Pharmacological Studies of GB-105 (N-Phenyl-N-acetylglycine Dimethylamide) and GB-302 (N-[*p*-Ethoxyphenyl]-N-acetylglycine Dimethylamide), in Special Reference to Comparative Studies with Acetanilide and Phenacetin

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Nippon Yakurigaku Zasshi (*Folia Pharmacological Japonica*), **57**, 435 (1961)

In the previous studies of a series of N-phenylglycine amide derivatives, the several derivatives were found to be less toxic than acetanilide (A) or phenacetin (P) and to possess almost the same analgesic activity as (A) or (P) in mice. GB-105 and GB-302, because of their relatively high activity and high solubility in water, were most interesting and examined pharmacologically. The results obtained were as follows:

1) The acute toxicity tests showed that GB-105 was 1/1.3 tol/2.6 as toxic as (A) or (P) in mice and 1/1.9 to 1/2.0 as toxic as (A) or (P) in rats and GB-302 was 1.8 to 2.1 times as toxic as GB-105 in mice or rats.

2) When tested for analgesic activity according to modified Haffner's method in mice, GB-105 and GB-302 had almost the same activity as (A) or (P).

3) GB-105 possessed no hypothermic action and GB-302 was much less hypothermic than (A) or (P) in normal mice. But GB-105 and GB-302 exhibited profound antipyretic action in febrile rabbits.

4) GB-105 and GB-302 showed moderate supression on the edema of rat's hindpaws induced by the local injection of formalin, egg-white, dextran and hyaluronidase.

5) GB-105 and GB-302 showed only slight and transient vasodepressor response and respiratory depression in anesthetized dogs.

6) GB-105 and GB-302 showed slightly negative chronotropic action in isolated rabbit auricle and weak vasodilatation in isolated rabbit ear vessel.

7) After the administration of GB-105 and GB-302 in man and cats, the methemoglobin formation was not observed at all.

8) Solubility of GB-105 and GB-302 in water at 20°C was 2.3 and 2.1 g/ml respectively.

The pharmacological properties suggest that they may be of some value as a water soluble antipyretic analgesic.

Studies on Pharmacological Action of 2-Anilinoacetamide Derivatives

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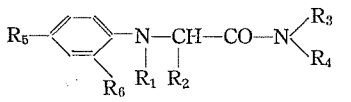
Screening tests were carried out, with special emphasis on toxicity and an-

algesic action, on numerous 2-anilinoacetamide derivatives, prepared for the purpose of decreasing the toxicity and increasing solubility of acetanilide and acetophenetidine with increase or retention of their pharmacological effect.

Two compounds were found to satisfy these obiectives: GB-105 and GB-302.



GB-105: R_1=$COCH_3$, R_3, R_4=CH_3, R_2, R_5, R_6=H

GB-302: R_1=COCH, R_3, R_4=CH_3, R_2, R_6=H, R_5=OC_2H_5

A Phrmacological Study of 6-Hydroxy-4a, 10-Trimethylene-1, 2, 3, 4, 4a, 9, 10, 10a-Octahydrophenanthridine

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The structure-activity relationship of various chemical compounds, which resembled to morphine in their structures and which were synthesized by Sugimoto *et al.*, has been reported. Among those compounds a reacemic 6-hydroxy-4a, 10-trimethylene-1, 2, 3, 4, 4a, 10, 10a-octahydrophenanthridine hydrochloride (DH-7), which have a nitrogen atom at 9-position of the morphinan ring, showed almost the same strong analgesic activities as morphine hydrochloride in a series of screening test.

Further studies of the analgesic activity of DH-7 and the comparative pharmacological studies of the drug with morphine hydrochloride and levorphanol tartrate are described in this report.

1. The pharmacological effects of DH-7 which resembled to that of morphine were as follows: the analgesic effect which was not inferior to that of morphine was antagonized by nalorphine. The same effect of DH-7 by the intraperitoneal injection was potentiated by beta-glucuronidase. The same effect was decreased and at last disappeared by its chronic daily administration. Among these effects, the hypothermic effect in mice and the hyperthermic effect in rats, miosis in rabbits and mydriasis in dog by the subcutaneous injection, the depressive effects on the spontaneous respiration and blood pressure of the anesthetized dog and rabbit, hyperglycemia in rabbits, inhibition of the transfer movement of intestine of mice, DH-7 was usually less active except the analgesic effect. Besides the stronger analgesic effect, DH-7 showed a powerful tendency toward the analgesic tolerance in mice.

2. The chronic administration of 4, 8 and 16 mg/kg of DH-7 to rats for 90 days did not reveal any effect on the body weight, blood picture and viscera.

Addenda

1) The abstinence symptoms of morphine addicted monkies were not suppressed by administration of 1-16 mg/kg of DH-7. Therefore, it seems that DH-7 has not physical dependence capacity.

2) From the result of clinical trials analgesic effect of 10 mg of DH-7 was