EFFECTS OF MORPHINE AS COMPARED WITH A MIXTURE OF MORPHINE AND DIAMINOPHENYLTHIAZOLE (DAPTAZOLE)

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Shaw and Shulman (1) have reported that 2,4-diamino-5-phenylthiazole hydrobromide (Daptazole) antagonizes the respiratory depressant effects of morphine. In 30 patients who received morphine plus diamino-phenylthiazole there were no signs of development of tolerance or addiction, although some of the patients received the mixture for five months (1). Concurrent administration of diaminophenylthiazole with morphine permitted a rapid acceleration of the dosage of morphine and thereby facilitated the treatment of severe pain in patients who had cancer (1). These authors also point out that diaminophenylthiazole by itself is nontoxic and does not precipitate symptoms of abstinence from morphine in addicted patients, whereas nalorphine depresses respiration and precipitates abstinence in addicted patients. Such a nontoxic opiate and opioid antagonist would be valuable in clinical practice.

In this report the effects of morphine plus saline are compared with those of a mixture of morphine plus diaminophenylthiazole, using single doses and chronic administration of each with the purpose of repeating certain aspects of the work of Shaw and Shulman (1) under better controlled conditions than those attainable in the usual clinical situation.

METHODS

General.—The same 5 healthy, male, nontolerant, former opiate addict volunteers were used throughout these studies. Consequently, each subject served as his own control in evaluating the effects of morphine plus saline as compared with the effects of morphine plus diaminophenylthiazole. Although the observers were aware of the drug being given and of the objectives of the experiment, a deliberate effort was made to prevent the subjects from becoming aware of these facts. The patients were told that the effects of two different com-
pounds on morphine were being tested. The volumes of solutions were the same at all times for corresponding doses of morphine plus saline, and morphine plus dianisopropylthiazole. During administration of single doses and during chronic administration of drugs, subjects were asked to describe the subjective effects induced by the drugs and to compare the effects with those of morphine.

*Effects of Single Doses.*—The effects of 60 mg. of morphine plus saline were compared with those of 60 mg. of morphine plus 30 mg. of dianisopropylthiazole in the same 5 subjects, according to the methods of Isbell and Fraser (2) and Fraser and Isbell (3).

*Chronic Administration of Drugs.*—The dosage of morphine plus saline as well as that of morphine plus dianisopropylthiazole (approx-

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![Graphs showing respiratory rate, respiratory minute volume, miosis, percentage change from control, rectal temperature, pulse rate, systolic blood pressure](image)

**Fig. 1.** Comparison of effects of single doses of 60 mg. of morphine plus saline with those of 60 mg. of morphine plus dianisopropylthiazole (Daptazol) in the same 5 subjects. No differences are apparent between these regimens.

approximately 1.2 mg. of dianisopropylthiazole for each milligram of morphine) was rapidly increased during the first ten days of administration of drugs until the daily dosage of morphine approximated 500 mg. The daily dosage of both morphine and dianisopropylthiazole was divided among four equal doses given intramuscularly. Patients were stabilized on the maximum dose of morphine for an additional eight days (fig. 2). During the entire eighteen days the average dosage of morphine when given with saline was 370 mg., whereas when morphine plus dianisopropylthiazole was given, the average daily dosage of morphine was 372 mg. During the entire eighteen days, the average daily dosage of dianisopropylthiazole was 444 mg. Two of the 5 subjects received morphine plus saline first, and 3 received morphine plus dianisopropylthiazole first. After eighteen days, drugs were with-
Fig. 2. Effects of chronic administration of morphine plus saline as compared with those of morphine plus daminophenylthiazole (Daptazol) in the same 5 subjects. Control A represents the average respiratory rate over a 10-day period prior to any of the subjects taking drugs, Control B, the average rate during the last 7 of 30 days when no drugs were given following methadone reduction. It is obvious that daminophenylthiazole did not antagonize depression of respiratory rate caused by morphine.

drawn by substitution and reduction of methadone. After withdrawal of methadone was complete, patients received no drugs for 30 days. The procedure was then repeated with the patients who received morphine plus saline first now receiving morphine plus daminophenylthiazole, and vice versa (fig. 2).

On the eighteenth day of chronic administration of morphine plus daminophenylthiazole in the first phase of the experiment, 2 subjects were switched from morphine plus daminophenylthiazole to morphine plus saline for twenty-four hours, and one subject was switched to morphine plus saline for only one dose. The objective was to ascertain if daminophenylthiazole had reduced toxicity owing to morphine. On the eighteenth day of receiving morphine plus saline, 2 subjects were given 30 mg. of daminophenylthiazole instead of saline to ascertain if it would precipitate symptoms of abstinence from morphine, and to determine whether daminophenylthiazole would reduce toxic symptoms.

