Animal pharmacology of oxapadol (MD 720111), a new non-narcotic analgesic

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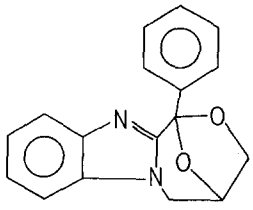
Summary. Oxapadol is a non-narcotic analgesic with an unusual chemical structure. It possesses analgesic activity in 4 species similar to that of other non-narcotic reference analgesics. It also shows antipyretic and antiinflammatory effects and in the analgesic dose range is devoid of undesirable neurological, gastro-intestinal and cardiovascular side-effects.

During preliminary neuropharmacological screening of a series of bridged oxazepine benzimidazoles[2], we noticed that certain compounds possessed non-narcotic analgesic activity. We report here the pharmacological profile of oxapadol, 4,5-dihydro-1-phenyl-1,4-epoxy-1 H, 3 H-[1,4] oxazepino [4,3-a] benzimidazole,



which was one of the most active in the series for analgesic activity and had the lowest incidence of undesirable effects.

The following analgesic tests were employed: the phenylbenzoquinone-induced writhing test[3] (rats and mice), the hot-plate test[4] (mice), the Randall-Selitto paw pressure test[5] (rats) and the tooth pulp test[6] (rabbits). Oxapadol and reference compounds were tested after a single oral administration. The table shows that oxapadol possesses analgesic activity close to that of aminopyrine or glaphenine but higher than that of acetaminophen or acetylsalicylic acid. In the phenylbenzoquinone-induced writhing test in the mouse, oxapadol remains active for at least 7 h. In further tests, oxapadol diminishes the behavioural signs of pain induced by bradykinin in the mouse[7] after i.p. injection and in the dog after administration through an indwelling catheter in the femoral artery[8, 9]. In the mouse the antibradykinin activity is close to that of acetylsalicylic acid and glaphenine but lower than that of aminopyrine. In the dog oxapadol was, however, less active than glaphenine (minimal active dose[10] for oxapadol and glaphenine: 200 and 100 mg/kg p.o., respectively).

The analgesic activity of oxapadol in the hot-plate test is not antagonized by 2.5 mg/kg i.v. naloxone, a dose which completely reverses the analgesic effect of a high dose of morphine (10 mg/kg s.c.). Oxapadol at doses up to 2000 mg/kg p.o. produces neither Straub tail, catalepsy nor hyperactivity in mice, effects thought typical of narcotic analgesics. In the cat oxapadol does not produce the so-called morphine mania syndrome at doses up to 80 mg/kg i.p. Moreover, in mice treated with oxapadol, in contrast to those treated with morphine, naloxone does not precipitate jumping, following the procedure described by Saelens et al.[11]. These results suggest that oxapadol does not possess morphine-like activity.

Oxapadol shows antipyretic activity on yeast-induced hyperthermia in rats[12]. This effect occurs at 12.5 mg/kg p.o., a non-hypothermic dose, and is similar to that of aminopyrine. In the acute stage of inflammation, oxapadol reduces carrageenan-induced paw oedema in rats[13] and the erythema formed in response to UV-irradiation in guinea-pigs[14], with ED 50's p.o. of 95 mg/kg and 45 mg/kg, respectively.

In the mouse oxapadol diminishes spontaneous activity[15] and potentiates the hypnotic effect (loss of righting-reflex) of thiopental only at doses starting from 200 mg/kg p.o., a dose 8 times higher than the ED 50 in the phenylbenzoquinone-induced writhing test. The fact that oxapadol reduces spontaneous activity and potentiates thiopental hypnosis at doses lower than those active in the hot-plate test probably reflects the lack of specificity of the hot-plate test for non-narcotic analgesics. Oxapadol, up to 400 mg/kg p.o., does not possess myorelaxant activity in the mouse (loaded grid test[16], traction test[17]), and, at the dose 5 times higher than the ED 50 in the tooth pulp test, does not change spontaneous electrical activity in the cerebral cortex, thalamus, dorsal hippocampus or reticular formation in the awake rabbit. Oxapadol does not produce ulcers in the rat and does not possess intestinal spasmolytic activity in the rabbit at 100 mg/kg by the intraduodenal route. In the awake normotensive rat, oxapadol does not change either the heart rate and the arterial pressure during 24 h after administration of 100 mg/kg p.o.

