BIPHASIC ACTION OF PENTAZOCINE IN MORPHINE-DEPENDENT RATS

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Accepted February 15, 1982

Abstract—The characteristic actions of pentazocine in morphine-dependent rats were investigated by a drug-admixed food (DAF) method. Pentazocine did not cause evident withdrawal signs when stopped after a continuous administration for 2 months at 3 different dose levels. A state of physical dependency on morphine was produced in rats by feeding them for 3 weeks with food that contained different levels of morphine. Animals exhibiting a moderate degree of morphine-withdrawal signs (17–18 hr after withdrawal) received a s.c. cross-administration with pentazocine at 0, 5, 10, 20, 40, 80, and 150 mg/kg. This drug at 20 mg/kg proved most suppressive of morphine-withdrawal signs, being about 1/4 as potent as codeine. In a dose range from 20 to 40 mg/kg, the action of pentazocine on the withdrawal signs was reversed, that is, doses not less than 40 mg/kg exerted a dose-related antagonistic action in all the 3 levels of morphine dependent rats. The challenge with levallorphan (2 mg/kg, s.c.) during the chronic application of pentazocine revealed slight withdrawal signs. These findings show that pentazocine has biphasic action on morphine dependence and suggests that this type of drug must have different properties from morphine type drugs.

A large number of clinical reports on dependence liability to pentazocine appeared from 1968 through 1969 (1–6). The clinical use of pentazocine also became popular in Japan, and pentazocine-dependent cases tended to increase among general patients and medical service people since 1971 (counting 55 cases in these 5 years), calling one's attention to the problem of pentazocine dependency.

Pentazocine is a drug rapidly metabolized in animals (7, 8) as well as in man (9, 10), and its analgesic effect lasts only for a short time such as 90 to 120 min. Koga (11) studied the dependence liability to pentazocine under a condition of continuous "exposure to drug" where the drug was always existing in the body using an intermittent i.v. infusion method which applied the drug automatically 24 times a day, and Laska and Fennessy (12) likewise studied the dependence on the same drug by a slow release emulsion method. Yanagita et al. (13) applied a gradually increased dose of pentazocine to monkeys by s.c. injection, 4 to 6 mg/kg, 4 times a day, for 60 consecutive days. A Drug-Admixed Food (DAF) method developed by the authors (14) was used in the present study. This method is easy to follow and not time-consuming, and as described in a previous paper of a study on the physical dependence on pethidine (15),
this method has been proven to be applicable to a dependence formation study on drugs rapidly metabolized or those which become quickly toxic as in the case of barbiturates when continuously applied (16).

Only few systematic studies on the dependence liability of laboratory animals to pentazocine have been published (1, 13, 17), and those results do not necessarily agree with one another. In their studies on cross-physical dependence between morphine and pentazocine, Koga (11) and Yanagita et al. (13) showed that the suppressive action on pentazocine against the signs of morphine withdrawal varied with the degree of morphine dependence (or the dose for maintaining morphine dependence); and in mildly morphine-dependent animals, pentazocine suppressed the signs of morphine withdrawal, but hardly suppressed or even tended to aggravate the signs of morphine withdrawal in severely morphine-dependent animals. From various aspects in their studies on the dependence liability to cyclazocine, benzomorphan derivatives analogous to pentazocine, Martin et al. (18), Jasinski et al. (2, 3), and Gilbert and Martin (19) indicated that the dependence on the benzomorphan derivatives was qualitatively different from that on morphine in subjective symptoms, withdrawal signs, and mode of antagonism against naloxone. In the present study, the physical dependence on pentazocine (oral route) and the cross-physical dependence liability to morphine were studied in comparison with those of codeine. Some new findings will be presented.

