HOMOBENZOMORPHAN COMPOUNDS WITH A POTENT NARCOTIC ANTAGONIST PROPERTY

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Abstract—In consequence of testing antagonistic activity on morphine-induced analgesia and respiratory depression of the 2'-hydroxy-6,10-dimethy-7,8-homobenzomorphan, it was found that the order of antagonistic activity is N-cyclopropylmeth (trans isomer TA-414 and cis isomer TA-576) > N-allyl (trans isomer TA-412) > N-dimethylallyl (trans isomer TA-413 and cis isomer TA-415) with respect to the influence of replacing antagonistic substitution on the tertiary nitrogen. The properties of TA-414 and TA-576 in this regard were higher than those of nalorphine but slightly less than levallorphan. Moreover, the narcotic antagonist action of TA-414 was of long duration, comparable to that of nalorphine. On the other hand, TA-414 was entirely lacking an agonistic (analgesic) activity even at large doses, while TA-576 equaled nalorphine and pentazocine in the potency of agonistic activity in mice. Conclusively, TA-414 appears to fall under the category of a pure antagonist such as naloxone.

In the United States today, heroin addiction is a major social, political, and economic problem and control is most difficult (1–3). The U.S. Government as well as scientists wish to utilize non-addicting narcotic antagonists as a better weapon than methadone in the battle against narcotic addiction and drug abuse (4, 5).

It was first suggested that nalorphine would meet the objectives in humans, but in fact the use of this drug proved unfeasible as the action was short in duration and there was a high incidence of hallucinogenic effects (6–9). It is also known that cyclazocine (10–13) and levallorphan (8, 10, 12), which have good potency as narcotic antagonists, exert hallucinogenic effects in humans. Since naloxone is a potent narcotic antagonist (14–18) and has no physical or psychic dependence liabilities following successive medication (17, 19, 20), this drug has practical therapeutic significance in the treatment of narcotic addiction (4, 5). The disadvantages of naloxone are a short duration of action when administered parenterally (19) and a low potency when given orally (18, 21).

Thus, new non-addicting narcotic antagonists that are effective and do not have the disadvantages of naloxone are greatly in demand.

The homobenzomorphan derivatives were synthetized by Takeda & Kugita and some revealed potent analgesic activity in mice (22).

In the present experiment, the authors attempted further studies on analgesic and nar-
cotic antagonist activities of the homobenzomorphan derivatives which are replaced by various N-antagonistic groups, and the results were compared with those of the standard narcotic antagonists, naloxone hydrochloride, levallorphan hydrochloride, nalorphine hydrochloride and pentazocine hydrochloride.

The chemical structures of the homobenzomorphan derivatives used are shown in Table 1.

TABLE 1. Chemical structures of homobenzomorphan compounds.

| Compound | R₁          | R₂         |
|----------|-------------|------------|
| TA-412   | -CH₂-CH=CH₂ | -CH₃(trans) |
| TA-413   | -CH₂-CH=C<CH₃ | -CH₃(trans) |
| TA-414   | -CH₂        | -CH₃(trans) |
| TA-415   | -CH₂-CH=C<CH₃ | wCH₃(cis)  |
| TA-576   | -CH₂        | wCH₃(cis)  |

MATERIALS AND METHODS

The animals used in this experiment were male dd-K strain mice and male albino rabbits. Each group included 6 mice or 3-4 rabbits. The test compounds were dissolved in water and injected s.c. to mice and i.v. to rabbits.

The LD₅₀ for acute toxicity and the ED₅₀ for analgesic activity were calculated according to the Weil's method (23), and the AD₅₀ (mean antagonistic dose) on morphine was graphically calculated.

1) Acute toxicity

Mice weighing 18-22 g were employed for observation of acute toxicity. The LD₅₀ of test compounds was calculated from the lethality 24 hr after administration.

2) Analgesic activity

Analgesic activity was assayed in mice by the following three methods.

Hot plate method: In mice weighing 15-16 g, this method was based on that described by Eddy & Leimbach (24). The end point for this test was when a mouse licked its hind feet or jumped. The time that a mouse remained on the hot plate until showing one of the above end points was measured using a stopwatch. The reaction time was determined
before, and 10, 20, 30, 45 and 60 min after administration of a test compound. Analgesia was assumed to be present if the reaction times of the drug-treated animals exceeded 1.5 times of their mean control reaction times.

**Haffner's method:** This assay in mice weighing 15–16 g was the tail pinch method of Haffner modified by Takagi et al. (25). The nociceptive stimuli induced with an artery clip (pressure of 450 g) were given to the tail root of a mouse. Mice which demonstrated fairly well the biting response to a clip were selected prior to medication, and determination of analgesia was made 15, 30, 45 and 60 min after administration. When animals did not attempt to bite a clip within 6 sec, analgesia was considered to be positive.

