CLINICAL TRIAL

'Debendox' in pregnancy sickness

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NAUSEA AND VOMITING OCCURRING WITHIN the first trimester of pregnancy are such common symptoms that they are universally used as diagnostic features of the condition. The symptoms can cause so much misery that the patient may come to regard her pregnancy as a trial rather than as a fulfilment. Consequently it is common practice to give simple dietary guidance together with anti-emetic drugs to all patients who request help.

The question as to which of the many preparations is the most suitable anti-emetic in pregnancy is an open one. This is surprising in view of the many years that have elapsed since such drugs as the phenothiazines were first introduced. Indeed, there are few reports in the literature on the clinical evaluation of drugs used in pregnancy sickness. This must be regarded as a significant omission in view of the vulnerability of the foetus early in pregnancy and the need for caution in prescribing any drug during the first trimester.

Since 'Debendox' (a mixture of dicyclomine, doxylamine and pyridoxine) had been in use for many years in our practice we felt that a formal double-blind assessment of the preparation might, in a small way, fill one of the gaps in existing knowledge. The absence of untoward side actions with 'Debendox', in particular teratogenesis, has been amply demonstrated by the passage of 12 years.

Material and methods

The trial was a double-blind comparison between 'Debendox' and inert dummy tablets of identical appearance. The condition treated was solely that of nausea or vomiting in early pregnancy. The tablets were supplied in bottles serially numbered from one to 100 and each contained 28 tablets, either the active product or lactose. A sealed code was available to us in case of emergency but this was not broken throughout the course of the trial, since no untoward reactions occurred.

Pregnant women who complained of nausea or vomiting in the first trimester of gestation were considered suitable for trial purposes, and were invited to take part in the study. No patient beyond the twentieth week of pregnancy was admitted to the trial, and in one case a patient entered the trial on two separate occasions with 'recurrent' pregnancies.

Two tablets each night at bedtime were used in every case; this is the recommended minimum effective dose. Treatment was given for 14 consecutive nights, the patient then being reviewed. This provided a stringent test since the manufacturer recommends an additional tablet in the morning and at lunch time if sickness is more severe and persistent throughout the day.

The only criterion of response was a change in grade of nausea or vomiting at the second visit compared with the first. Information was kept on specially printed data cards suitable in size for the NHS record envelope. A 'flag label' on each bottle was detached at entry into the trial and secured to the individual record card to ensure accuracy. The symptoms were graded according to severity as follows:

Grade 0 — No nausea or vomiting (only applicable on the second visit)
Grade 1 — Slight nausea only which is acknowledged only on questioning
Grade 2 — More severe nausea complained of by the patient spontaneously
Grade 3 — Vomiting once or twice a day
Grade 4 — More severe vomiting three or more times a day.

The data was collected by an independent observer with training in medical statistics, who

assessed the results 'blind' and commented impartially on the outcome of the study.

Results

Data relevant to the work are summarized in the tables. From these it may be seen that there was a high 'placebo effect' with the inert tablets, presumably related both to random variation in severity and to spontaneous remission in symptoms with the passage of time. Pregnancy sickness remits anyway about the end of the first trimester. There was a greater

TABLE I

A. SUMMARY OF OVERALL RESPONSE

Active		*Placebo*	
Better	*Not*	*Better*	*Not*
29	12	22	18
Total 41		Total 40	
Success: 70·7 per cent (29 in 41)		Success: 55·0 per cent (22 in 40)	

B. RESPONSE BY DURATION OF PREGNANCY

(1)	*8 weeks or less*				*More than 8 weeks*			
Better		*Not*			*Better*		*Not*	
Active	*Placebo*	*Active*	*Placebo*		*Active*	*Placebo*	*Active*	*Placebo*
16	12	8	10		13	10	4	8
28		18			23		12	
Total 46					Total 35			
Active response=66·6 per cent Placebo response=54·5 per cent					Active response=76·5 per cent Placebo response=55·5 per cent			

(2)	*Less than 10 weeks*			*10 weeks or more*			
Better		*Not*		*Better*		*Not*	
Active	*Placebo*	*Active*	*Placebo*	*Active*	*Placebo*	*Active*	*Placebo*
20 *per cent* (71·4)	14 *per cent* (53·8)	8	12	9 *per cent* (69·2)	8 *per cent* (57·1)	4	6

improvement with the active tablets, significantly better than the theoretical 50 per cent improvement which would be expected from purely random fluctuations in severity ($p<0.05$). The difference from the observed control value of 55 per cent improvement does not quite achieve conventional statistical significance. Nevertheless, the trend seems sufficient to justify the conclusion that 'Debendox' is effective in alleviating pregnancy sickness, especially since a minimal dose was used. There were no untoward side effects.

