ANTIHISTAMINE DRUGS IN TREATMENT OF NAUSEA AND VOMITING DUE TO STREPTOMYCIN

BY

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Nausea and vomiting occur in a proportion of patients undergoing prolonged treatment with streptomycin (Heilman and others, 1945; Committee on Chemotherapeutics, National Research Council, 1946; Nichols and Herrell, 1946; Farrington and others, 1947; Streptomycin Committee of Veterans Administration, 1947; Medical Research Council, 1948). This toxic manifestation has been observed in 17 (35%) of 49 patients treated at the Brompton Hospital during the Medical Research Council trials of streptomycin in pulmonary tuberculosis, but in only four have symptoms been severe and persistent.

Such toxic symptoms as urticaria are probably due to hypersensitivity either to streptomycin or to impurities in the preparations used. It was thought that the nausea and vomiting might be caused in the same way and might therefore respond to antihistamine drugs. In the first few cases in which "benadryl" was tried there appeared to be some response, but the symptoms were too slight and transient to assess it accurately. It was possible to carry out controlled investigations in four patients with more severe toxic symptoms.

The symptoms were abolished or considerably reduced when benadryl capsules were given and returned when they were withheld.

Case Reports

Case 1.—A woman, aged 23, with bronchopneumonic pulmonary tuberculosis complained of transient nausea and vomiting on the 10th day of treatment with 0.5 g. of streptomycin hydrochloride six-hourly. Symptoms recurred on the 29th day and rapidly increased in severity. Ten days later the nausea was intense and she vomited after every meal. Benadryl, 50 mg., was given eight-hourly. There was an immediate response, and during the next seven days she had only slight early-morning nausea. Benadryl was discontinued; morning vomiting then returned, lasting for four days until the benadryl was resumed, when it ceased abruptly. Twelve days later benadryl was once more stopped; after three days the severe nausea and vomiting returned. Again benadryl had an immediate effect and the vomiting ceased.

Case 2.—A man, aged 23, with bronchopneumonic tuberculosis developed an urticarial rash on the 18th day of treatment with 0.5 g. of streptomycin hydrochloride six-hourly. On the 23rd day benadryl, 50 mg., was given, and this dose was continued eight-hourly for four days. The rash disappeared. Two days after stopping benadryl he complained of giddiness and vomited once. Benadryl, 50 mg., was given four-hourly and there was no further vomiting during the next two days. Benadryl was discontinued; four days later slight morning nausea occurred. The nausea increased whilst the giddiness decreased. After ten days benadryl was restarted in doses of 50 mg. eight-hourly. The nausea disappeared, but it recurred two days after benadryl was stopped. Three days later benadryl was again given and the nausea at once subsided.

Case 3.—A man, aged 49, with pulmonary tuberculosis and tuberculous bronchitis complained of abdominal discomfort and flatulence on the 10th day of treatment with 0.5 g. of streptomycin hydrochloride six-hourly. Five days later the symptoms became worse, particularly after the midday meal. Benadryl, 50 mg., was given at noon and 6 p.m. This controlled the afternoon abdominal discomfort, but five days later severe giddiness and early-morning nausea developed. The nausea improved after the midday dose of benadryl. The dosage was increased to 100 mg. at 6 a.m. and 50 mg. at noon and 6 p.m. There was considerable improvement in the morning nausea, but the giddiness was unaffected. The nausea remained moderately well controlled, but several times the omission of a dose led to an immediate increase in the discomfort.

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Control Tests

It seemed possible that suggestion might have played a part in the apparent response. Capsules identical with those containing the benadryl were filled with lactose. These were substituted for the benadryl capsules without the patients' knowledge. Each time the inert capsules were used the symptoms returned, but they disappeared when the capsules containing benadryl were resumed.

Case 1.—On the 74th day the patient had remained free from nausea and vomiting for three days with a dose of 50 mg. of benadryl eight-hourly. Lactose capsules were substituted. Next day the symptoms reappeared with their former severity and continued without remission for two days. The lactose capsules were withdrawn and benadryl capsules substituted. Vomiting ceased after the first dose. Thereafter benadryl was continued until streptomycin treatment ended on the 144th day; no further vomiting occurred, although there was occasional slight nausea. She remained free from toxic symptoms during the next seven weeks. A second course of streptomycin treatment was then started, and after three days the severe and persistent vomiting recurred. Streptomycin was discontinued, the patient's condition being too desperate to warrant its continuance.

