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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2 C. Fauran, J. Eberlé, M. Turin, G. Raynaud and C. Gouret, U.S. Patent 3951.968, April 20, 1976.
3 E. Siegmund, R. Cadmus and G. Lu, Proc. Soc. exp. Biol. Med. *95*, 729 (1957).
4 N.B. Eddy and D. Leimbach, J. Pharm. exp. Ther. *107*, 385 (1953).
5 L.O. Randall and J.J. Selitto, Archs int. Pharmacodyn. *111*, 409 (1957).
6 B. Laffargue, Annls Pharm. franç. *21*, 47 (1963).
7 R.B.P. Burns, N.J. Alioto and K.E. Hurley, Archs int. Pharmacodyn. *175*, 41 (1968).
8 F. Guzman, C. Braun, R.K.S. Lim, G.D. Potter and D.W. Rodgers, Archs int. Pharmacodyn. *149*, 571 (1964).
9 N. Taïra, K. Nakayama and H. Hashimoto, Tohoku J. exp. Med. *96*, 365 (1968).
10 L.M. Fucella, G. Corvi, F. Gorini, V. Mandelli, G. Mascellani, F. Nobili, J. Pedronetto, N. Ragini and I. Vandelli, J. clin. Pharmac. *17*, 177 (1977).
11 J.K. Saelens, F.R. Granat and W.K. Sawyer, Archs int. Pharmacodyn. *190*, 213 (1971).
12 S.S. Adams, P. Hepborn and J.S. Nicholson, J. Pharm. Pharmac. *20*, 305 (1968).
13 C.A. Winter, E.A. Risley and G.W. Nuss, Proc. Soc. exp. Biol. Med. *111*, 544 (1962).
14 C.V. Winder, J. Wax, V. Burr, M. Been and C.E. Rosière, Archs int. Pharmacodyn. *116*, 261 (1958).
15 J.R. Boissier and P. Simon, Archs int. Pharmacodyn. *158*, 212 (1965).
16 E. Frommel, Archs Sci., Genève, *10*, 107 (1957).
17 L. Julou and S. Courvoisier, J. clin. exp. Psychopath. *17*, 25 (1956).
18 F. Boureau, B. Laquais, M. Vadrot and J.-C. Willer, Experientia, in press.
19 J.T. Litchfield and F. Wilcoxon, J. Pharm. exp. Ther. *96*, 99 (1949).

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

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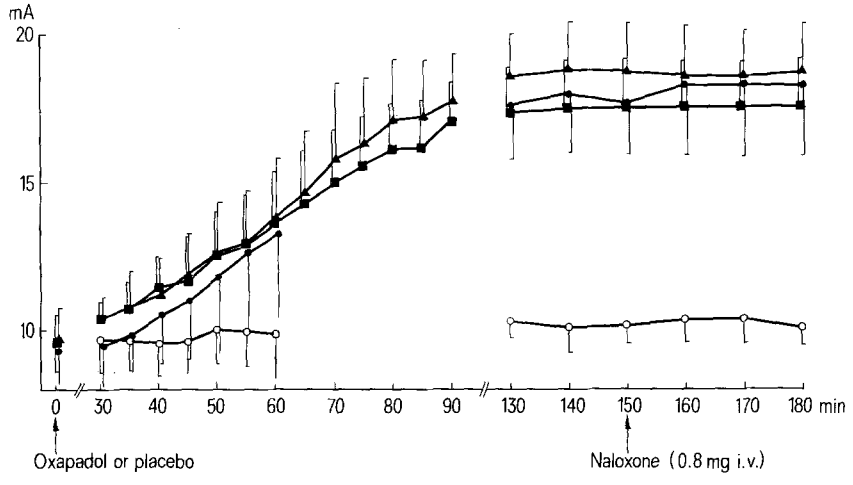
Summary. The effects of oxapadol, a new non-narcotic analgesic, were tested in man using the electrically-induced nociceptive flexion reflex in the flexor muscles of the lower limb as an index of pain. The drug caused a significant increase in the threshold of the reflex whereas no change was noted with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

the 2nd part the effects of 800 mg were compared with 600 mg following a similar design to determine whether the effect previously observed depended on the dose. During each experimental session, the subjects' nociceptive reflex threshold was measured during the 5 min immediately preceding p.o. administration of the drug or placebo in order to determine the initial baseline (T0).

After drug administration the reflex was tested again between T30 and T60 in the 1st stage (1000 mg vs placebo) and between T30 and T90 in the 2nd stage then, between T130 and T180 in both stages. At T150, in the 2nd stages, the subjects were given an injection of naloxone (0.8 mg i.v.) to test whether the drug effect could be modified by this specific narcotic antagonist[7].

The numerical data of the threshold of the nociceptive reflex were analyzed separately for the 2 stages according to the method described by Wallenstein and Fisher[8]. The analysis indicated no overall carry over effects. The interactions treatment × time were then tested in each of the 2 stages and following by individual comparisons.