Discussion

The cause and incidence of nausea and vomiting in pregnancy is uncertain and there are many theories about both these factors. It is reasonable to presume that the basic cause is a

physical one, perhaps related to rapidly rising oestrogen levels, and that there may be an added psychological component in some patients. Theoretically pyridoxine deficiency can aggravate vomiting through a chemical effect and it is common practice to add this vitamin to antinausea pills. However, one group of workers (Diggory and Tomkinson 1962) were unable to demonstrate a significant difference in tablets containing the vitamin from those that did not. The present product under trial contained 10 mg dicyclomine hydrochloride (an antispasmodic), 10 mg doxylamine succinate (an anti-emetic antihistamine) and 10 mg pyridoxine hydrochloride (Vitamin B6). This is formulated in a special sugar coating, designed to release the ingredients about six hours after ingestion to provide therapy on awakening when it is most needed.

Geiger, Fahrenbach and Healey (1959) first reported on a study of this compound in 146 patients and followed this work with a controlled, double-blind study of 52 patients. They reported a satisfactory therapeutic response, statistically superior to that produced by an

TABLE II

PARITY AND AGE

(To illustrate that the active and placebo groups were evenly matched)

Parity	*Active*	*Placebo*	*Total*
0	16	15	31
1	14	15	29
2	10	5	15
3	1	3	4
4 or more	0	2	2

Age not stated — 9 (5A and 4P)

36 patients on *active* — range 16–39 years — average 25·1 years

36 patients on *placebo* — range 19–36 years — average 24·1 years

TABLE III

'SIDE EFFECTS' MENTIONED BY PATIENTS

Active	*Placebo*
'Feeling weak' (2 patients)	Constipation
'Wind'	Tiredness and giddiness
'Furry sensation in mouth'	Tiredness
Tiredness (2 patients)	'Sleepy'
Lack of energy, 'funny feelings'	Depression
Drowsiness (3 patients)	
Constipation	
Headache	
12 side effects in 41 patients *i.e.* **29·2** per cent	6 side effects in 40 patients, *i.e.* **15** per cent
Total 18 side effects in 81 patients, *i.e.* **22·2** per cent	

inert placebo. However, conditions of obstetric practice in the United States of America are sufficiently different from those in Great Britain to justify repeating the work here. The results of our study demonstrate that this combination of substances is effectively anti-emetic, and suitable for use in early pregnancy. It does not answer the question as to which of the three constituents is the 'active' ingredient.

A high placebo response may reasonably be expected, bearing in mind the nature of the condition which remits spontaneously with the passage of time. We hope to extend this study

to find out whether the individual components of the product are as effective singly as they are in combination.

Summary

A double-blind comparison of 'Debendox' and an inert control, in the treatment of early pregnancy sickness was carried out in general practice.

The data show the expected high placebo effect related to spontaneous remission of the disorder. Greater relief of symptoms occurred with the active drug and the statistical pattern is sufficiently definite to justify a conclusion that this preparation is effective and useful.

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VOLUNTARY SERVICE

Friends in need

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THE WELFARE STATE cannot do everything and indeed should not. The voluntary services remain important both for the giver and the receiver. Therefore we give an account of 'Friends in Need' as an example of what can and should be done.

'Friends in Need' evolved from a house discussion-group of varying denominations. At one meeting the group felt a particular responsibility for giving help, as it was needed within the local community, as a practical expression of their Christian faith. As a family doctor was a member of the discussion group, it was decided to approach his practice as a source of people in need.

The practice consists of eight general practitioners serving approximately 20,000 patients. There are two health vicitors, two district nurses and two midwives attached to the practice as well as a surgery nurse, and it provides modern and personal care for its patients from purpose-built premises in the centre of the city. The patient–doctor relationship is of particular importance to the doctors and they are especially aware of the dangers of losing this within a large practice organization. This practice mainly draws its patients from a cathedral city and the surrounding villages. giving a wide cross-section of the population and both rural and twon practice. Despite the cate of the practice and the many welfate services, there are still particular human needs which cannot be catered for. 'Friends in Need' can help the doctor by saving him time in cases which basically need human sympathy, time and understanding rather than his expertise and medical knwoledge. 'Friends in Need' can also be called upon for more mundane routine tasks such as 'fetching' and 'carrying' which, because of the speed and solitariness of life in modern towns, is a necessity of our time.

How does this organization work? At present there are 75 helpers involved; four co-ordinators form the link between the practice and the group. The doctors, health visitors and nursing staff are issued with a list of the co-ordinators, their telephone numbers, the days of the week on which they are on duty and the particular times at which they will be available. In emergency the co-ordinator can be called at any time. Initially the discussion group formed the nucleus of the group of helpers, but since then others have joined from all parts of the city. If