**MATERIALS AND METHODS**

1. Dependence formation to pentazocine: Sprague-Dawley rats (6 weeks of age) were divided into 4 groups, each consisting of 6 animals. Animals of the first group were administered pentazocine in a range from a low to a high dose (group A), the second group given the drug from a low to an intermediate dose (group B), the third group administered a low dose of pentazocine constantly for a long period (group C), and the last group was the untreated control (group D). Each animal was allowed to eat freely from either of 2 food containers, one containing twice as much pentazocine-admixed as the other. As the drug dependence was developed, animals would tend to eat preferably the food with a heavier drug content. Group A and B were fed initially with a pair of food-admixtures with pentazocine contents of 0.5 and 1 mg per g of food and these were gradually increased up to 4- and 6 mg/g food, and moreover, 6 mg/g food (group A) was administered after 77 days. During this period, the drug was withdrawn for 24 hr before increasing the dosage as well as about midway during one dose level feeding. Group B was fed initially with pentazocine at 0.5 and 1 mg/g food for 7 days, then at 1 and 2 mg/g food for 18 days, further at 2 mg/g food for 7 days, and finally the drug was naturally withdrawn. Animals were exposed to the drug totally for 32 days. Group C was fed with pentazocine at 0.5 and 1 mg/g food for 7 days, then at 1 and 2 mg/g food for 18 days, further at 2 mg/g food for 7 days, and finally the drug was naturally withdrawn. Animals were exposed to the drug totally for 32 days. Group C was fed with pentazocine at 0.5 and 1 mg/g food for 32 days with no increase in the dosage before withdrawal. Group D was fed only with normal food throughout the experiment (naive control).

2. Manifestation of withdrawal signs with levallorphan: During the continuous administration with pentazocine to the 3 groups of rats described under 1, each group received 2 mg/kg of levallorphan s.c. at different times: group A at 7 and 15 days when the dose of pentazocine reached 4 and 6 mg/g food, respectively, group B at 12 days with pentazocine at 1 and 2 mg/g food, and group C at 19 days with the unchanged initial dosage of 0.5 and 1 mg/g food. These animals were investigated for general behaviors and measured for body weight and
food consumption at intervals during the 24 hr after the challenge with levallorphan. Morphine-dependent groups prepared with 1/4 and 1/2 mg/g food (M-L₁) and 1/8 and 1/4 mg/g food (M-L₂ group) for not less than 3 weeks were challenged with 2 mg/kg of levallorphan. The body weights of rats used in this experiment were 230–250 g.

3. Cross-physical dependence liability to pentazocine in morphine-dependent rats: For the purpose of investigating the cross-physical dependence between morphine and pentazocine, 3 groups of rats (N=6) were prepared differently in the degree of physical dependence on morphine or in the maintenance doses of morphine dependence. Highly dependent rats (M-H group) were prepared by feeding them with food containing morphine at both 1 and 2 mg/g food, intermediately dependent ones (M-I group) were fed with 0.5 and 1 mg/g food, and lightly dependent ones (M-L₂ group) were fed with morphine at 1/8 and 1/4 mg/g food. All groups were fed as described above for 3 weeks. The control animals were fed only with normal food (naive control).

The cross-administration of pentazocine was started at a) 0 hr (when the animals were non-withdrawn dependent state) or b) 17–18 hr after withdrawal of morphine when the moderate withdrawal signs became manifest.

a) M-H and M-I groups of morphine-dependent rats (body weight: 350–380 g) received pentazocine at 20 mg/kg s.c. The control rats were fed only with normal food during the same period. The cross-administration with pentazocine was performed starting from 0 hr (morphine-dependent state) up to 24 hr after morphine withdrawal at intervals of 2 to 3 hr. The cross-administration was then stopped, and the animals were examined for the relapse of withdrawal signs during the following 24 hr. At the end of this period or 48 hr after morphine withdrawal, the animals were put back on the same foods as before.