**Writhing method:** The inhibition of acetic acid-induced writhing response in mice weighing 18–22 g was determined by a modification of the method of Koster et al. (26). Mice were injected i.p. with 10 ml/kg of 1% acetic acid solution 10 min after administration of a test compound and the number of writhings per animal was counted for 5 min starting at 10 min after the acetic acid injection. Analgesia was regarded as being present in the case of more than 50% reduction in comparison with the mean writhing number of control animals which had been administered physiological saline instead of a test compound.

3) **Antagonistic activity**

Narcotic antagonist activity was determined using morphine hydrochloride as an agonist.

**Antagonism of morphine-induced analgesia:** Antagonistic activity on morphine analgesia in mice was assayed by Haffner's method (25). Test compounds were simultaneously injected to mice with morphine 10 mg/kg s.c., which induced analgesia in approx. 80–100% of mice. The AD50 was defined as the dose required to abolish morphine analgesia in 50% of the experimental mice treated with morphine.

**Antagonism of morphine-induced respiratory depression:** Rabbits weighing 2.6–3.2 kg were anesthetized with urethane 1.2 g/kg s.c. Respiration was recorded with a multipurpose polygraph through the trachea, and the frequency of respiration was counted. A dose of morphine sufficient to induce severe respiratory depression (10 mg/kg i.v.) was administered, after which an i.v. dose of the test compound was given. The AD50 was defined as the dose which produced a 50% antagonism of morphine-induced depression in the respiratory frequency per min.

4) **Effect on respiration and blood pressure**

In rabbits weighing 2.6–3.2 kg, respiration and blood pressure were recorded through the trachea and the cervical artery respectively, using the same apparatus as that employed in the test for morphine antagonism.

**RESULTS**

1) **Acute toxicity**

Lethal potencies of test compounds are given in Table 2. At lower doses, the homobenzomorphan compounds did not exert any behavioral changes. These compounds,
injected in doses over approx. LD50/3, induced a slight relaxation of muscle tone similar to that observed with naloxone, levallorphan and nalorphine. At higher doses, mice demonstrated severe respiratory depression and died. Acute toxicity of the homobenzomorphan compounds was generally more potent than the other narcotic antagonists, naloxone, levallorphan and nalorphine.

2) Analgesic activity

As shown in Table 2, analgesic activity of the homobenzomorphan compounds except for TA-415 and TA-576 was not observed even with doses up to 22.5 mg/kg s.c. in the hot plate or writhing method and with doses up to 40 mg/kg s.c. using Haffner's method. Such inactivity was quite similar to that observed with naloxone and levallorphan. On the other hand, TA-415 and TA-576 revealed no analgesic activity up to 22.5 mg/kg s.c. and 40 mg/kg s.c. in the hot plate and Haffner's methods respectively, but these compounds inhibited acetic acid-induced writhing. The ED50 in the writhing method was shown to be approx. 20 mg/kg s.c. for TA-415 and 3.9 mg/kg s.c. for TA-576, as demonstrated in Table 2. Although the analgesic potency of TA-576 was slightly more potent than that of nalorphine and pentazocine, the dose response curve was relatively flat and writhings were not completely inhibited even at a dose of 22.5 mg/kg s.c.

| Compound   | LD 50 mg/kg s.c. (95% C.L.) | Analgesic ED 50 mg/kg s.c. (95% C.L.) |
|------------|-----------------------------|--------------------------------------|
| TA-412     | 113.5 (87.8–146.7)          | Hot plate: a,                   |
| TA-413     | 89.7 (69.4–115.9)           | b,                    |
| TA-414     | 104.0 (85.3–126.9)          | c,                    |
| TA-415     | 183.7                       | a, b,                  |
| TA-576     | 55.1 (43.8–69.3)            | a, b,                  |
| Naloxone   | >225.0                      | a, b,                  |
| Levallorphan| >225.0                     | a, b,                  |
| Nalorphine | 670.0                       | a, b,                  |
| Pentazocine| 190.1 (148.1–244.0)         | 14.5 (8.3–23.6)         |

a, b and c: No effect with doses up to 22.5, 40 and 100 mg/kg s.c., respectively.

