STUDIES ON THE PHYSICAL DEPENDENCE OF A NEW CENTRAL ANALGESIC; 1-(m-METHOXYPHENYL)-2-DIMETHYLAMINOMETHYL CYCLOHEXANOL (1) HCL (CG-315)

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Since earlier studies with nalorphine in humans demonstrated analgesia (1, 2) without producing dependence of the morphine type (1–3), a considerable effort has been made to discover a drug having similar characteristics, but without undesirable psychic effects. Pentazocine was found to be in this category (4–7).

Recently, 1-(m-methoxyphenyl)-2-dimethylaminomethyl cyclohexanol (1) HCl (hereafter referred to as CG-315) was synthesized as a new central analgesic, by Grünenthal Co., Ltd., West Germany. Henmi et al. (8, 9) demonstrated that analgesic action of CG-315 is similar to that of dihydrocodeine and also potentiates the response to adrenaline of nictitating membrane and cardiovascular organs in cats. Experiments were carried out to evaluate the physical dependence liability in rats.

MATERIALS AND METHODS

Donryu S strain white rats of both sexes, weighing from 80 to 100 g were used for all experiments. The rats were kept in individual cages and maintained on a commercial diet (CA-1, Nippon CLEA Co., Ltd., Tokyo). Food and water were not restricted. Animals were usually weighed daily, the mean body weight of control and drug-treated groups being recorded.

In the present experiments, the animals were divided (at random) into four groups of twenty. Rats in the first group were given four s.c. injections of morphine daily at 6 hr intervals (6 a.m., noon, 6 p.m. and midnight) for 60–75 consecutive days, unless otherwise noted. The initial dose of morphine was 20 mg/kg/day during the first week (5 mg/kg injected daily × 4; hereafter stated only as the daily dose), 40 mg/kg in the second week, 60 mg/kg in the third week, 80 mg/kg in the 4th week and 100 mg/kg in the 5th week. Animals in this group were maintained at this dose until sacrificed. In the second group of rats given CG-315 (group A), the initial dose of the drug was 20 mg/kg in the first week, 40 mg/kg in the second week, 60 mg/kg in the third week, 90 mg/kg in the 4th week and 120 mg/kg in the 5th week, while in another group (group B) given CG-315, 20 mg/kg was used in the first week, 50 mg/kg in the second week, 80 mg/kg in the third week, 120 mg/kg...
in the 4th week and 160 mg/kg in the 5th week. Rats in these groups were maintained at these doses until sacrifice. The 4th group, control, was given the same amount of the solvent.

All the test drugs were dissolved in 0.1% acetate buffer (pH 7.1).

The evaluation of physical dependence was based on a marked fall of body weight 24 hr after withdrawal from chronic drug administration or by employing levallorphan.

The analgesic effect of test drugs was measured according to a modified Haffner's method (10).

RESULTS

1) Effects of morphine and CG-315 on rats during chronic treatment and withdrawal

With morphine administration it was possible, irrespective of sex difference, to maintain the body weight of rats at control levels even under the stated dosage schedule (Figs. 1, 2). Substituting saline for morphine in these groups or administering levallorphan, a prominent abstinence syndrome developed including considerable weight loss, diarrhea, irritability etc., however CG-315 did not prevent the occurrence of withdrawal signs as above mentioned, when substituted for morphine in the chronically treated animals. When morphine was readministered to these animals during withdrawal, the increase in body weight was rapid and soon restored to normal levels.

In CG-315 treated groups, there appeared a slight reduction in the growth curve from the end of the second week, but no significant change in general behavior was observed. Unlike the morphine-treated group, rats chronically treated with CG-315 did not show any great decrease in body weight or prominent abstinence signs after abrupt withdrawal of the drug or challenging by levallorphan.

In order to clarify the development of physical dependence of CG-315, body weight

![Fig. 1. Body weight of male rats during chronic treatment with an increasing dose of both drugs.](image-url)
change was plotted every 6 hr. Although the fall of the mean body weight in the CG-315 treated group was greater during the first 6 hr than it was in the morphine group, the spontaneous recovery of body weight in the CG-315 group 12-24 hr later was more rapid than that in the morphine group (See Fig. 3). Furthermore, in cross-administration experiments, decrease in body weight in the morphine group could not be prevented, while substitution of morphine in CG-315 group produced no significant effect (Fig. 4).