b-1) Three groups of morphine-dependent rats, M-H, M-I, and M-L₂ were prepared. All 3 groups received pentazocine 20 mg/kg s.c. every 3 to 5 hr for the period from 17 hr until 48 hr after morphine withdrawal. After the cross-administration, animals were completely off any drug, and they were examined for general behaviors and measured for body weight until they recovered in body weight up to the level before the cross-administration. The control group again was fed only with normal food.

b-2) Seven groups (N=6) of rats (body weight: 230–250 g) which had developed physical dependence on morphine (M-I groups of rats) received pentazocine at 0, 5, 10, 20, 40, 80, and 150 mg/kg for investigating the dose-response relationship in the suppressive action of pentazocine on the morphine-withdrawal signs. The cross-administration was performed every 3 hr from 17 hr until 48 hr after morphine withdrawal. Rats were kept off morphine completely for 5 to 6 days after the cross-administration for the purpose of investigating whether morphine dependence was maintained or cross-dependence had been induced. During the cross-administration period that ensued, the animals were examined for general behaviors and measured for body weight.

b-3) For the purpose of comparing the cross-physical dependence liability to pentazocine with that to codeine, the suppressing actions of these 2 drugs on morphine withdrawal signs were studied in terms of a dose-response relationship. Rats (body weight: 230–250 g) made dependent on morphine (M-I groups of rats) were divided into 7 groups, each consisting of 6 animals. Of these groups, 3 received codeine s.c. at 5, 10, and 20 mg/kg between 18 and 48 hr after morphine withdrawal, followed by a
9-day complete withdrawal. Three other groups likewise received pentazocine at 5, 10, and 20 mg/kg. Each drug was applied every 3 hr. The control group received the cross-administration with saline in place of codeine or pentazocine.

MATERIALS AND METHODS

1. Dependence formation to pentazocine: Average pentazocine intake during the period of gradually increased dosage schedule was 53 mg/kg/day at the initial stage (0.5 and 1 mg/g food), 244 mg/kg/day at 4 and 6 mg/g food, and 388 mg/kg day at the final stage (6 mg/g food). During the period of gradually increased pentazocine in group A, neither weight gain was retarded nor was food consumption depressed, and virtually no abnormal signs were observed in the general behavior. Throughout the administration with a couple of days for intermission, as stated in Methods, withdrawal signs such as diarrhea, hyperirritability, loss in body weight, etc. were hardly observed. Figure 1 shows changes in body weight during the 24 hr after the final administration with pentazocine at 6 mg/g food (group A). Animals showed slight abnormality in the circadian rhythm of body weight and significant reduction in body weight from 4 to 12 hr after pentazocine withdrawal. However, no severe withdrawal signs were evolved in any of the groups (group A to C) where different administration schedules were applied.

Physical dependence formation to pentazocine was a good contrast to that in the case of morphine. During feeding with morphine in the M-L1 and M-L2 groups of rats, the withdrawal of morphine from the food for 2 days after 7 days feeding (Fig. 2) resulted in a significant weight loss. Food and water consumption by morphine withdrawal in the M-L1 group decreased in parallel with loss in body weight. However, in rats maintained at a lower dose level of morphine (M-L2 group), alteration in food and water by drug withdrawal were slight compared with that of body weight in the M-L1 group. The fact indicates that change...
in body weight is a more sensitive indicator in morphine type dependence than changes of food and water intake.

2. Manifestation of withdrawal signs with levallorphan: Figure 3 shows the results of the challenge with s.c. levallorphan to a group on the high maintenance dose for pentazocine, and the signs of pentazocine-withdrawal were hardly induced. When the rats dependent on morphine in the M-L₁ (31 mg/kg/day) and M-L₂ (10 mg/kg/day) groups were challenged with the same dose of levallorphan, the signs of withdrawal, e.g., “wet dog shakes”, diarrhea, piloerection, and severe weight losses (by about 7%) were induced in the M-L₁ group; while only mild signs of withdrawal were noticed with the narcotic antagonist and remained only for a short period in the M-L₂ group, although this group had exhibited such significant weight losses as 5 to 6%, 24 hr after the natural withdrawal prior to the levallorphan challenge (Fig. 2).