At the conclusion of the eighty-four days involved in comparing morphine plus saline and morphine plus Daptazol, all subjects were continued for sixty more days on the same dose of morphine alone (no additional dilution with saline or daminophenylthiazole), and the clinical course evaluated.

The first day methadone was substituted for morphine plus
saline or morphine plus dianopropylthiazole, each patient received his regular dose of morphine at 6 a.m. plus one-half his daily dose of methadone, and the remainder of the methadone dose was given twelve hours later. Dosage of methadone was based on the dose of morphine given and averaged 125 mg. during the first twenty-four hours. This dose of methadone was progressively decreased until, on the eighth day, only 5 mg. were given. The reduction schedule was calculated as the minimum dose which could be administered and yet avoid the appearance of any significant symptoms of abstinence during gradual withdrawal of methadone.

Before and during chronic administration of drugs, rectal temperature, pulse and respiratory rates, and blood pressure were measured three times daily after ten minutes rest in bed. Caloric intake and body weight were recorded daily. In 2 of the subjects, hours of sleep were recorded on a 24-hour basis at half-hour intervals throughout the eighteen days of drug administration in both phases of the experiment. In the remaining 3 subjects, “inactivity” was evaluated on a 24-hour basis instead of hours of sleep. A patient was recorded as being “inactive” if he lay prone on the bed for five minutes or more during any half-hour interval, regardless of whether he was asleep.

Results

Effects of Morphine Plus Saline as Compared to Those of Morphine Plus Dianopropylthiazole in Single Doses.—The effects of 60 mg. of morphine plus saline, as compared with 60 mg. of morphine plus 30 mg. of dianopropylthiazole on respiratory rate, respiratory minute volume, miosis, rectal temperature, pulse rate, and systolic blood pressure, are illustrated in figure 1. It is apparent that the objective effects of morphine plus saline cannot be distinguished from those of morphine plus dianopropylthiazole on any of these measurements. The subjects were unable to distinguish the subjective effects of morphine plus dianopropylthiazole from those of morphine plus saline; some preferring one combination as compared with the other, and vice versa.

Effects of Morphine Plus Saline as Compared to Those of Morphine Plus Dianopropylthiazole During Chronic Administration.—There were no statistically significant differences in respiratory and pulse rates, rectal temperature, blood pressure, hours of sleep, “inactivity,” caloric intake, and body weight in these 5 subjects when morphine plus saline was compared with morphine plus dianopropylthiazole. When morphine plus saline was administered, the average respiratory rate was depressed to an average of 9.94 respirations per minute from an average of 17.37 per minute during a 10-day control period (fig. 2). Similarly, the administration of morphine plus dianopropylthiazole depressed the respiratory rate in these 5 subjects to 9.82 per minute from an average of 18.3 per minute during a 7-day control period (fig. 2).
On the eighteenth day of administration of morphine in the first phase of the experiment, when dianminophenylthiazole replaced saline or vice versa, no objective or subjective changes were noted. Furthermore, when dianminophenylthiazole and saline were discontinued after the eighty-fourth day in the second phase of the experiment, no significant changes occurred either in the men who had been receiving morphine plus dianminophenylthiazole, or in the men who had been receiving morphine plus saline.

Substitution and Subsequent Reduction of Methadone for Morphine Plus Dianminophenylthiazole or Morphine Plus Saline.—The former was effected in 3 of 5 patients and the latter in 2 patients. The results were entirely comparable in both instances. Since the initial dose of methadone (125 mg. daily) would have provoked severe toxic symptoms in nontolerant subjects (4), and since this did not occur, one must conclude that patients who received morphine plus dianminophenylthiazole had as much cross-tolerance to methadone as those who received morphine plus saline. As long as methadone was administered, no patient showed significant signs of abstinence, but when methadone was discontinued, all patients developed mild but definite symptoms of abstinence which persisted for 8 to 10 days.

Discussion

Since the effects of morphine plus dianminophenylthiazole were equivalent to those of morphine plus saline in both single dose tests and chronic studies in 5 men who served as their own controls, the observations of Shaw and Shulman (1) are not confirmed. Observations, however, in these postaddicts would indicate that it is possible to increase the dose of morphine much more rapidly than has heretofore been thought possible. Rapid acceleration of dosage may be of practical value in the treatment of intractable pain, such as that which occurs in certain types of cancer.

Summary

Single doses and chronic administration of morphine plus saline produced effects identical with those of morphine plus, 2,4-diamino-5-phenylthiazole, hydrobromide (Daptazole). In nontolerant former opiate addicts, the dosage of morphine given alone may be rapidly increased to 500 mg. daily within ten days.

References