SOME PHARMACOLOGICAL PROPERTIES OF MORPHINE-7,8-OXIDE (MORPHINE EPoxide)

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Morphine-7,8-oxide (morphine epoxide) is assumed to be a metabolite of morphine. Morphine epoxide in antinociceptive action was practically as potent as morphine. The development of tolerance in antinociceptive action was slower in the rats treated with morphine epoxide than in the rats with morphine. Furthermore, morphine epoxide was less potent than morphine in the inhibition of abstinence syndrome.

Keywords — morphine epoxide, morphine-7,8-oxide, antinociceptive action, analgesic action, tolerance abstinence syndrome

INTRODUCTION

Codeine-7,8-oxide (codeine epoxide) was recently identified as a new metabolite of codeine. Therefore, morphine-7,8-oxide (morphine epoxide, Fig. 1) is assumed to be a metabolite of morphine. Findings of Takayanagi et al.2) using electrically stimulated guinea pig ileum suggested that morphine epoxide had a potent narcotic analgesic activity as described in the previous report of Miyata et al.3) and epoxidation of 7,8-double bond of morphine resulted in a trend for a decrease in the dependence liability. Furthermore, Mori et al.4) 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 morphine epoxide.

MATERIALS AND METHODS

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 Vasile).5) 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, 30 mg/kg of morphine epoxide or 15 mg/kg of morphine were given subcutaneously every 4 h to male Wistar strain rats (60 to 100 g in body weight). Antinociceptive activities of both drugs were measured after every injection.

The rats (80 to 100 g) were made dependent

FIG. 1. Chemical Structure of Morphine-7,8-oxide (Morphine Epoxide)
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/d, the second week, 40 mg/d, the third week, 60 mg/d and the fourth week, 80 mg/d.6-8) The body weight of the treated animals rapidly decreased upon withdrawal, the mean decrease being 23.6 ± 2.5 g (mean ± S.E.). After the confirmation of the decrease in body weight upon withdrawal, the animals were further treated with 40 mg/kg of morphine at 10 a.m. and 6 p.m. Next week, the animals were divided into 4 groups of 5 rats each. The control group was administered saline and the others were used as test groups which were subcutaneously injected with morphine or morphine epoxide. Decrease in the body weight was measured 24 h after the injection.

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

RESULTS

The antinociceptive action of morphine epoxide is shown in Fig. 2. A parallel line assay was employed for the antinociceptive potency ratio using morphine as a standard. Morphine epoxide was 0.62 times as potent as morphine and its 95% fiducial limits were 0.09 and 1.05. Antinociceptive actions of morphine (4 mg/kg, s.c.) and morphine epoxide (4 mg/kg s.c.) were abolished by the 15 min pretreatment of the mice with naloxone (1 mg/kg, s.c.) (data not shown). These results are consistent with the data obtained in the electrically stimulated ileum of the guinea pig.21

The antinociceptive actions of morphine epoxide and morphine were gradually reduced when morphine epoxide (30 mg/kg s.c.) or morphine (15 mg/kg, s.c.) were repeatedly administered every 4 h. The antinociceptive activity of morphine in the animals treated with morphine disappeared after the 10th administration of morphine while the morphine epoxide-treated rats still responded to morphine epoxide even after the 10th administration (Fig. 3). In the animals treated with either drug more than 4 times, the antinociceptive action of morphine was significantly smaller than that of morphine epoxide (Fig. 3).

Decrease in body weight of the rats repeatedly treated with morphine was 23.8 ± 2.6 g (mean ± S.E.) after the injection of saline instead of morphine. When morphine epoxide (40 mg/kg, s.c.) was injected instead of morphine, the mean decrease of body weight of the rats repeatedly treated with morphine was 18.2 ± 1.8 g. The body weight decreased with subcutaneous

FIG. 2. Dose Response Curves of Morphine Epoxide and Morphine in the Antinociceptive Action

Ordinate: antinociceptive effect is shown as the ratio of threshold pressure (g) after and 30 min before injection, abscissa: log dose (M). ●: morphine and ○: morphine epoxide. The drugs were administered subcutaneously. Each point is presented as a mean with S.E. of 7 experiments.
injection of 20 mg/kg morphine, the mean being 2.1 ± 2.5 g. This decrease in body weight was not significant. However, the increase of body weight was observed with subcutaneous injection of 40 mg/kg morphine, the mean being 1.8 ± 0.3 g. These are demonstrated in Fig. 4.

DISCUSSION

The antinociceptive potency ratio (0.62) of morphine epoxide relative to morphine was similar to the values obtained by Miyata et al.\textsuperscript{23} and by Takayanagi et al.\textsuperscript{29} The 95% fiducial limits (0.09 to 1.05) suggest that morphine epoxide is almost

\begin{figure}
\centering
\includegraphics[width=\textwidth]{threshold_pressure}
\caption{Development of Tolerance in the Antinociceptive Activity
Ordinate: threshold pressure (g) and abscissa: time (h) after administration. ○: with saline (s.c.), □: with morphine (15 mg/kg, s.c.) and ●: with morphine epoxide (30 mg/kg, s.c.). Each point presented is the mean with S.E. of 8 experiments. 1st, 2nd, 4th, 7th, and 10th administrations of the drugs, respectively.}
\end{figure}
as potent as morphine. This antinociceptive action of morphine epoxide was antagonized by naloxone, suggesting that this compound was a narcotic analgesic drug. These findings supported the results of Takayanagi et al.\(^2\) that the inhibitory action of morphine epoxide on electrically stimulated guinea pig ileum was antagonized by naloxone.

The results shown in Fig. 3 demonstrate that the development of tolerance is slower in the rats treated with morphine epoxide than in the rats treated with morphine when either drug was given repeatedly to the rats.

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 prevented by morphine at 20 and 40 mg/kg but not by morphine epoxide of 40 mg/kg. These results suggest that morphine epoxide is less potent than morphine in the inhibition of abstinence syndrome. The similar results were obtained on codeine epoxide.\(^3\) Introduction of the 7,8-epoxy moiety into morphine skeleton trends toward some decrease in dependency liability and in development of tolerance, as suggested previously in the electrically stimulated ileum of guinea pig.\(^4\)

REFERENCES