3. Cross-physical dependence liability to pentazocine in morphine-dependent rats; a) The cross-administration of pentazocine exerted potent suppressive effects on the appearance of withdrawal signs of morphine in both groups which had different maintenance dose level (M-H: 58 mg/kg/day, M-I: 36 mg/kg/day on average) from each other (Fig. 4), indicating the same mode of suppressive action on morphine withdrawal signs, irrespective of the degree of physical dependence on morphine. Moreover, when the rates of suppression of weight loss in these 2 groups were compared with that in the control group immediately and 2 hr after the final cross-administration, the rates were 70 and 71% in the M-I group and 55 and 54% in the M-H group. In other words, it was shown that the potency of suppressive action of a certain dose of pentazocine, 20 mg/kg, was inversely proportional to the
degree of morphine dependence. When the untreated control rats were likewise administered continuously with pentazocine at 20 mg/kg, no toxic influence was seen on either body weight gain or food consumption. The same continuous s.c. administration with

![Graph showing time course changes in body weight and cumulative food consumption following the challenge with levallorphan to rats repeatedly applied pentazocine on a gradually increased dosage schedule (on day 15 at the dose level of 4 and 6 mg pentazocine/g food) shown in the text and also to rats dependent on morphine. Each group consisted of 6 rats. Each plot denotes the mean of 6 rats.]

*Fig. 3.* Time course changes in body weight and cumulative food consumption following the challenge with levallorphan to rats repeatedly applied pentazocine on a gradually increased dosage schedule (on day 15 at the dose level of 4 and 6 mg pentazocine/g food) shown in the text and also to rats dependent on morphine. Each group consisted of 6 rats. Each plot denotes the mean of 6 rats.

![Graph showing difference in weight loss suppression by cross-application with pentazocine at 20 mg/kg on morphine withdrawal from 2 groups of rats different maintenance dose of morphine dependence. After 24 hr withdrawal following the cross-application with pentazocine (at the marked 48 hr in the figure), the animals were put on morphine-admixed foods of the same concentrations as before the withdrawal to observe their recovery from weight losses due to the withdrawal. The value for each group denotes the mean of 6 animals.]

*Fig. 4.* Difference in weight loss suppression by cross-application with pentazocine at 20 mg/kg on morphine withdrawal from 2 groups of rats different maintenance dose of morphine dependence. After 24 hr withdrawal following the cross-application with pentazocine (at the marked 48 hr in the figure), the animals were put on morphine-admixed foods of the same concentrations as before the withdrawal to observe their recovery from weight losses due to the withdrawal. The value for each group denotes the mean of 6 animals.
pentazocine at 20 mg/kg hardly caused general toxicity in morphine-dependent rats.

b-1) The signs of morphine withdrawal were obviously suppressed in all three groups of morphine-withdrawn rats, M-H (maintenance dose: 67 mg/kg/day on average), M-I (37 mg/kg/day on average) and M-L2 (12 mg/kg/day on average), with pentazocine at 20 mg/kg starting 17 hr after morphine withdrawal; and this suppression was in almost the same manner as observed in the aforementioned cross-administration with pentazocine starting immediately after morphine withdrawal (Fig. 5). When the suppression of morphine withdrawal signs with pentazocine was expressed in terms of weight loss rate 2 to 3 hr after the administration with pentazocine (the rate at the start of morphine withdrawal being referred to as 0%), the weight loss was completely suppressed in the M-L2 group by the second cross-administration (up to 40 mg/kg in total), -1.8% in the M-I group after the third administration (to 60 mg/kg in total), and still -5.2% in the M-H group even after the fifth administration (to 100 mg/kg in total). The suppressive action of this drug on morphine-withdrawal signs and the cross-physical dependence liability with morphine were further revealed by the abrupt weight loss in animals by withdrawal following the cross-administration with pentazocine. In other words, the more intensely the signs of morphine withdrawal were suppressed, the more severe the signs were relapsed (Fig. 5).