These results suggest that physical dependence on CG-315 is hardly present on the basis of body weight loss, and if present, is far milder than that on morphine.
2) Development of tolerance to both morphine and CG-315

Determination of analgesic effects was done every fourth day after beginning the experiment. In the morphine group, on the first day of the experiment, morphine in a dose

![Graph showing effect of cross-administration between two drugs.](image)

**Fig. 4.** Effect of cross-administration between the two drugs. Drugs were substituted at 6 a.m. and returned at the point indicated by the arrow.

![Graph showing effect of chronic administration on rat adrenal weight.](image)

**Fig. 5.** Effect of chronic administration of both drugs on rat adrenal weight. Each bar represents the mean of 20 rats.
of 5 mg/kg produced an analgesic effect in almost every animal. After 40 days of chronic treatment, 25 mg/kg caused a similar effect in only about 10%. After administration of levallorphan, a slight increase of the analgesic effect was observed. In the CG-315 group, on the other hand, the drug in a dose of 30 mg/kg produced an analgesic effect in about 70% in the beginning, and even after 40 days, CG-315 in a dose of 60 mg/kg still showed a positive effect in about 30%. A cross-injection between CG-315 and morphine revealed a mild mutual reduction of the analgesic effect.

Thus, development of tolerance to CG-315 was observed to be comparatively slower than to morphine.

3) Effect of chronic treatment on rat adrenals

It is well known that chronic administration of morphine in rats causes hypertrophy of the zona fasciculata of the adrenal cortex (11–16). As shown in Fig. 5 repeated injections of CG-315 unlike morphine, failed to cause an increase in adrenal weight in male and female rats.

DISCUSSION

Akera and Brody (17) reported that loss of body weight upon withdrawal is the best index of addiction in rats. They further emphasized that observations on the state of the animal during chronic drug administration would vary with size and the frequency of the dose, for example, morphine should be given at least three times daily, since the duration of action of morphine is less than 8 hr. Any change resulting from the single or twice daily injection may result from repeated withdrawal or stress rather than from chronic effect of morphine per se.

Thus, to evaluate the physical dependence of CG-315 in rats, the drug was administered four times daily at 6 hr intervals and treatment was continued over 5 weeks with a gradual increase in dosage schedule, while simultaneously comparing reactions to morphine.

First, a slight reduction in the growth curve appeared during CG-315 chronic administration, but significant changes in general behavior were not observed. Moreover, unlike the morphine treated group, rats chronically treated with CG-315 showed neither any great loss of body weight nor prominent abstinence signs after abrupt withdrawal of the drug or challenging by levallorphan, though there was a slight loss of body weight 24 hr after withdrawal of CG-315, suggesting that a moderate dependence on the drug may be present.

Consequently, the change in body weight was plotted every 6 hr. Although the fall of body weight in CG-315 treated group was greater during the first 6 hr, the spontaneous recovery of body weight with CG-315 12–24 hr later was more rapid than that with morphine. Furthermore, in cross-administration experiments, the fall in body weight in the morphine group could not be prevented, while substitution with morphine in the CG-315 group produced no significant effect.

Akera and Brody (17) demonstrated that recovery of body weight after abrupt withdrawal of morphine was slow and at 9 days the animals had not completely regained the
weight loss after withdrawal. Therefore, evidence that spontaneous recovery of body weight in CG-315 treated rats was seen within 12–24 hr after withdrawal suggests that physical dependence on CG-315 is hardly present on the basis of body weight loss, and if present, it is far milder than that on morphine.

On the other hand, development of tolerance to CG-315 in the chronically treated rats was confirmed, though it was apparently slower than that to morphine.

In the present study, increase in adrenal weight was seen during chronic treatment with morphine, but not with CG-315. This result relates to the findings reported by Yano et al. (18, 19) that morphological changes of the mitochondria in adreno-cortical cells of rats treated with repeated injections of morphine after abrupt withdrawal were apparently observed, however, this was not the case with the CG-315 chronically-treated rats.

SUMMARY
1. Physical dependence liability of CG-315, a new central analgesic, was examined by measuring the decrease in body weight in chronically treated rats after abrupt withdrawal or by utilizing levallorphan.
2. Physical dependence on CG-315 was not observed, however, a moderate tolerance to the drug did develop.
3. Increase in adrenal weight in CG-315 treated rats was not seen, unlike the case of rats under morphine treatment.

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