3) Antagonistic activity

Antagonism of morphine-induced analgesia: Among the homobenzomorphan compounds, TA-576 possessed the most potent antagonistic activity on morphine analgesia, as is shown in Table 3. On the other hand, the antagonistic activity of TA-414 was approximately the same as that observed with nalorphine but was less potent than the activity of levallorphan and naloxone. The antagonistic activity of other homobenzomorphan compounds was very weak in comparison with the standard antagonists except for pentazocine. As TA-415 produced only a 25% blockade of morphine analgesia even at a high dose of 30 mg/kg s.c., the AD50 could not be determined.
TABLE 3. Antagonistic activity of homobenzomorphan compounds on morphine-induced analgesia in mice and respiratory depression in rabbits.

| Compound  | AD50 mg/kg (s.c.) | Analgesia |
|-----------|-------------------|-----------|
| TA-412    | 0.32              | 0.095     |
| TA-413    | 3.8               | 1.6       |
| TA-414    | 0.069             | 0.062     |
| TA-415    |                   | 3.1       |
| TA-576    | 0.021             | 0.060     |
| Naloxone  | 0.0010            | 0.0044    |
| Levallophan| 0.040             | 0.014     |
| Nalorphine| 0.078             | 0.16      |
| Pentazocine| 6.0               | 1.5       |

a : At a dose of 30 mg/kg s.c., a 25% blockade of morphine analgesia was observed.

Antagonism of morphine-induced respiratory depression: When rabbits were injected with morphine 10 mg/kg i.v., the respiratory rate decreased more than 90% as compared with the premedication status and this depression lasted at least for 3 hr. TA-414 and TA-576 at a dose of 0.01 mg/kg i.v. slightly antagonized morphine in respiration tests, while administration of 0.2 mg/kg i.v. of both compounds revealed approx. 80-90% antagonism in decreasing respirations of the rabbits treated with morphine. In order to completely abolish the respiratory depression of morphine, doses of more than approx. 3 times AD50

TABLE 4. Duration of antagonistic activity of homobenzomorphan compounds on morphine-induced respiratory depression in rabbits.

| Compound & dose (mg/kg i.v.) | Percent of antagonism% mean±S.E. | 2 min | 5 min | 10 min | 20 min | 30 min | 45 min | 60 min | 90 min | 120 min | 150 min |
|-----------------------------|----------------------------------|------|------|-------|-------|-------|-------|-------|-------|--------|--------|
| 0.9% Saline                 |                                  | 0.6  | 0.1  | -1.2  | -4.7  | -3.2  | -1.7  | -1.2  | 0.9    | 2.0    | 1.9    |
| TA-412                      | 0.285                            | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| TA-414                      | 0.186                            | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| TA-576                      | 0.180                            | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| Naloxone                    | 0.0132                           | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| Levallophan                 | 0.042                            | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| Nalorphine                  | 0.48                             | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |
| Pentazocine                 | 4.5                              | 0.7  | 0.6  | -1.2  | -3.8  | -3.3  | -3.8  | -3.7  | -4.2   | -5.7   | -4.7   |

a : Each value was calculated according to the following formula.

\[ \text{Percent of antagonism} = \frac{\text{A} - \text{B}}{\text{A}} \times 100 \]

A : No. of respirations before morphine injection.
B : No. of respirations after morphine injection.
C : No. of respirations after test compound injection which followed morphine.

b : Time after test compound injection.
of each compound were required.

The antagonistic potency of TA-414 and TA-576 was approx. 1/5 and 1/14 times that seen with levallorphan and naloxone respectively, as is shown in Table 3. The antagonistic potency of TA-412 was 1.7 times of nalorphine, whereas this activity was weak in TA-413 and TA-415.

Table 4 shows the duration of antagonistic activity of the homobenzomorphan compounds on morphine in test of respiration of rabbits when a dose of triple the AD50 of each compound was injected. An antagonism of respiratory depression following TA-414 0.186 mg/kg i.v. was observed immediately and reached a maximum a few minutes after administration, as illustrated in Fig. 1. Such a potent action gradually disappeared and severe decrease in respirations reappeared after one hr. Regarding duration of antagonistic action, TA-414 almost equalled that of nalorphine and was slightly lower than levallorphan, while with TA-576, the duration was equal to that of levallorphan. With TA-412 the duration was less than that with naloxone.

