SUBARACHNOID AMMONIUM SULFATE THERAPY FOR INTRACTABLE PAIN *

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FOR the last twenty years Drs. William Bates and B. D. Judovich and the late Dr. J. B. Carnett have studied intensively the types and methods of treatment of pain. From these studies they have classified pain into two general types, somatic and sympathetic, or visceral, pain. The differentiation of each is best described in Bates's recent paper entitled "Control of Somatic Pain (1)."

In summing up his recommendation for the treatment of somatic pain, Bates says:

"Regional infiltration appears to be the most efficacious method of treatment for somatic pain. It is also of value in diagnosis. The use of the pitcher-plant extract, in many patients, has afforded prolonged relief as compared with procaine. Injections of solutions of ammonium inorganic salts both locally and intraspinally have given promising results. The advantages are nontoxicity and absence of tissue damage."

As a result of the reports by Bates and his co-workers (1, 2), my associates and I decided to employ the subarachnoid ammonium sulfate therapy for relief of intractable pain. In many instances, we found it difficult to differentiate between intractable somatic and sympathetic, or visceral, pain. Therefore, we elected to employ this therapy for all patients complaining of nerve root pain. In a small series of 58 patients, 50 had true nerve root pain. Subsequent studies demonstrated that four patients were morphine addicts. In four patients the diagnosis of nerve root pain was questionable.

Bates (2) has presented in detail the chemistry, pharmacology, his clinical experiments, and a method or technic of injection with intraspinal or subarachnoid ammonium sulfate solution. The active principle in the original solution, the pitcher-plant solution, is the ammonium ion. Its mode of action is the depression of the unmyelinated "C" fibers of the somatic nerve. Experimentally, it has been shown that the ammonium solution has no effect on the unmyelinated "C" fibers of the sympathetic or visceral nerve.

The optimal dose of ammonium sulfate recommended for intraspinal injection is 200 to 400 mg. in 5 cc. of distilled water. The technic we employed differs only in minor respects from that recommended by

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Bates. Three hundred milligrams in divided doses of 150 mg. on successive days were given to the first 10 patients. The next 10 patients received 200 and 300 mg. doses, alternately, on successive days. The remaining 38 patients received single 300 mg. doses. Since there is an initial exacerbation of the preexisting pain, with gradual disappearance of pain, when ammonium sulfate alone is employed, 100 mg. of procaine hydrochloride * was added to each dose irrespective of the amount of ammonium sulfate. The procaine has a twofold purpose: (1) it affords relief from this initial exacerbation of pain, and (2) it acts as a true index of height of anesthesia attained, that is, the upper levels of nerve root areas bathed by this mixture of ammonium sulfate and procaine.

We injected the solution in the lumbar interspaces, no higher than the first lumbar. By using gravity and barbotage for diffusion, we obtained satisfactory height of anesthesia in all patients. The highest level desired and attained was approximately at the eighth cervical segment in a patient with metastatic pulmonary malignancy.

As stressed by Bates (2) and borne out by the results in our earliest injections, it is imperative to employ barbotage and thoroughly dilute the total volume with spinal fluid during the period of injection.

Our results were not as encouraging as those reported by Bates. Of the 50 patients with true nerve root pain, 33 received initial relief of pain. Table 1 lists the primary pathologic condition and the number of

TABLE 1

Pathologic condition	No. of cases	Patients obtaining relief
Metastatic malignancy from:		
Uterus and cervix	16	12
Prostate	6	0
Gastro-intestinal organs	15	11
Lungs	1	1
Breast	3	2
Melanotic sarcoma	1	1
Arachnoiditis	7	6
Arthritis	1	0
Total	50	33

patients experiencing initial relief.

When the somatic pain is relieved after proper injection and loss of procaine anesthesia, there is no impairment of the sensation of touch, pressure, pin prick, or temperature, nor is there any motor weakness of the treated segment or areas.

A cordotomy was recommended for the 17 patients on whom the treatment failed. Fifteen submitted to this operation. A period of three days usually elapsed between the ammonium sulfate injection and the cordotomy. The site chosen for this nerve sectioning was approximately at the level of the second or third thoracic nerve segment.

* Early in this series, a few patients received 10 mg. of pontocaine in glucose solution in place of procaine in an attempt toward better control of the height of anesthesia. Very little difference was noted from the results obtained with 100 mg. of procaine.

This operation afforded an excellent opportunity to visualize within the subarachnoid space any clinical changes resulting from this procaine-ammonium sulfate solution. Exposure revealed a normal, glistening, white spinal cord with no evidence of irritation or hyperemia.

Subsequent follow-up of the 33 patients with initial relief from pain as a result of the ammonium sulfate treatment has demonstrated poor results as to permanent relief. In the majority of these patients the relief from pain lasted approximately three weeks. Three patients, suffering from arachnoiditis, had permanent relief from pain.

