PHARMACOLOGICAL PROPERTIES OF CODEINE-7,8-OXIDE (CODEINE EPOXIDE), A NEW METABOLITE OF CODEINE

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Codeine-7,8-oxide (codeine epoxide) (Fig. 1) was recently identified as a new metabolite of codeine (1). Findings of Takayanagi et al. (2) using electrically stimulated guinea-pig ileum suggested that codeine-7,8-oxide had a potent narcotic analgesic activity as described in the preliminary report of Miyata et al. (3), and epoxidation of 7,8-double bond of codeine resulted in a trend for a decrease in the dependence liability. Furthermore, Yoshimura and his co-workers (4-6) found that the antinociceptive actions of morphine-6-glucuronide and morphine-6-sulfate were 2 to 3 times as potent as morphine, while morphine-3-glucuronide, a major metabolite, had no biological activity.

In this paper we studied the antinociceptive activity, development of tolerance and the inhibitory activity of abstinence syndrome to clarify pharmacological properties of this new metabolite of codeine.

Antinociceptive activity was measured after subcutaneous injection in the conscious male Wistar rats (80 to 100 g in body weight) with a Randal-Sellito apparatus (Ugo Basile). Pressure was given to a hind paw and the maximal pressure measured was 250 g.

In order to test development of tolerance in antinociceptive activity, 10 mg/kg of codeine-7,8-oxide or 20 mg/kg of codeine were given subcutaneously every 4 hr for 3 days to male Wistar strain rats (60 to 100 g in body weight). Antinociceptive activities of both the drugs were measured after every injection.

The rats (80 to 100 g) were made dependent on morphine by a daily subcutaneous injection of morphine. The dose of morphine was increased during a period of 4 weeks until a daily dose of 80 mg/kg (40 mg/kg twice a day at 10 a.m. and 6 p.m.): the first week, 20 mg/day, the second week, 40 mg/day, the third week, 60 mg/day and the fourth week, 80 mg/day (7, 8). The body weight of the treated animals rapidly decreased upon withdrawal, the mean decrease being 24.5±1.5 g (mean±S.E.). After the confirmation of the decrease in body weight upon withdrawal, the animals were further treated with 20 mg/kg of morphine at 10 a.m. and 6 p.m. Next week, the animals were divided into 6 groups of 7 rats. A control was administered saline and the others were used as test groups which were subcutaneously injected with morphine, codeine or codeine-7,8-oxide. Decrease in the body weight was measured 24 hr after the injection.

Statistical significance was evaluated by the Student’s t-test. Drugs used: codeine phosphate (codeine; Sankyo Co. Japan), morphine hydrochloride (morphine; Sankyo Co. Japan), naloxone hydrochloride (naloxone; Sankyo Co. Japan) and codeine-7,8-oxide which was synthesized according
to Uba et al. (9). All the drugs were dissolved in physiological saline.

The antinociceptive action of codeine-7,8-oxide is shown in Fig. 1. A parallel line assay was employed for the antinociceptive potency ratio using codeine as a standard. Codeine-7,8-oxide was 2.05 times as potent as codeine and its 95% fiducial limits were 1.95 and 2.15. Antinociceptive actions of codeine (10 mg/kg, s.c.) and codeine-7,8-oxide (5 mg/kg, s.c.) were abolished by naloxone (1 mg/kg, s.c.) which was a sufficient dose to abolish the antinociceptive action of morphine (2.5 mg/kg, s.c.) (Fig. 1). The doses of codeine-7,8-oxide, codeine and morphine were equipotent.

The antinociceptive actions of codeine-7,8-oxide and codeine were gradually reduced when codeine-7,8-oxide (10 mg/kg, s.c.) or codeine (20 mg/kg, s.c.) was repeatedly administered every 4 hr. The antinociceptive activity of codeine in the animals treated with codeine disappeared after the 10th administration of codeine, while the codeine-7,8-oxide-treated rats still responded to codeine-7,8-oxide even after the 13th administration (Fig. 2). In the animals treated with either drug more than 7 times, the antinociceptive action of codeine was significantly smaller than that of codeine-7,8-oxide (Fig. 2).

Decrease in body weight of the rats repeatedly treated with morphine was 23.4±2.6 g (mean±S.E.) after the injection of saline instead of morphine. When codeine-7,8-oxide (40 mg/kg, s.c.) was injected instead of morphine, the mean decrease of body weight of the rats treated with morphine was 11.2±2.0 g. The body weight was increased with subcutaneous injection of 80 mg/kg of codeine which was equipotent to a dose of 40 mg/kg codeine-7,8-oxide in antinociceptive action, the mean being 3.1±0.9 g. The rats treated with 20 mg/kg morphine lost 1.2±2.3 g, while an increase of body weight was observed with 40 mg/kg morphine, the mean being 6.0±0.5 g. The body weight of the 7 rats untreated with morphine increased when saline was injected (Fig. 2).

The antinociceptive potency ratio (2.05) of codeine-7,8-oxide, a new metabolite of codeine (1) relative to codeine was similar to the value of obtained by Miyata et al. (3). This antinociceptive action of codeine-7,8-oxide was antagonized by naloxone, suggesting that the metabolite was a narcotic analgesic drug. These findings supported the results of Takayanagi et al. (2) that the inhibitory action of codeine-7,8-oxide on electrically stimulated guinea-pig ileum was antagonized by naloxone.

The results shown in Fig. 2 demonstrate that the development of tolerance is slower in the rats treated with codeine-7,8-oxide than in the rats treated with codeine when
either drug was given repeatedly to the rats in an equipotent dose.

Decrease in body weight upon withdrawal is one of the most clearly observed components in the narcotic abstinence syndrome. Most components of the narcotic abstinence syndrome can be suppressed by administration of an opiate or an opiate agonist. Decrease in body weight was partially prevented by codeine-7,8-oxide at 40 mg/kg (s.c.), but completely prevented by codeine at 80 mg/kg (s.c.) which was an equipotent dose to 40 mg/kg codeine-7,8-oxide in this study. These results suggest that codeine-7,8-oxide is less potent than codeine in the inhibition of the abstinence syndrome when the equipotent doses for antinociceptive action were used. In this study, the metabolic conversion of codeine to codeine-7,8-oxide resulted in an increase in the antinociceptive action or analgesic action.

REFERENCES


4) Mori, M., Oguri, K., Yoshimura, H., Shimomura,