b-2) The action of pentazocine cross-administered from 17 hr up to 48 hr after morphine withdrawal in morphine-dependent animals (maintenance dose: 55 mg/kg/day on average) was characteristic of an agonist-antagonist mixture (Fig. 6). From the dose-

![Fig. 5. Suppression of weight loss by cross-application of the same dose of pentazocine (20 mg/kg, s.c.) to 3 groups of rats (N=6) different maintenance dose of morphine dependence and relapse of withdrawal signs due to withdrawal following the cross-application. The black bar along the abscissa denotes the period of cross-application of pentazocine to rats from which morphine had been withdrawn. Arrows in the figure denote cross-application of pentazocine.](image)
Response relationships for doses from 5 to 150 mg/kg of pentazocine, the biphasic action of pentazocine on morphine dependence was clearly demonstrated. From the time course of body weight after the first 6, 12, 24, and 30 hr of the cross-administration and from the relapse of withdrawal signs at 2, 17, 24, 48, and 72 hr after cessation of pentazocine administration, the doses of pentazocine smaller than 40 mg/kg showed obvious agonistic (suppressive) action on morphine-withdrawal signs; and doses higher than 40 mg/kg reacted rather antagonistically on morphine withdrawal signs. The 5-day complete withdrawal following the final cross-administration clearly revealed that the weight loss relapsed in animals receiving pentazocine not larger than 20 mg/kg, while those receiving the drug at a dose not smaller than 40 mg/kg conversely tended to regain body weight.

b-3) Dose-related suppression of weight loss by morphine withdrawal (maintenance dose: 55 mg/kg/day on average) was obvious from 3 hr (21 hr in Fig. 7) after the cross-administration. The difference in potency of the suppressing action on the signs of morphine withdrawal among doses manifested clearly 18 hr (36 hr in Fig. 7) after the cross-administration; especially, the difference between 10 and 20 mg/kg of codeine became clear (Fig. 7). On the whole, the cross-administration with pentazocine at 20 mg/kg exerted the same degree of suppressing effect as codeine at 5 mg/kg by the same route of administration. There was a correlation between the degree of withdrawal signs relapsing during the complete withdrawal of the drug and the dose of cross-administration with either of these 2 drugs, that is, the signs were more severe in proportion to the dose of either drug (Fig. 7). Thus, it was revealed that a dose of s.c. pentazocine not more than 20
mg/kg suppressed the morphine withdrawal signs dose-dependently and that this suppressing action was about 1/4 as potent as that of codeine.

**DISCUSSION**

Pentazocine is known to act as an antagonist against the analgesia, respiratory depression, and Straub's tail reaction of morphine on naive animals, and pentazocine itself was shown to have morphine-like actions such as analgesia, respiratory depression, etc. (20–25). In a study of the analgesic action of pentazocine using a dose range from 4 to 48 mg/kg (s.c.), Gray et al. (26) showed that the analgesic action of this drug, unlike the dose-dependent analgesic action of morphine, tended to be weaker when it was used in higher doses. Its mode of action against morphine dependence is said to be as a weak opiate-antagonist or an agonist-antagonist mixture, but there are still various opinions about this (1, 11–13, 19, 27).

Fraser and Rosenberg (1) and Jasinski et al. (3) reported that 10 to 20 mg/kg of pentazocine exerted similar actions to those of 10 mg of morphine when applied to man, but 40 mg of the former exerted unpleasant subjective effects, unlike the latter. They further showed that when morphine was substituted for by pentazocine in morphine-dependent patients, a low dose suppressed the signs of morphine withdrawal, although not completely; while a high dose, like a placebo, failed to exert any withdrawal-suppressing effects, but acted undesirably rather than allowing a natural morphine withdrawal per se. Pentazocine in a high dose thus worked rather as an antagonist against morphine dependence in man.

