(154)

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ADDICTIVENESS OF TWO BENZIMIDAZOLE DERIVATIVES

Preliminary Report

Hunger, et al (1) and Gross and Turian (2) have found that some basically substituted benzimidazole derivatives have analgesic activity. Since these compounds constitute a completely new chemical class of analgesics, two compounds were referred to the Addiction Research Center, USPHS Hospital, Lexington, Kentucky, for determination of their addictive potentialities in man. This report presents the work accomplished prior to May 1, 1959. It is preliminary in nature and does not contain sufficient information to warrant any final statement of the addictiveness of the compounds as compared with morphine and codeine. It is presented at this time for purposes of information only.

The specific compounds referred for study were 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitro benzimidazole (Ba-19390, NIH-7586, ARC I-G-1) and 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfonate (Ba-20684, NIH-7607, ARC I-G-2). In this report, the drugs will be identified by their NIH code numbers.

As a class, these compounds possess a morphine-like spectrum of pharmacological activity (2,3,4). They are

B-143

analgesic in mice and rats, cause the Straub reaction in mice, sedation and miosis in dogs, excitement and pupillary dilatation in cats, and respiratory depression in rabbits and other animals.

NIH-7586 was analgesic in mice (2,3,4) by both subcutaneous and oral routes [ED-50=1.5 mg/kg (3)]. In addicted monkeys, it was twice as potent as morphine in suppressing abstinence from morphine (5). Some preliminary clinical experimentation has been done in Switzerland (4). In man, NIH-7586 is reported to have a good analgesic effect in doses of 15 mg subcutaneously or 25-50 mg orally. Respiratory depression was reported after intravenous administration, no "excessive" respiratory depression after subcutaneous administration, and no respiratory depression after oral administration (4). However, Dr. N. B. Eddy received information that the compound was to be marketed for oral administration only because of respiratory depression after parenteral administration.

NIH-7607 is an extremely potent compound in animals. The ED-50 (subcutaneously) for analgesia in mice was 0.0012 mg/kg (3). NIH-7607 is about 1700 times as potent as morphine in this species. NIH-7607 was 1500 times as potent (0.002 mg NIH-7607=3 mg morphine) subcutaneously in alleviating abstinence in the addicted monkey. No information on trials in man is available.

Methods

Drugs. Because of reports of respiratory depression after parenteral administration, the oral route of administration was used exclusively. NIH-7586 was available in compressed tablets each containing 25 mg. NIH-7607 was given in solution in distilled water in concentrations of 0.01 and 0.1 mg per ml. Drugs were administered with patients in the fasting state. Identity of the drugs was unknown to the patients but was known to the observers ("single-blind").

Effects of single doses. These tests were conducted in non-tolerant former morphine addicts who volunteered for the experiments. Drugs were administered at 7:30 a.m. Observations were made at hourly intervals until 11:30 a.m. and at intervals of two hours thereafter until 9:30 p.m. At each observation the patient completed a simple questionnaire consisting of the following questions: "I feel the medicine"; "The feeling is like: morphine, marihuana, barbiturates, benzedrine, heroin"; "I don't feel anything"; "I am relaxed"; "I have a drive"; "I am nauseated"; "I am sleepy"; and "I would like more". At each observation time, the diameter of the pupils was determined under conditions of constant light and accommodation by comparing the size of the pupils with those of blackened circles in 1-mm steps on a card (Experienced observers agree as to

size of pupil within 1 mm using this simple method). The aides also made general observations and notes on the behavior of the patients. Initial doses used were 25 mg of NIH-7586 and 0.01 mg of NIH-7607. The doses were gradually increased from trial to trial until definite subjective and objective effects were obtained, after which a sufficient number of patients were given the dose found to be effective in the preliminary trials to permit a rough quantitative evaluation of potency in inducing subjective effects as compared with morphine or codeine.

In the case of NIH-7586, subjective and objective morphine-like effects began to appear when 100 mg were given, so 13 patients received this amount of the drug. In the case of NIH-7607, morphine-like effects began to appear when two doses of 0.15 mg were administered at an interval of two and one-half hours, or after a single dose of 0.25 mg.

The questionnaires completed by the patients were scored as negative (denial of any subjective effect), positive for opiates (effects reported to be like those of morphine or heroin), positive for other drugs (reported to be similar to those of barbiturates, marihuana, or benzedrine), or questionable (some subjective effect reported but no definite identification of being similar to any drug was made).