Case 2.—On the 59th day the patient had remained free from nausea and vomiting for one day with a dose of 50 mg. of benadryl eight-hourly. Lactose capsules were substituted. The following day the nausea and vomiting reappeared and remained for three days. The lactose capsules were withdrawn and benadryl capsules substituted. There was no further nausea or vomiting. Twice more, on the 76th and 91st days, benadryl was discontinued without substitution of inert capsules; the symptoms recurred within two days and each time ceased abruptly when benadryl was restarted. On the 98th day lactose capsules were again substituted. Symptoms reappeared two days later and disappeared rapidly when the benadryl capsules were resumed. Thereafter there was no further vomiting or nausea, benadryl being stopped at the time of the last streptomycin injection on the 123rd day.

To eliminate the slight sedative action of benadryl as a cause of the response a similar experiment was carried out with identical capsules containing ½ gr. (32 mg.) of phenobarbitone. Substitution of these for the benadryl capsules was followed by immediate exacerbation of the symptoms, and resumption of benadryl capsules by an equally dramatic return to the original condition.

Case 3.—On the 90th day the nausea and vomiting had been moderately well controlled for over eight weeks with a dose of 100 mg. of benadryl at 6 a.m. and 50 mg. at noon and 6 p.m. Substitution of phenobarbitone capsules began at the evening dose. The following morning there was considerably increased nausea and the patient vomited once. The severe nausea lasted two days. Benadryl was then resumed and the nausea decreased after the first dose. Thereafter slight occasional nausea remained up to and beyond the end of streptomycin treatment. The dose of benadryl was gradually reduced, but four weeks after stopping streptomycin there was still slight morning nausea when the benadryl dose was omitted. The severe giddiness was still present.

The experiment was repeated in another case with similar results, both benadryl and "antistin" being used. This was the only one of the severe cases of nausea in which it was possible to withdraw antihistamine drugs before the end of streptomycin treatment.

Case 4.—A woman, aged 20, with bronchopneumonic pulmonary tuberculosis complained of slight giddiness on the 21st day of treatment with 1 g. of streptomycin hydrochloride in a

single daily injection. On the 27th day slight morning nausea appeared and four days later she began to vomit. Benadryl, 50 mg. eight-hourly, was started on the following day. During the next twelve days there was no nausea and she vomited only once. Identical capsules containing phenobarbitone were substituted. Twenty-four hours later the vomiting reappeared. The next day the same capsules containing 100 mg. of antistin were substituted; vomiting ceased after the first dose. Antistin in tablet form was continued for ten days. After its withdrawal neither nausea nor vomiting reappeared and she remained free from these symptoms throughout the remainder of the 32 weeks of streptomycin treatment.

In at least three of these cases we would have had to stop the streptomycin if we had not been able to control the nausea and vomiting. With the continuous administration of benadryl it was possible to complete the full four-months course. We would emphasize, however, that giddiness due to streptomycin was not relieved by the antihistamine drugs.

Summary

Antihistamine drugs were found to relieve the nausea and vomiting which sometimes occur during treatment with streptomycin. This conclusion was supported by control tests in four severe cases. Giddiness due to streptomycin was not relieved.

We are grateful for the co-operation of the physicians of the Brompton Hospital under whose care the patients were admitted. We also wish to thank the hospital pharmacists for help with the control tests and Messrs. Parke, Davis and Co. for a supply of empty capsules.

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TETANY FOLLOWING REMOVAL OF A PARATHYROID ADENOMA WITH BONE DISEASE: FINALLY ALLEVIATED WITH CALCIFEROL

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When a parathyroid adenoma has caused extensive bone disease its removal is followed by severe tetany. This report illustrates the value of calciferol and the uselessness of parathormone in the treatment of such a case.

Case History

The patient, a woman aged 43, was admitted on June 1, 1947, with backache dating from 1940 and general weakness which had caused her to become bedridden. She had kyphosis and sacral deformity, and radiographs revealed extreme decalcification of the entire skeleton. The blood calcium was 12.2 mg. per 100 ml., phosphorus 3 mg. per 100 ml.; alkaline phosphatase 45 King-Armstrong units per 100 ml., and urea 32 mg. per 100 ml.

