

THE ANALGESIC EFFECTIVENESS OF MORPHINE SOLUTIONS CONTAINING SODIUM BISULFITE*†

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In studies at the Massachusetts General Hospital on the analgesic potency of certain new synthetic narcotics (1), aqueous morphine sulfate solutions made up freshly every three weeks initially provided the standard for comparison of analgesic activity. In order to decrease the frequency with which fresh solutions were necessary, 0.1 per cent sodium bisulfite was added to the morphine solutions to increase their stability. This concentration of sodium bisulfite added to procaine or epinephrine solutions has been reported to increase their toxicity when given subcutaneously or intramuscularly, presumably by a specific local capillary effect which tends to increase the rate of drug absorption (2). Since an increase in analgesia from morphine might be expected from an increased rate of absorption, a study was made of the possible influence of sodium bisulfite on the analgesic activity of morphine.

METHOD

The method used for determination of analgesic potency has been presented in detail elsewhere (1). Patients who had pain after operation provided the subjects for study. In the routine treatment of the pain, the drug to be studied and morphine were given alternately to individual patients as often as necessary. All drugs were prescribed on the basis of milligrams per 70 kg. of body weight. Morphine, the standard for comparison, was always given as 10 mg. per 70 kg. Evaluations of pain relief following each dose were made by trained technicians according to rigid criteria. The technicians, nurses and patients were never aware of the nature or dosage of the drugs used.

RESULTS

The data in table 1 were obtained during investigations of the potency of certain new synthetic narcotics. In these studies each dose of syn-

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TABLE 1

ANALGESIC POTENCY OF MORPHINE SULFATE (10 MG./70 KG.) WITH AND WITHOUT ADDED SODIUM BISULFITE IN TWO GROUPS OF PATIENTS

	Morphine Sulfate	Morphine Sulfate with 0.1% Sodium Bisulfite
Number of Patients	221	395
Total Doses	339	605
Analgesic Doses	259	451
Per Cent Relief	76.4	74.6

thetic narcotic was always alternated with a standard dose of morphine sulfate (10 mg. per 70 kg.). Initially, the alternate morphine doses were of fresh aqueous morphine solutions (10 mg. per cubic centimeter). After several months morphine-bisulfite solutions (10 mg. per cubic centimeter, with 0.1 per cent sodium bisulfite) were substituted as the standard. The relative analgesic potency of these two solutions was determined by the frequency with which pain relief followed these doses of morphine. Only the first four narcotic doses after operation in any single patient were considered here. Since postoperative pain reaches maximal intensity soon after operation, these early doses are most useful in determining analgesic potency. From these data, there is no difference in the analgesic potency of these solutions.

Since the data in table 1 were obtained from two separate groups of patients, a sampling error could account for these results. In order to eliminate this possibility, an additional group of patients was studied. In this group the two morphine solutions (one with and one without sodium bisulfite) were given alternately in the same dose to individual patients and the frequency of pain relief determined. Two lower dose levels (5 and 8 mg. per 70 kg. of body weight) were used in order to insure that an increase in analgesic potency could be demonstrated if present. These data are shown in table 2. Clearly, the addition of sodium bisulfite has not increased the analgesic potency of morphine.

COMMENT

Richards (3) first reported that the toxicity of epinephrine solutions given intramuscularly or subcutaneously was increased by the addition

TABLE 2

ANALGESIC POTENCY OF MORPHINE SULFATE AT VARIOUS DOSE LEVELS WITH AND WITHOUT ADDED SODIUM BISULFITE IN THE SAME GROUP OF PATIENTS

No. of Pta.	Dose, mg. per 70 kg.	Without Bisulfite			With Bisulfite		
		Total Doses	Analgesic Doses	Per Cent Relief	Total Doses	Analgesic Doses	Per Cent Relief
36	5	59	41	69.5	59	41	69.5
20	8	30	22	73.3	30	21	70.0
44	12	59	49	83.1	59	46	78.0

of 0.1 to 0.2 per cent sodium bisulfite. This observation was confirmed by Lawson and Thienes (4) and by West (5). The toxicity of procaine solutions and neosynephrine solutions was similarly increased by the addition of sodium bisulfite, but not by the addition of closely related chemicals (6). Since this increase in toxicity was not present when the drug and the bisulfite were given in different sites or when the combination was given intravenously, the phenomenon was thought to be a specific effect of bisulfite on the capillaries at the site of injection tending to increase the rate of drug absorption. Recently, Richards (7) observed that rutin effectively protected animals against this bisulfite effect, lending support to this hypothesis.

Although the addition of 0.1 to 0.2 per cent sodium bisulfite increased the toxicity of epinephrine and procaine two to six times, no increase in the analgesia from therapeutic doses of morphine was observed in this study. This failure may be the result of (a) differences in dosage (therapeutic versus toxic), (b) the absence of a "bisulfite phenomenon" when combined with morphine or (c) a magnitude of change too small to be detected by this technic. Since sodium bisulfite is so popular an addition to pharmaceutical solutions as an antioxidant and stabilizer, it may be wise to investigate changes in the magnitude of effects of therapeutic doses of other drugs to which this chemical has been added.

CONCLUSIONS

Sodium bisulfite, 0.1 per cent, when added to aqueous morphine solutions neither increases nor decreases the analgesia following therapeutic doses of morphine. Reasons for the absence of a bisulfite effect are suggested.

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