COMPLICATIONS

Three transient complications usually accompany the therapy, namely, nausea or retching, headache, and paresthesias. Forty-eight patients (82.7 per cent) experienced moderate to severe degrees of nausea and retching, with more retching than vomiting. This retching began approximately twenty minutes after the injection. I recall vividly the first patient so treated—a 64 year old man with metastatic malignancy. Twenty minutes after the injection *, retching began and progressively increased in severity. One and one-half hours after this injection the blood pressure began to rise gradually from 140 to 230 mm. systolic and from 80 to 100 mm. diastolic. I did not know what treatment would alleviate this retching, but, recalling our experience with hiccup, I elected to try intravenous atropine, grain $\frac{1}{100}$, in the hope of attenuating the paroxysms. The retching had continued over a period of approximately four hours. The paroxysms subsided, and within one hour the blood pressure had returned to 150 mm. systolic and 90 mm. diastolic. The next patient received intravenous atropine, grain $\frac{1}{100}$, fifteen minutes after the onset of retching, with the subsidence of paroxysms. To the third and subsequent patients, atropine was given soon after the onset of retching, with considerable relief. If these patients moved appreciably, their paroxysms returned for a few moments, but were considerably attenuated.

As a result of these experiences with intravenous atropine, we elected to consider a moderate dose of atropine as premedication. Atropine, grain $\frac{1}{100}$, was given subcutaneously one hour before operation to all patients. Morphine, grain $\frac{1}{6}$, was also given to many. This preoperative dose of atropine served a twofold purpose. First, it tended to lessen the intensity of the paroxysms of retching. Secondly, it served as an index to the patient's sensitivity to atropine or allied belladonna derivatives. The classical signs of atropine or belladonna sensitivity developed in five patients. In such patients, the use of atropine intravenously might be dangerous. This complication, the tendency to nausea and retching, subsided approximately twelve hours after the injection of the ammonium sulfate.

* This patient was in the group in which pontocaine-glucose was employed in place of procaine.

The second transient complication was headache, the so-called post-spinal headache. Thirty-three patients (51.7 per cent) experienced such headache. Early in this series of injections we were fortunate in obtaining information on its etiology. Until we were more familiar with this therapy and its results, we elected to divide the recommended optimal dose. Initial spinal fluid pressures were taken before each injection. Also, a specimen of spinal fluid was sent to the laboratory for cell count and total protein determination before each injection. In 20 patients receiving divided doses of ammonium sulfate, the cell count and protein determinations were essentially normal. But in those patients experiencing the headache, the initial pressure manometer readings were very low—approximately 50 to 70 per cent of the previous day's normal readings. The treatment employed for these headaches was fluids given intravenously, usually 1,500 cc. of 5 per cent glucose in saline solution twice a day. When all but 200 cc. of each 1,500 cc. of fluid had been given, 10 units of pituitrin was given subcutaneously. Surprising relief resulted from this combination. Most of the headaches were relieved within twenty-four hours, and all were relieved in forty-eight hours.

The third transient complication was a mild to moderate degree of paresthesia, a sensation of burning, principally on contact, over the buttocks and sacrum. This occurred in 15 patients (30.4 per cent). It was especially prevalent when a total of 500 mg. was employed and when free dilution and barbotage were unsatisfactory. These paresthesias lasted from two to fourteen days. Patients with this complication obtained temporary relief with codeine, grain ½, and aspirin, grains 10, as required.

Two patients, who were unable to void for a prolonged period, required a transurethral prostatic resection. One patient had an unfortunate accident, not so much the direct result of the ammonium sulfate, five weeks. Subsequent investigation demonstrated that, in addition to the metastatic malignancy, he had prostatic hypertrophy, which required a transurethral prostatic resection. One patient had an unfortunate accident, not so much the direct result of the ammonium sulfate, but rather of an error in judgment. Suffering from intense pain secondary to a metastatic compression fracture of the ninth thoracic vertebra, she was given ammonium sulfate and procaine intraspinally. Although she experienced relief of pain, she had complete paralysis below the area of fracture following the injection. Undoubtedly, the patient had a transection of the cord. The primary site of malignancy was carcinoma of the breast with extensive bone metastasis.

RESULTS

Our results with ammonium sulfate injections were not as good as those reported by Bates (3) or as favorable as we had hoped to obtain.

Yet in view of the rare occurrence of serious complications, these injections are indicated as a method of conservative treatment in all patients complaining of somatic or true nerve root pain. If no relief is obtained, the more radical procedure of cordotomy is advised.

REFERENCES

1. Bates, William: Control of Somatic Pain, Am. J. Surg. 59: 83–86 (Jan.) 1943.
2. Bates, William, and Judovich, B. D.: Intractable Pain, Anesthesiology 3: 663–672 (Nov.) 1942.
3. Bates, William, and Judovich, B. D.: Personal communication to the author.

THE HICKMAN MEDAL—RALPH M. WATERS, M.D.

The Henry Hill Hickman medal award for 1944 has been given to Ralph M. Waters, M.D. This announcement is received here with pride and the conviction that the honor is well deserved. Dr. Waters' continued leadership in anesthesiology, his many contributions to organization, education and improved clinical practices have long since won for him the grateful admiration of his confreres in this hemisphere. The recognition now accorded him by the British Medical Society adds another endorsement to the esteemed position his efforts have gained.

The Hickman Medal, as the award is commonly known, is given for outstanding contributions and service to the specialty. Previous recipients are Wesley Bourne, M.Sc., M.D., Montreal, Canada; I. W. Magill, M.B., D.A., London, England; and Arthur E. Guedel, M.D., Los Angeles, California.

Dr. Waters received a congratulatory letter announcing the award from R. J. Minnitt, President of the Section of Anaesthetics of the Royal Society of Medicine. The medal itself was sent by the Secretary of the Royal Society of Medicine to the American Embassy in London with a request that it be forwarded to this country. This was done, and the medal was sent to Dr. Waters by the Department of State.