociceptive properties of hydroxyzine chloride.

Antinociception was evaluated by the method of Paalzow & Paalzow (1973). The tail of adult male rats was stimulated for 1 s using square waves at a frequency of 125 pulse/s, pulse width 1.6 ms, through thin needles inserted subcutaneously. In each animal the thresholds for motor response (tail withdrawal and hind quarter movement), for vocalization response and for vocalization after-discharge were determined before and 30 min after drug administration. According to Hoffmeister & Kronenberg (1966) the motor response is of spinal origin, the vocalization response involves the medulla, the vocalization after-discharge the thalamus, hypothalamus and rhinencephalon and represents the affective component of pain.

Hydroxyzine (12.5 mg/kg i.p.) exerted no antinociception; however at a dose of 25 mg/kg it reduced slightly the motor response and at 50 mg/kg exerted a weak antinociceptive action as shown in Table 1. Morphine sulphate (2.5 mg/kg s.c.) exerted a well detectable antinociceptive effect. Hydroxyzine potentiated the effect of morphine on the motor response and on the vocalization after-discharge. A small effect on the vocalization response occurred with 25 mg/kg. Hydroxyzine seems therefore to affect mostly the spinal and emotional components in the pain reaction. A comparison between hydroxyzine and other minor tranquillizers is in progress.

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Table 1 Effect of morphine, hydroxyzine and their combination on nociceptive reaction in the rat

			% increase of threshold (mean ± s.e. mean)		
Drugs	*Dose (mg/kg)*	*Route*	*Motor response*	*Vocalization*	*Vocalization after-discharge*
Hydroxyzine	25	i.p.	18.5 ± 0.9^{+}	1.6 ± 0.03	11.1 ± 0.6
Hydroxyzine	50	i.p.	45.4 ± 2.7^{++}	21.3 ± 1.7	24.2 ± 1.4^{+}
Morphine	2.5	s.c.	29.3 ± 1.3^{++}	75.6 ± 4.8^{++}	84.7 ± 6.2^{++}
Morphine	5	s.c.	32.7 ± 2.8^{+}	88.9 ± 15.2^{++}	143.1 ± 29.4^{++}
Hydroxyzine + Morphine	12.5 2.5	i.p. s.c.	*38.8 ± 0.5^{++}*	72.9 ± 7.0^{++}	*151.7 ± 28.3^{++}*
Hydroxyzine + Morphine	25 2.5	i.p. s.c.	*36.2 ± 1.1^{++}*	*110.6 ± 4.8^{++}*	*280.1 ± 32.7*

Groups of 5 rats
Differences from thresholds before treatment: P values $^{+}<0.05$ $^{++}<0.01$
The italicized figures are significantly different when compared with morphine 2.5 mg/kg with $P < 0.01$.

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Some observations on the behavioural responses to metoclopramide in the pig and the guinea pig

N. ELY, I.R. RUMBLE & D.F. SHARMAN

Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge CB2 4AT

Paradoxical responses to neuroleptic drugs are frequently observed in the pig (Marsboom & Symoens, 1968). In our studies on the use of such drugs in the pig we have often seen repetitive oral behaviour as an unwanted side effect. Fry & Sharman (1976) described the stereotyped snout-rubbing that can occur in some pigs following an intravenous injection of metoclopramide, a drug that shows several similarities with neuroleptic drugs when tested in the rat. This behavioural response in the pig was almost identical with the behaviour of pigs from the same herd that had been treated with apomorphine (0.5–1.0 mg/kg, i.v.). Metoclopramide causes an increase in the concentration of homovanillic acid (HVA), a metabolite of dopamine, in the brains of rats and mice and also produces catalepsy in these species (Ahtee, 1975; Ahtee & Buncombe, 1974; Costall & Naylor, 1973).

Following the administration of metoclopramide (5 mg/kg, i.p.) to pigs there were increases in the concentration of HVA and of 3,4-dihdroxyphenylacetic acid (DOPAC) in the striatum.

In the guinea pig, metoclopramide has been reported to have little or no effect on drug-induced dyskinesias or stereotypies with doses up to 32 mg/kg i.p. (Costall & Naylor, 1976). In our experiments with guinea pigs, metoclopramide was injected subcutaneously at the back of the neck. With doses of 25–100 mg/kg no catalepsy was observed. Doses of 75 mg/kg and above caused a stereotyped nose-rubbing with infrequent gnawing after about 15 minutes. This behaviour resembled that seen after apomorphine (1 mg/kg, s.c.) but the nose-rubbing was the most prominent behavioural response with metoclopramide, whereas gnawing characterized the response to apomorphine. The behavioural response to apomorphine (1 mg/kg s.c.) could be suppressed by metoclopramide in a dose of 25 mg/kg s.c. Metoclopramide (100 mg/kg, s.c.) caused an increase in the concentration of HVA in the striatum, the largest increase being observed in the medial part of this tissue. The stereotyped response to metoclopramide in the guinea pig has some pharmacological characteristics similar to those of the dyskinesias that can be induced by the intra-striatal injection of dopamine (Costall & Naylor, 1975).

Recent evidence has suggested that blockade of the dopamine receptors on cells in the striatum is not necessary for the activation of dopamine-containing neurons following the administration of neuroleptic drugs (Garcia-Munoz, Nicolaou, Tulloch, Wright & Arbuthnott, 1977; Di Chiara, Porceddu, Fratta & Gessa, 1977). The paradoxical behavioural response seen after metoclopramide is similar to that which ensues from drug treatments that are thought to bring about the activation of dopamine receptors in the brain. Such behaviour could thus be a result of the activation of dopaminergic neurons either without the blockade of post-synaptic dopamine receptors subserving behaviour, or overcoming the blockade.

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