Koga (11) and Yanagita et al. (13), on the other hand, revealed that the mode of action of pentazocine substituted for morphine dependence changed with the maintenance dose for morphine dependence rather than with its dose for cross-administration. These data proved a weak sup-
pressing action of pentazocine on the withdrawal signs of morphine, but they did not find a biphasic action for pentazocine. As a result of experiments on cross-physical dependence liability to pentazocine at 7 dose levels (5–150 mg/kg, s.c.) in rats exhibiting moderate signs of morphine withdrawal (at 17 hr after morphine withdrawal) not more than 20 mg/kg of pentazocine was found to suppress the morphine withdrawal signs in a dose-related manner while not less than 40 mg/kg conversely showed a dose-dependently weaker agonistic action on morphine dependence (Fig. 6). When morphine-dependent rats at 3 grades of maintenance dose of morphine dependence received pentazocine at 20 mg/kg this dosage regimen proved to exert an obvious suppressing action on the signs of morphine withdrawal in all the 3 groups (Figs. 4, 5). The present authors observed that this drug exerted a biphasic action which depended on the cross-administered doses rather than on the degree of morphine dependence.

Jaffe and Martin (28) hypothesized this different mode of action on subjective effects, analgesic action, respiratory depression, and antagonism with narcotic antagonists between morphine and pentazocine in terms of 3 narcotic receptors, e.g., μ, κ and σ. Morphine exerted an effect as an agonist on μ and κ receptors, and on the other hand, pentazocine acts antagonistically on μ receptors and agonistically to κ receptors as well as morphine-type drugs. The present experiment suggests that a large dose of pentazocine (more than 40 mg/kg, s.c.) primarily acts on the κ receptor and secondarily on μ receptor, which rather precipitates the withdrawal signs of morphine.

The dependence formation of pentazocine has already been confirmed in rats by Goode (27), Koga (11), and Laska and Fennessy (12). They all used a continuous infusion method or a slow releasing drug solution, that is, rats were exposed to high doses of pentazocine. In our present experiment, pentazocine in relatively low doses markedly suppressed the signs of morphine withdrawal. However, repeated administration of a low dose level of this drug (43 mg/kg/day) was hardly accompanied by distinct withdrawal signs as compared with potency to maintain morphine dependence. This finding agreed with that by Deneau and Seevers (17) and by Fraser and Rosenberg (1), indicating that pentazocine would produce a mild physical dependence.

Furthermore, the rats on repeated administration of pentazocine-admixed food were challenged with levallorphan, but no distinct withdrawal signs were precipitated in these animals compared with those on morphine, codeine, or pethidine treatment (14, 15). Keats and Telford (22) reported that neither levallorphan nor nalorphine exerted any antagonistic action on the respiratory depression with pentazocine. Fraser and Rosenberg (1) showed that there was no difference between the response of pentazocine-dependent patients to the challenge with saline or nalorphine. Our present results were very similar to their data.

On the other hand, Gilbert and Martin (19) observed that about 20 times the dose of naloxone required for the precipitation of withdrawal signs of morphine was needed to precipitate withdrawal signs of cyclazocine, and they considered that far larger doses of levallorphan would be required in the case of dependence on the benzomorphan derivatives compared with those in the case of dependence on morphine-type drugs. In our present experiment, more large doses of levallorphan or the pure antagonist naloxone would precipitate pentazocine withdrawal signs.

Since it is likely that pentazocine-type analgesics will be further developed from
now on, the result of the present study suggests the necessity for characterizing
such drugs thoroughly by careful performance of physical dependency tests.

Acknowledgement: The present study was subsidized in part by the Drug Research
Grant by the Ministry of Health and Welfare, Japan for the “method of evaluation of drug
dependence in small animals.”

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