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CLINICAL TRIAL OF BUCLIZINE HYDROCHLORIDE FOR VOMITING OF PREGNANCY

BY

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Many drugs have been used in attempts to relieve nausea and vomiting of pregnancy. Except in sporadic cases the results are disappointing, which is not surprising when the cause of this condition continues to be obscure. In mild degree these symptoms are accepted by most patients as a necessary evil; in moderate degree they cause considerable distress; in severe degree hyperemesis gravidarum results, a condition which may threaten life and which requires urgent treatment.

Buclicine hydrochloride ("vibazine") has the chemical formula 1-(p-chlorobenzhydryl)-4-(p-tertio-butylbenzyl)-diethylene-diamine dihydrochloride and is an anti-histaminic of low toxicity (Schiller and Lowell, 1956). It has been shown to be effective in cases of allergy (Blatt, 1955), post-operative vomiting (Klein-Vercautere, 1954), and motion sickness (Chinn, 1955), and it seemed likely that it might be equally efficacious in vomiting of pregnancy.

In carrying out a clinical trial to investigate this, cases of moderate degree were chosen, the response of those of mild degree being too difficult to elucidate and the occurrence of those of severe degree being too rare to obtain sufficient material. An occasional case of severe nausea with slight vomiting and a few cases of hyperemesis gravidarum, which occurred during the time of the investigation, were included.

Material

Between January 25 and December 11, 1955, 1,267 new patients attended the antenatal clinics at Willesborough, Folkestone, and Buckland Hospitals; 33 of these had symptoms severe enough to include them in the investigation. During the same time three patients were seen in their own homes. One patient is included twice in the series, excessive vomiting occurring at the eighth and again at the thirty-seventh week. The age of patients varied from 18 to 36 years. Their distribution according to parity is shown in Table I, according to symptoms in Table II, and according to stage of pregnancy in Fig. 1.

TABLE I.—Parity of 36 Patients

Gravida ..	1	2	3	4	6	7
No. of cases ..	17	11	4	2	1	1

The duration of vomiting before treatment was between 3 and 70 days, the average being 30 days. One patient complained of it for 120 days! The severity varied from vomiting twice a day to vomiting "everything." Of those cases occurring between the sixth and ninth weeks, 50% had been vomiting for a week, 25% for two weeks, 25% for

TABLE II.—Symptoms

Symptoms	No. of Cases
Nausea, severe ..	3
Excessive vomiting ..	30
Hyperemesis gravidarum ..	3

four weeks. In the group between the tenth and fourteenth weeks, the majority of patients had been vomiting three to four times daily for at least four weeks. Most of the patients treated after the thirty-fifth week had suffered throughout pregnancy from intermittent vomiting, which had become severe shortly before treatment.

Acetone was detected in the urine in eight patients; unfortunately it was not tested for in some cases.

FIG. 1.—Distribution of patients according to stage of pregnancy.

Treatment

Prior to treatment all patients were examined to exclude an organic cause for vomiting. At the beginning of the investigation the dose of buclizine hydrochloride prescribed was 50 mg. nocte, this being supplemented after three days by 25 mg. mane if the response was not satisfactory. Later, 50 mg. nocte and 25 mg. mane was prescribed at the outset, as this was found more effective. Twenty patients were treated with 50 mg. nocte, 13 with 50 mg. nocte and 25 mg. mane, two in-patients and two out-patients with 50 mg. nocte and 25 mg. t.d.s., and one in-patient and one out-patient with 25 mg. t.d.s. One patient of her own accord found she obtained the best result by taking 25 mg. nocte and 50 mg. mane. The only contraindication to these higher doses seemed to be that sleepiness was induced in some patients in the daytime.

Six patients were treated in hospital. Four of these were admitted on account of the severity of their vomiting, one for treatment of bronchiectasis, and one for social reasons.

The duration of treatment varied from five days to three months, the average being two weeks.

Results

An analysis of the results is shown in Table III. The time interval between the onset of treatment and patients

TABLE III

Result	No. of Cases
Complete relief ..	19 (53%)
Marked improvement ..	5 (14%)
Improved ..	7 (19%)
No effect ..	2 (5.5%)
Worse ..	3 (8.5%)

TABLE IV

Days prior to improvement ..	1	2	3	4	5	6	7
No. of patients ..	10	12	5	1	1	1	1

experiencing relief was short in most cases, many patients stating that they were greatly relieved the following day. An analysis of the number of days between the onset of treatment and response is shown in Table IV.