Difference in the size of the pupils after the drugs was calculated by subtracting the diameter after the drugs from the diameter prior to the drugs. The area under the time action curve for pupillary constriction was then calculated by the method of Winter and Flataker (6).

Substitution of NIH-7586 and 7607 for 24 hours. Five patients who were addicted to and stabilized on 60 mg ~~mg~~ of morphine sulfate four times daily were available for these tests. The patients received their last dose of morphine at 4:00 p.m. In the succeeding twenty-four hours the patients received NIH-7586 and 7607 orally in doses and at intervals which were thought, on the basis of preliminary experiments, to be approximately equivalent to 10 to 40 per cent of the patients' accustomed dose of morphine. Since these patients would have received three doses of 60 mg of morphine (total of 180 mg) in the 24-hour period (the fourth dose of 60 mg would fall at the 24th hour), the doses of drugs under test were thought to be equivalent to 18 to 72 mg of morphine sulfate. In the case of NIH-7586, the doses selected were 25 and 50 mg at 10:00 p.m., 6:00 a.m. and 10:00 a.m. of the test period. In the case of NIH-7607, the doses chosen were 0.05 and 0.1 mg at 10:00 p.m., 2:00 a.m., 6:00 a.m., 10:00 a.m. and 12:00 M of the test period. Observations for the intensity of abstinence were hourly from the

14th (6:00 a.m.) to the 24th (4:00 p.m.) hour after giving the last dose of morphine and the intensity of abstinence calculated in "hourly-points" by the method of Himmelsbach (7). The area under the time action curve was calculated by the system of Winter and Flataker thus converting the data to a single figure, termed "point-hours".

The data were compared with data obtained in another experiment in which 9 patients received 18 mg (10 per cent of their accustomed dose), 36 mg (20 per cent), and 90 mg (50 per cent) of morphine sulfate subcutaneously in similar tests. Regression lines, estimate of the potency of NIH-7586 and NIH-7607 given orally as compared with the potency of morphine given subcutaneously, and 95 per cent confidence limits, were calculated according to the methods described by Bliss (8).

Results

Subjective Effects. The results are presented in Table 1 and are compared with the results obtained with 20 and 30 mg of morphine sulfate orally and with 60 and 90 mg of codeine sulfate orally in another experiment. Five of 13 patients who received 100 mg of NIH-7586 reported that the effects were similar to those of an opiate, whereas 7 of 14 patients who received 20 and 30 mg of morphine orally reported positively for opiates. In the case of codeine, 5 and 6 of 14 patients reported

B-138

positively for opiates; thus, as judged by this system, NIH-7586 appears to be roughly one-third to one-fifth as potent as morphine in inducing subjective effects and is roughly equal to codeine in this respect. Six of 7 patients who received 0.25 mg of NIH-7607 reported positively for opiates. Therefore, NIH-7607 appears to be more than 80-120 times as effective as morphine orally as an "euphoriant". After these doses of both NIH-7586 and 7607, behavior of the patients resembled that seen after morphine with alternating periods of somnolence and wakefulness ("coasting", "nodding"), scratching, increased loquaciousness, etc. being observed.

Pupillary Constriction. Mean figures for pupillary constriction expressed as the area under the time action curves are shown in Table 2. The results, with respect to rough relative potencies of NIH-7586 and NIH-7607, agree with those described under "subjective effects".

Suppression of Abstinence. Both NIH-7586 and NIH-7607 partially suppressed abstinence from morphine in the doses used. The results are shown in Figure 1. As indicated in the figure, 1 mg of morphine subcutaneously was equivalent to 2.62 (1.00-6.59) mg of NIH-7586 orally, and 1 mg of NIH-7607 orally was equivalent to 59.3 (15.55-136.5) mg of morphine subcutaneously. The curves

met the requirements for significance of slope and parallelism. The figures in parentheses are the 95-per cent confidence limits.

Discussion

Both NIH-7586 and NIH-7607 induce morphine-like subjective effects and suppress symptoms of abstinence from morphine. Both drugs, therefore, have addictive properties. The data, however, are insufficient to permit any statement about the degree of addictiveness as compared with morphine or codeine at this time. Further work on the relative euphoriant potencies, and cautious exploration of the effects of the two drugs when given hypodermically seems indicated. In addition, since these compounds are the prototypes of a new chemical series of analgesics, a direct addiction experiment with one of them seems indicated.

Quantitatively, NIH-7607 is the most potent suppressor of abstinence known. It is, however, probably not as potent in man as in the monkey.