A diagnosis of hyperparathyroidism was made, and on July 15 Professor C. F. W. Illingworth removed a small adenoma from one parathyroid gland.

After operation the serum calcium fell abruptly (Fig. 1) and tetany developed. Parathormone was started on the day after operation, 80 units being given intramuscularly. The dose was increased until 200 units were given daily, but no rise in the serum calcium occurred even after the initial doses. During this period the patient received intravenous calcium gluconate (10–20 ml. of a 20% solution two or three times a day) and 12 g. of calcium lactate orally per day. In order to facilitate

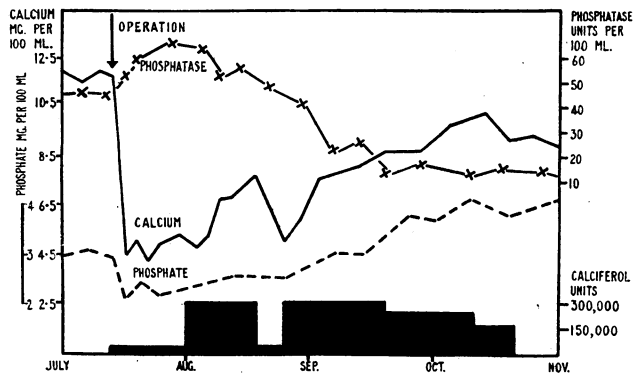

FIG. 1.—Showing the immediate fall in the calcium and phosphate and rise in the phosphatase which occurred after operation. During administration of calciferol the calcium and phosphate gradually rose, and the phosphatase fell, to normal.

absorption of calcium a low phosphorus diet (0.56 g.) and 40,000 units of calciferol were given daily. In spite of these measures the patient's condition rapidly deteriorated. In addition, she became uncooperative, refusing to have injections, and parathormone was stopped on the 14th post-operative day, when the serum calcium was still less than 5 mg. per 100 ml. As a last resort a transfusion of 2½ pints (1.42 litres) of fresh citrated

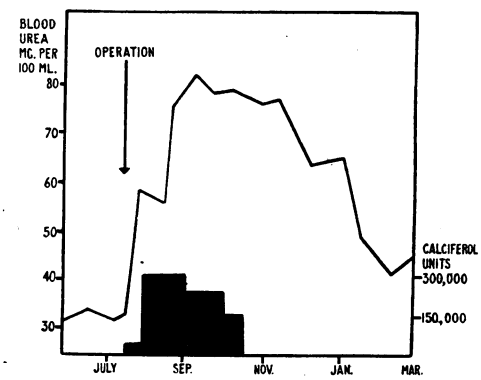

FIG. 2.—Showing rise of blood urea after operation and during calciferol treatment. It fell again after cessation of the drug.

blood (Group A) was given. The result was disastrous. Four hours later tetany, more severe than had hitherto occurred, developed, although examination of the blood showed that there had been no further drop in calcium.

An attempt was then made to raise the serum calcium by increasing the daily dose of calciferol to 300,000 units (6 ostelin tablets, each of 50,000 units). Three days later definite improvement was noted; thereafter the serum calcium gradually rose (Fig. 1), and signs of tetany disappeared and were not again elicited. At no time did the patient show any intolerance to the calciferol, which was stopped on Oct. 22 after a total of 19,000,000 units had been given. The blood urea, however, which rose after operation, remained high until some time after the drug had been stopped (Fig. 2). The patient was discharged

TABLE I.—*The Serum Calcium, Phosphate, and Alkaline Phosphatase after Cessation of Calciferol Treatment*

Date	Serum Calcium (mg /100 ml.)	Serum Phosphate (mg./100 ml.)	Serum Alkaline Phosphatase (King–Armstrong Units per 100 ml.)
30/10/47 ..	9·1	4·0	10·2
21/11/47 ..	8·6	3·8	—
19/12/47 ..	8·5	—	9·0
16/1/48 ..	10·2	3·5	8·6
24/2/48 ..	8·8	3·1	—
10/3/48 ..	9·0	3·2	8·6