The distribution of the results according to the stage of pregnancy is shown in Fig. 2. Of the two patients who did not experience any effect, the mental approach and environment of one were unstable and difficult. No treatment proved of any avail other than separating her from her home surroundings. The other patient stated that she

FIG. 2.—Results according to stage of pregnancy.

continued to vomit all the time regardless of any treatment, but at no time was her general condition affected. Of the three patients who stated they were worse following therapy, one vomited violently four hours after taking buclizine hydrochloride and did not take any further tablets, one thought her vomiting was more violent during her week's treatment, and one felt ill but took the tablets for only three nights. Unfortunately there was no opportunity to analyse the last patient's statement, as her frame of mind was such that she departed from the out-patient department with her notes.

One patient in the successful group complained that her vomiting was more violent after the first two nights, but she then experienced relief and was pleased to continue with the treatment.

In the successful group two patients had a previous history of hyperemesis gravidarum. One had had a therapeutic termination for hyperemesis at the second month in 1950, and, during her second pregnancy in 1951, treatment in hospital for 14 weeks from the sixth week had been necessary. During the present pregnancy promethazine hydrochloride had already been tried; buclizine hydrochloride was started at the ninth week and continued until the seventeenth week, but at no time was admission indicated. The dosage at first was 25 mg. t.d.s. and 50 mg. nocte, but eventually it was found that 50 mg. on waking in the morning and 25 mg. at midday gave the desired result.

The other patient had been admitted during her first pregnancy at the sixth, twenty-second, and twenty-sixth weeks for hyperemesis. During the present pregnancy buclizine hydrochloride was started at the eighth week on a dosage of 50 mg. nocte and 25 mg. mane. Treatment was continued for three months, during which time she vomited on only four occasions. After the first week it was found that 50 mg. nocte was sufficient.

In six patients who had received treatment for seven to ten days, vomiting recurred at the end of the course. In five this was controlled as soon as treatment was restarted; in the sixth, a patient at the eighth week of pregnancy, vomiting ceased spontaneously after three days, no further treatment being required.

Comment

In drawing any conclusion from a survey into the value of a drug for vomiting of pregnancy it is essential to remember that the aetiology of this condition is not understood and is probably multiple. It is well known that many patients suffering from vomiting will improve after reassurance, and may improve on inert therapy.

All the patients in this survey were given their tablets direct from the hospitals concerned. In most cases it proved impossible to keep from them the fact that the medicine prescribed was not in general use, as normally patients are referred to their own doctors for drugs.

Even after taking into account the possible improvement resulting from "suggestion therapy," the high percentage of patients benefiting would appear to indicate a good thera-

peutic response to buclizine hydrochloride. Many of these patients had previously been treated with other drugs, including antihistamines.

The only adverse factors were drowsiness, when 50 mg. nocte and 25 mg. t.d.s. were prescribed for out-patients, and the incidence of violent vomiting in two patients mentioned.

Summary

The results of a clinical trial into the value of buclizine hydrochloride ("vibazine") for excessive vomiting of pregnancy are analysed.

Thirty-six patients out of 1,267 attending antenatal clinics were treated.

The results showed that 53% of the patients were completely relieved, 14% were much improved, 19% were improved, 5.5% were the same, and 8.5% were worse.

I wish to thank Mr. John Buttery for allowing me to include patients under his care and Messrs. Pfizer Ltd., Folkestone, Kent, for making this clinical trial possible by their generous supply of vibazine.

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BAD GASTRECTOMIES

BY

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The first gastrectomy for ulcer was performed in 1881, by Rydygier in Poland. The main modifications of the operation were worked out in Europe in the nineteenth century and appeared in the European textbooks in 1900. The modification which I use to-day was described by Krönlein, of Zürich, in 1885. In those early days, before the placement of stoma and loops was well understood, various forms of obstruction were encountered. To deal with these Braun, of Königsberg, described in 1892 an anastomosis between afferent and efferent limbs, which now bears his name. Kappeler, of Münsterlingen, in 1898 described an improvement, a "suspension method" designed to prevent rather than to cure, in which the afferent limb of the loop is fixed above the stoma in such manner that kinking is prevented and the stomach empties its contents into the efferent limb. The stitches used for this suspension are now called after Kappeler.

A Keen Rivalry

By the end of the nineteenth century operative techniques had been established, and then began a critical long-term evaluation of end-results which covered the first two decades of the century. In 1906, at a surgical congress in Berlin, Rydygier showed in good digestive health, and 25 years after operation, the first patient ever to have had gastrectomy for ulcer. A keen and critical rivalry sprang up between the great European schools of gastric surgery, most of them directed by pupils of Billroth. Wedge resections, sleeve resections, gastro-enterostomy, pylorotomy, and extended resection battled for the mastery. By 1920 the advocates of extensive gastrectomy, led by Finsterer, Eiselsberg, and Haberer, had won the day, and this operation.