In view of its marked analgesic and antipyretic activity, its high therapeutic ratio and the absence of undesirable side-

Acute toxicity and analgesic activity of oxapadol and reference compounds

Drug	Acute toxicity	Phenylbenzoquinone-induced writhing		Bradykinin-induced writhing	Hot-plate	Randall-Selitto paw pressure	Tooth pulp
	LD 50[a]	ED 50[b]		ED 50[b] mg/kg p.o.	ED 50[c]	ED 50[d]	ED 50[e]
	Mice	Mice	Rat	Mice	Mice	Rat	Rabbit
Oxapadol	> 2000	27	37	170	380	40	80
Acetaminophen	830	215	> 100	Not tested	> 400	400	125
Acetylsalicylic acid	700	72	65	180	> 400	80	> 400
Aminopyrine	1050	28	60	80	94	45	27
Glaphenine	1900	15	48	110	> 400	65	100

[a] Lethal dose in 50% animals within 7 days after drug administration. [b] Dose reducing by 50% the control writhing score 0.5 h after drug administration. [c] Dose reducing by 50% the control forepaw-licking latency 0.5 h after drug administration. [d] Dose increasing by 50% the control retraction threshold of the yeast-inflamed hind paw 1 h after drug administration. [e] Dose increasing by 1 V the pre-drug electrical stimulation-induced gnawing threshold in 50% animals 0.5 h after drug administration (LD 50's and ED 50's were determined graphically following Litchfield and Wilcoxon[19]).

effects at analgesic doses or of morphine-like activity, we have proposed that oxapadol be tested for its analgesic activity in man. Clinical pharmacological findings in normal man are consistent with our animal data[18].

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Human neuropharmacological findings with oxapadol (MD 720111), a new non-narcotic analgesic

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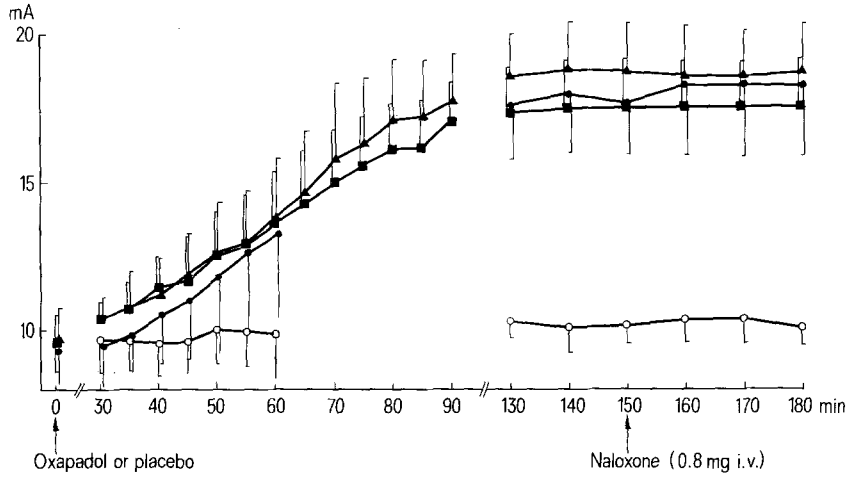
Summary. The effects of oxapadol, a new non-narcotic analgesic, were tested in man using the electrically-induced nociceptive flexion reflex in the flexor muscles of the lower limb as an index of pain. The drug caused a significant increase in the threshold of the reflex whereas no change was noted with placebo.

The present paper describes an experimental study of a newly developed drug oxapadol[2] which has shown analgesic activity in animal tests[3].

It has been shown[4,5] that the electrically-induced flexion reflex of the lower limb in man could be used as an experimental index of pain. This reflex can be modulated either by analgesic drugs (inhibition of the reflex, increase in its threshold) or by algogenic drugs (facilitation of the reflex, decrease in its threshold).

Experiments were carried out on 10 young (20–29 years) healthy volunteers chosen among medical students or physiologists. All of them were carefully briefed before the sessions in order to avoid any element of anxiety or surprise[6]. They were carefully installed in an armchair specially designed to obtain good muscular relaxation.

The drug oxapadol was studied at 3 doses (600, 800 and 1000 mg) against a placebo contained in tablets identical in size and appearance. Each subjet was used as his own control and was consequently tested 4 times. The experiment was conducted in 2 stages. In the 1st stage, to test overall efficacy, 1000 mg oxapadol were compared with placebo according to a double-blind cross over design. In



Variations of the threshold of the nociceptive flexion reflex as a function of time after different drug administrations: oxapadol at the 3 doses tested (△ 600 mg, ■ 800 mg, ● 1000 mg) increases the nociceptive flexion threshold whereas placebo (○) is without effect (mean values and SD). Naloxone does not antagonize the effect of oxapadol.