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On the relation between the analgesic activity of meptazinol and its plasma concentrations in rats, mice and monkeys

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Meptazinol, [m-3-ethyl-1-methylhexahydro-1H azepin-3-yl)phenol hydrochloride] has been shown to possess analgesic properties in animals (Goode & White, 1971) and to be capable of relieving severe pain in man (Oosterlinck & De Sy, 1975). This communication describes studies carried out to determine whether a relation exists between the intensity of the drug's effects and its plasma concentrations.

Preliminary indications that such a relation might exist were seen from the higher plasma concentrations and the greater potency associated with an intravenous compared with an oral dose of the drug. More extensive studies have now been carried out in which the intensity of the analgesia has been compared with the plasma concentrations of the drug in rats, mice and monkeys.

Analgesic activity in rats was measured by the tail flick test described by D'Amour & Smith (1941). Thus a group of eight female rats received the drug orally at 25 mg kg^{-1} while another group was dosed intravenously at 8 mg kg^{-1}. The intensity of the analgesia was measured at various times up to 8 h after dosing. Plasma concentrations of meptazinol were determined by the method described by Franklin, Aldridge & White (1976) using additional groups of animals dosed with N-$^{14}CH_3$-labelled material. Drug concentrations in a plasma at the precise time of measurement of analgesia were derived from a graph of $\log_{10}$ observed plasma concentrations against time.

Analgesic activity in mice was measured by the acetylcholine-induced writhing test described by Collier, Hammond & others (1964). Thus groups of ten male mice were dosed orally with meptazinol at 25 mg kg^{-1} and the analgesic activity determined at various times up to 2 h after dosing. Plasma concentrations of the drug were determined on pooled samples obtained from groups of five mice which were killed at various times after receiving the ^{14}C-labelled drug at 25 mg kg^{-1}. Again drug concentrations at the precise times of measurement of analgesia were derived from regression analysis of the observed data points.

The results presented in Fig. 1 show that there was a good correlation of analgesic activity and plasma concentrations of the drug. After oral administration of the compound to rats a correlation coefficient of 0·80 (n = 7) was found between $\log_{10}$ plasma concentration and intensity of analgesia. A somewhat better correlation coefficient of 0·90 (n = 7) was observed after intravenous dosage of the compound.

In mice an excellent correlation of analgesic response and plasma concentration was observed, the correlation coefficient being 0·96 (n = 11).

Although no similar studies were conducted in monkeys, no analgesic activity could be demonstrated in the Rhesus monkey after oral administration of the compound up to 80 mg kg^{-1} (Malis, unpublished results) and plasma concentrations in the Patas

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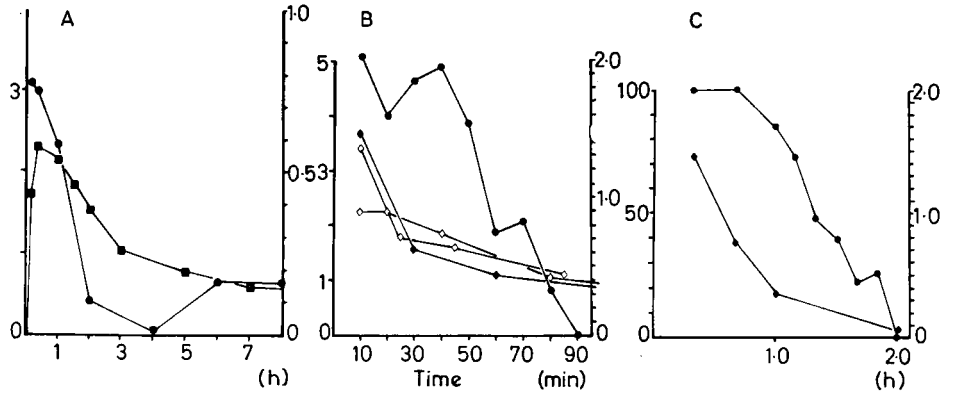

FIG. 1A. Correlation of ■—plasma concentrations of meptazinol (μg ml^{-1}), and ●—analgesic activity (mean increase in response time, s) in the rat after oral administration of the drug at 25 mg kg^{-1}. Analgesia was determined in a group of 8 rats using the tail flick test. Plasma concentrations were determined in a further group of 7 animals. Analgesia activity: l.h. ordinate; plasma concentration of drug r.h. ordinate.
B. Correlation of ◇◇◆ —plasma concentrations of meptazinol (μg ml^{-1}) and ●—analgesic activity (mean increase in response time, s) in the rat after intravenous administration of the drug at 8 mg kg^{-1}. Analgesia was determined in a group of 8 rats using the tail flick test. Plasma concentrations were estimated in a further group of 3 animals. Ordinates as in A.
C. Correlation of ◆—plasma concentrations of meptazinol (μg ml^{-1}) and ●—analgesic response (% inhibition of writhing) in the mouse after oral administration of the drug at 25 mg kg^{-1}. Analgesia was determined in groups of 10 mice at each time point using the acetylcholine writhing test. For measurement of plasma concentrations further groups of 5 mice were exsanguinated at various times after dosing. Analgesic response l.h. ordinate; plasma concentration of drug r.h. ordinate.

monkey, were very low after oral dosage (Franklin & Aldridge, 1976).

The correlation observed between the analgesic activity of meptazinol and its plasma concentrations is consistent with the suggestion that this compound elicits its pharmacological effects per se. Furthermore, metabolic studies have shown the major metabolite in animals and man (Franklin & Aldridge, 1976, Franklin & others, 1976) to be the glucuronide conjugate which is unlikely to contribute to the drug's pharmacological effects. A minor metabolite of the drug, identified as 7 oxo-meptazinol, has been shown to be devoid of analgesic activity (Franklin & others, 1976).

While good correlations of intensity of analgesia and plasma concentrations have been established by other workers for some analgesics, e.g. pentazocine (Berkowitz & Way, 1971) morphine, methadone and codeine (Miller & Elliot, 1954), with other analgesics such as propoxyphene (Wolen, Gruber & others, 1971) and 1-α-acetyl methadol (Sung & Way, 1954) no such relations could be found. For meptazinol a good correlation of the drug's biological effects and its plasma concentrations has been established. This finding could have important clinical implications since it should enable therapy to be based on plasma concentration measurements.

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