The figure shows that oxapadol at the 3 doses tested increased the nociceptive flexion threshold, whereas placebo was without effect. Between oxapadol 1000 mg and placebo the difference became significant ($p \leqslant 0.05$) at T40. In the 2nd part of the session (T130–T180) the increase of the threshold was stable and the difference between oxapadol and placebo was highly significant ($p \leqslant 0.01$).

The results obtained with oxapadol at 800 mg are similar to those obtained with 1000 mg but 600 mg are slightly more active; a significant difference ($p \leq 0.05$) between 600 mg and 800 mg is apparent at T70.

These results are similar to those obtained with other non-narcotic analgesics[4,9,10] (acetylsalicylic acid, glaphenine).

No subjects reported any undesirable side effects such as drowsiness, nausea or dyspnea at doses which markedly attenuated the nociceptive reflex.

Naloxone when injected at T150, where the inhibition of the nociceptive reflex was maximal, was without effect. It suggests that oxapadol-induced inhibition of pain sensation does not result from morphine-like activity.

In conclusion, oxapadol, a chemically original compound which shows analgesic activity in animal tests, reduces experimentally-induced pain in normal human subjects. These results together with preliminary clinical findings suggest that oxapadol may represent a new type of non-narcotic analgesic.

1 Centre de Recherche Delalande, 10, rue des Carrières, F-92500, Rueil-Malmaison (France).
2 Oxapadol: 4,5-dihydro-1-phenyl-1,4-epoxy-1H, 3H-[1,4]oxazepino[4,3-a]benzimidazole. C. Fauran, J. Eberlé, M. Turin, G. Raynaud and C. Gouret, U.S. Patent 3591.968, April 20, 1976.
3 G. Mocquet, A. Coston and M. Jalfre, Experientia, in press.
4 J.C. Willer and N. Bathien, Electromyogr. Clin. Neurophysiol. *15*, 127 (1975).
5 J.C. Willer, Pain *3*, 69 (1977).
6 J.C. Willer, Physiol. Behav. *15*, 411 (1975).
7 F. Boureau, J.C. Willer and C. Dauthier, J. Neuropharmac. *17*, 565 (1978).
8 S. Wallenstein and A.C. Fischer, Biometrics *33*, 261 (1977).
9 J.C. Willer and N. Bathien, Pain *3*, 111 (1977).
10 J.C. Willer, N. Bathien and A. Hugelin, in: Advance in Pain Research and Therapy, vol. 1, p. 131. Ed. J.J. Bonica and D. Albe-Fessard. Raven Press, New York 1976.
11 A. Lundberg, in: Progress in Brain Research, Physiology of Spinal Neurons, vol. 12, p. 135. Ed. J.C. Eccles and J.P. Schade. Elsevier, Amsterdam 1964.

A novel effect of cobalt treatment on calcium-dependent responses of the cockroach salivary gland

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Summary. After incubation in calcium-free solutions containing cobalt, the readmission of calcium caused prolonged but reversible hyperpolarization of acinar cells of cockroach salivary glands and prolonged fluid secretion. It is suggested that cobalt treatment increases the permeability of the acinar cell membrane to calcium.

The presence of cobalt ions is known to inhibit the release of neurotransmitter from nerve terminals[2] and the generation of calcium dependent action potentials[3]. These effects are generally believed to result from the inhibition by cobalt of calcium entry into cells[4]. Cobalt also inhibits fast axoplasmic flow[5] and augments the spontaneous release of neurotransmitter[2].

These effects have been taken to imply that cobalt enters cells and displaces calcium from intra-cellular binding sites[4]. We report here a novel effect of cobalt treatment, namely the enhancement of calcium dependent electrical and secretory responses of an exocrine gland, which suggests that cobalt can induce a prolonged but reversible increase in membrane permeability to calcium.

The electrical experiments were made on isolated salivary glands of *Nauphoeta cinerea* (Olivier)[6] bathed in flowing solution containing (mM) NaCl, 160; KCl, 1; Tris-HCl pH 7.6 buffer 5. Usually the control solution contained 5 mM $CaCl_2$ and the conditioning solutions had no added calcium and either 5 mM $CoCl_2$ or 5 mM $MgCl_2$ or 1 mM $MgCl_2$ plus 1 mM EGTA; modifications are mentioned below. Cells were impaled with microelectrodes containing 3 M potassium acetate.

Figure 1,a illustrates the transient hyperpolarization which occurred when the preparation was re-exposed to a calcium-containing solution after a period of exposure of about 15 min to a calcium-free solution[7]. 7 such responses were recorded: in 6 the duration was less than 3 min, and in the 7th less than 5 min. Figure 1,b illustrates the large prolongation of the response to the readmission of calcium after a period of exposure to a calcium-free solution containing 5 mM cobalt. Such a response occurred in more than 20 experiments.

In some of these the duration could not be determined because the electrode was dislodged before the resting potential had returned to its control value but in several it was clear that some degree of hyperpolarization remained 1 h after the readmission of calcium. The effect was reversible and could be obtained more than once in the same preparation. The hyperpolarization was not abolished