**Fig. 1. Typical records of reversal of morphine depressed respiration after administration of TA-414, levallorphan and naloxone in rabbits.**

4) Effect on respiration and blood pressure

TA-414 exerted no apparent change in respiration and blood pressure of rabbits with doses up to 0.5 mg/kg i.v., but it caused some decrease in the respiratory rate after an injection of 1–3 mg/kg i.v., as illustrated in Fig. 2. Increase in arterial blood pressure by 10–20 mmHg followed the respiratory depression. Naloxone, nalorphine and levallorphan resulted in a transient increase in the rate as well as the depth of respirations after injection of over approx. 2 mg/kg i.v., and severe respiratory arrest occurred in rabbits given pentazocine 5 mg/kg i.v.
DISCUSSION

Narcotic antagonists can be classified into two categories: those which have analgesic activity and those which fail to have an analgesic effect even after administration of very high doses. The former includes narcotic antagonist analgesics such as cyclazocine (11, 27, 28), nalorepine (29, 30) and pentazocine (31-34), while the latter includes non-analgesic antagonists such as naloxone (14-18) and levallorphan (8, 10, 12, 35).

Naloxone in particular is classified as a pure narcotic antagonist and has very high narcotic antagonist properties with no physical or psychic dependence liability (17, 19, 20). This being the case, this drug is widely used in various pharmacological investigations and recently was utilized in the U.S.A. as a form of chemotherapy for addicts (4, 5). Commercial use has necessarily been limited as the duration of action is short (19). As addicts must go to a hospital to be treated, the duration of the blocking action of narcotic antagonists is a major factor to be considered. Thus a number of compounds with potent narcotic antagonist activity such as EN-1639 (4, 5, 36), 1-BC-2605 (4, 5) and M-5050 (5, 37) were synthesized in several laboratories. These compounds have limited effectiveness as analgesics, but when injected into animals are longer acting than naloxone regarding the narcotic blocking effect.

Thus, the research on longer-lasting non-addicting narcotic antagonists with less agonistic activity was highlighted by scientists when adequate treatment of drug addicts was being considered.

Among the representative N-substituted homobenzomorphans studied in this experiment, the compounds with N-cyclopropylmethyl substitution (TA-414 and TA-576) exhibited more potent antagonistic activity on morphine than those with other N-antagonistic substitutions, N-allyl (TA-412) and N-dimethylallyl (TA-413 and TA-415). The trans isomer TA-414 showed almost the same potency as the cis isomer TA-576 in narcotic antagonism, and both these compounds possessed a slightly less potency than levallorphan but were more potent than nalorepine in this regard. Moreover, TA-414 of the duration of narcotic antagonist action was quite long and was comparable to nalorepine. TA-576 was somewhere between naloxone and levallorphan in duration of this property.

Tests in morphine-addicted monkeys by Villarreal & Seevers (38) showed that the ca-
pacity for precipitating abstinence syndrome is about 1/10 for TA-412 and 1/3 for TA-414 that is as potent as nalorphine but none for TA-413 and TA-415, and that TA-414 is longer lasting than nalorphine. The peak effect is sustained about 3 times longer than nalorphine.

Moreover, TA-576 exerted an agonistic (analgesic) property comparable to nalorphine and pentazocine in potency when tested under the writhing method, while the trans counterpart TA-414 possessed no agonistic (analgesic) property at doses of less than 22.5 mg/kg s.c. in either the hot plate or writhing methods in the tests done herein. It was found that the trans homobenzomorphans were all devoid of an agonistic (analgesic) property with weak to potent antagonistic activity and this property was not apparent in the cis counterparts.

TA-414 showed no agonistic effect on the respiratory rate at 8 times the antagonistic dose (0.5 mg/kg i.v.) in rabbits, however, at higher doses (1-3 mg/kg i.v.), weak agonistic properties such as respiratory depression and increase in blood pressure were present. Although a number of nalorphine-like antagonists depress respiration in humans (39-43), this action is not generally seen in other species (44). In this experiment, transient stimulation of respiration by naloxone, levallorphan and nalorphine was seen in rabbits anesthetized with urethane, thus indicating that these antagonists also have a certain agonistic property in respiration.

A pure antagonist should have no agonistic properties such as analgesia, respiratory and certain reflex depression or miosis. As the agonistic property of TA-414 in respiration was very weak as compared with its antagonistic activity to morphine, it is presumed that various side effects similar to morphine or related narcotic analgesics are extremely weak. A greater toxicity than naloxone, nalorphine and levallorphan was observed with TA-414, however the question for side effects need not been considered as narcotic antagonist activity of this compound was demonstrated following administration of doses well below the LD50.

Thus, the homobenzomorphan compound TA-414 with potent antagonistic activity is devoid of agonistic properties and appears to fall under the same category as that of naloxone and levallorphan. In addition, TA-414 could be used prophylactically to prevent narcotic addiction as an antagonist such as naloxone, providing it has no untoward effects in humans such as physical or psychic dependence liability, hallucinogenic action etc. such as is seen with nalorphine, cyclazocine and levallorphan.

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