hot water test at the usual water temperature of 55°C. At 45°C however, pentazocine is active and produces a bell-shaped log dose response curve with analgesia decreasing at higher, non-toxic doses. The new oripavines show curves of similar shape at 45, 55 and 65°C, respectively, and analgesia can be demonstrated even at the highest temperature. They are considerably more effective than pentazocine in this test but in contrast to etorphine and morphine, their efficacies diminish with increase in stimulus strength. Comparable results have been obtained with these oripavines in the similar rat tail flick test.

Primary dependence studies in mice (method of Saelens, Granat & Sawyer, 1971) suggest that 289-M, 6007-M and 6029-M have physical dependence capacities similar to pentazocine and less than codeine. From 30 day primary dependence studies in monkeys (method of Deneau & Seevers, 1964), the antagonist-precipitated abstinence syndrome (A.S.) can be ranked as follows: pentazocine=6029-M (low A.S.) <6007-M (A.S. absent on day 14 and non morphine-like on day 28) <289-M (moderate A.S.).

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Some properties of WY 22811, a new analgesic compound

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Since the discovery that some opiate-antagonist drugs have analgesic properties (Lasagna & Beecher, 1954; Harris & Pierson, 1964) and the subsequent finding that such analgesics have low addiction liability in man (Isbell, 1956; Fraser & Rosenberg, 1964) there has been considerable interest in finding improved compounds of this type.

Wy 22811 (*m*-(3-ethyl-1 methylhexahydro-1*H*-azepin-3-yl) phenol hydrochloride) is a potent analgesic compound which injected by the subcutaneous route is approximately equipotent with pentazocine in the rat tail radiant heat test (Bonnycastle & Leonard, 1950) and the mouse acetylcholine writhing test (Collier, Hammond, Horwood-Barrett & Schneider, 1964). Wy 22811 was well absorbed by the oral route since in the same tests, potencies relative to pentazocine were 3·2 in rats and 15 in mice. Optical resolution of Wy 22811 yielded two enantiomers which showed similar subcutaneous and oral analgesic potencies to the racemate.

Wy 22811 and both enantiomers resemble pentazocine in showing opiate-antagonist activity. Thus, on intravenous infusion, these compounds reversed the symptoms of severe morphinism in rats after a high subcutaneous dose of morphine and also, after

subcutaneous injection, they precipitated withdrawal symptoms in morphine dependent rats. The (−)-enantiomer was a more potent antagonist than the (+)-enantiomer.

In a test of dependence liability (Goode, 1971) it was found that, at doses equi-analgesic to the maintenance dose of morphine, Wy 22811 and its enantioners resembled pentazocine in not preventing withdrawal weight loss in morphine dependent rats. This result indicates the possibility of a very low dependence liability for these compounds since the addictive analgesics codeine and methadone completely inhibit weight loss in this test.

In contrast to morphine, neither Wy 22811 nor its enantiomers affected defaecation in the rat at oral doses in the analgesic range and had no significant effect on conscious rat blood pressure up to toxic doses. In the anaesthetized cat Wy 22811 reversed ouabain and adrenaline-induced arrhythmias and ventricular fibrillation induced by hypothermia. When injected in the rat paw, the compound also caused less irritation (volume increase) than morphine or pentazocine.

It is concluded that Wy 22811 is likely to be a useful analgesic combining moderate potency with a low incidence of side effects in rats, cats and monkeys.

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