Summary

1. A preliminary examination of the addictive potentialities of 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitro benzimidazole (NIH-7586) and 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfate (NIH-7607) has been made.

B-136

2. Both NIH-7586 and NIH-7607 cause pupillary constriction and morphine-like subjective effects in non-tolerant former morphine addicts. NIH-7586 is 1/5th to 1/3rd as potent as morphine in inducing subjective effects, whereas NIH-7607 is 80 to 120 times as potent as morphine.

3. Both NIH-7586 and NIH-7607 will suppress symptoms of abstinence from morphine.

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Table 1

Subjective Effects of NIH-7586 (Ba-19390, I-G-1) and NIH-7607 (Ba-20684, I-G-2) Given Orally

Drug	Dose Mg.	No. of Ss.	Number of Patients Responding			
			Positive for Opiates	Positive for Other Drugs	Questionable	Negative
NIH-7586	100	13	5	1	3	4
NIH-7607	0.25	7	6	1	0	0
Morphine *	20	14	7	1 [1]	3	3
Morphine *	30	14	7	2	3	2
Codeine *	60	14	5	1 [1]	4	4
Codeine *	90	14	6	1	5	2
Placebo *	--	14	1	[1]	1	12

For method of scoring, see text.

Figures in brackets represent patients who also reported positively for opiates.

* Data from another experiment.

B-132

Table 2

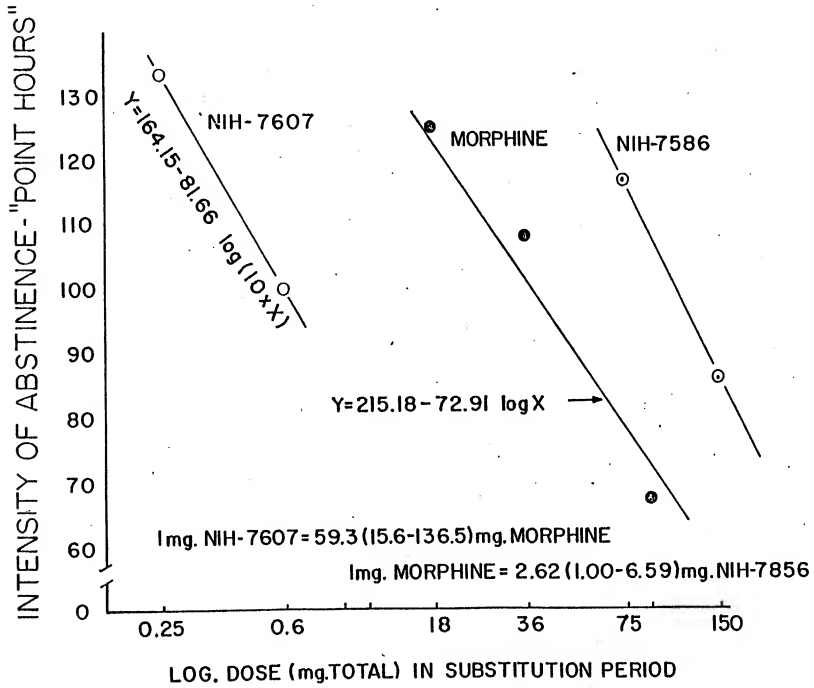
Pupillary Constriction After NIH-7586 (Ba-19390, I-G-1) and NIH-7607 (Ba-20684, I-G-2)

Drug	Dose (mg)	No. of Ss.	Mean Area Under Curve (Mm Hours ± S.E.)
NIH-7586	100	13	8.14 ± 0.81
NIH-7607	0.25	7	10.9 ± 1.35
Morphine Sulfate *	20	14	11.4 ± 2.5
Morphine Sulfate *	30	14	17.1 ± 3.2
Codeine Sulfate *	60	14	9.0 ± 1.7
Codeine Sulfate *	90	14	14.4 ± 2.4
Placebo	--	14	0.4 ± 1.63

* Data from another experiment.

D-131

B-130


INTENSITY OF ABSTINENCE - "POINT HOURS"
130
120
110
100
90
80
70
60
0
Y=164.15-81.66 log(10xX)
NIH-7607
MORPHINE
NIH-7586
Y=215.18-72.91 log X
1mg. NIH-7607 = 59.3 (15.6-136.5) mg. MORPHINE
1mg. MORPHINE = 2.62 (1.00-6.59) mg. NIH-7856
0.25
0.6
18
36
75
150
LOG. DOSE (mg. TOTAL) IN SUBSTITUTION PERIOD