

Transient cerebral ischaemic attacks—management and prognosis

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Summary

Fifty patients who had recently had a transient ischaemic attack took part in a double-blind cross-over trial of sulphinyprazone 200 mg 4 times daily against placebo. Each treatment was given for 4 months. The incidence of recurrences was much greater in the initial 4 months but there was no difference between the 2 treatments. A follow-up of 39 of the patients showed that 2 years later 90% of those who had not had a recurrence during the 8 months had suffered no further neurological events whereas of those who did have a recurrence during the study only 47% had no further neurological events.

Introduction

Transient cerebral ischaemic attacks (TIAs) may be the first clinical warning of an impending major stroke (Acheson and Hutchinson, 1971). Since TIAs are probably caused by platelet emboli, drugs which reduce the tendency of platelets to aggregate into thrombi (Turpie and Hirsch, 1978) should be useful in protecting patients with TIAs from disaster. However, there are many difficulties in evaluating the efficacy of such drugs. If the physical signs have disappeared before the patient is seen by a doctor, the diagnosis may have to be based on the history alone. The clinical picture may be complicated by intercurrent illnesses since the patient is often elderly. Finally, there are the problems of checking compliance, of interference by intercurrent medication, and of ensuring follow-up supervision and evaluation. For all these reasons it is unlikely that a trial from any one centre will provide unequivocal evidence on the value of antiplatelet drugs in preventing strokes, and multicentre trials produce their own uncertainties. In the authors' view the best way of assessing the effectiveness of drug treatment of

TIAs may be to mount a number of trials each from a single centre and report them separately.

A double-blind cross-over study was therefore carried out comparing sulphinyprazone, a drug known to reduce platelet aggregation (Maguire *et al.*, 1980), with placebo in patients referred to the Selly Oak Hospital, Birmingham, with a clearcut history of one or more TIAs. It was also thought important to add to the knowledge of the natural history of TIAs by conducting a follow-up survey after completion of the therapeutic trial.

Patients and methods

Patients

All patients referred to the hospital over a 3-year period were considered for the trial. Fifty patients, 35 men and 15 women, were selected on clinical criteria. Their mean age was 63 ± 10 years. Entry to the trial depended upon a clear history of a transient weakness of one or both limbs on one side, or amaurosis fugax, full recovery within 48 hr, and ability to enter the trial within 3 weeks of the last attack. Patients were excluded if they were suffering from severe renal or hepatic disease, uncontrolled hypertension, gout or active peptic ulceration. All patients underwent full clinical investigation to determine what factors were associated with the TIAs; they were excluded from the trial if a cardiac lesion likely to be a cause of emboli was found. Finally, prior therapy with anticoagulant or antiplatelet drugs was also an exclusion criterion.

Methods

Sulphinyprazone study. The study was performed by 4 physicians who took turns to run a weekly clinic devoted to trial patients. The patients attended at 4-weekly intervals, returning to the same physician

each time. At the first visit they underwent full clinical assessment, which included a full drug history, a 12-lead ECG, chest radiography, blood count and a 10-point serum biochemical profile. Relevant clinical and laboratory details were entered on to a pro forma.

On entry, patients were instructed to take either sulphinyprazole 800 mg daily in 4 divided doses or matching placebo for 4 months, crossing over to active drug or placebo for a further 4 months. Treatment order was randomized and the study was performed double-blind. Each patient was provided with a list of aspirin-containing drugs to avoid, and instructed to take paracetamol if analgesics were required. At each clinic visit during the 8 months, as a part of the clinical review, the occurrence of TIAs, stroke, and any new symptoms or potential side effects of treatment was recorded on the pro forma. Urine was assayed for the presence of drug to check compliance, and a tablet count was made.

Follow-up study

In order to follow the progress of the patients included in the drug study, a questionnaire was sent to the GPs of all patients completing the initial 8-month period and those who had sustained neurological events lasting longer than 48 hr resulting in premature withdrawal from the study. The questionnaire was completed 17–37 months after admission to the drug trial (mean, 28 months). Information was sought on whether the patients had suffered any further neurological events such as TIAs or stroke, and if they were still having sulphinyprazole. If a patient had died, the cause was ascertained. Details were successfully obtained on every patient.

Results

Sulphinyprazole trial

Fifty patients entered the trial, of whom 35 completed the 8-month period, 4 suffered major complications and a further 11 were withdrawn. The withdrawals included 5 patients with other medical disorders, 4 who failed to comply with medication, one who left the area and one who complained of indigestion whilst taking sulphinyprazole. Analysis was therefore performed on 39 patients of whom 16 started on sulphinyprazole and 23 on placebo. Compliance with the regimen, as determined by tablet count and urinalysis, was satisfactory.

Major complications

The 4 major complications comprised 2 deaths from stroke, and 2 non-fatal strokes. These latter 2 patients were then withdrawn from further participation in the trial. Of the 4 major complications, 3 occurred during the first 4 months, and 3 while

taking placebo. One patient died of a stroke whilst on sulphinyprazole, and the other death from stroke occurred on placebo during the second 4-month period. Both non-fatal strokes occurred shortly after entering the trial and whilst on placebo.

Further TIAs

Thirteen patients continued to have one or more TIAs during the trial as shown in Table 1. Nine

TABLE 1. Distribution of TIAs depending on treatment and order effect. (a) placebo/active, (b) active/placebo

Patient	(a) <i>No. of TIAs</i>		
	before entry	on placebo	on active treatment
D.H.	7	5	0
D.B.	1	1	0
E.H.	(several)	1	0
H.S.	1	6	9
T.B.	1	6	0
M.T.	1	5	0
H.G.	1	4	0

Patient	(b) <i>No. of TIAs</i>		
	before entry	on placebo	on active treatment
E.W.	1	1	1
R.P.	1	0	1
H.B.	12	20	16
L.B.	1	1	1
H.G.	2	4	7
D.B.	9	> 28	52

experienced them predominantly in the first 4 months, 2 in the second 4-month period and 2 with equal frequency in both periods. Seven had their attacks mainly while taking placebo, 4 mainly on sulphinyprazole and 2 had an attack during both treatment periods.

All neurological events

These results are summarized in Table 2. Two factors confound the analysis of drug effect. Firstly there was a marked order effect, since 12 patients (9 with predominant TIAs and 3 with strokes) of the total of 17 experiencing neurological events had them in the first 4-month period. Secondly, all but one of the drop-outs also occurred in the first 4 months and, by chance, the majority of these patients had been allocated to active treatment first.

Overall the effect of sulphinyprazole was not significant. Considering the results from the first 4-month period separately, 9 out of 23 patients on placebo had neurological events compared with 7 out of 16 on sulphinyprazole.

TABLE 2. Relationship of neurological events to treatment and order

Number of patients	Treatment period	Treatment order		Total
		Placebo/sulphinpyrazone	Sulphinpyrazone/placebo	
Having neurological events in each period	Placebo	9	6	15
	Sulphinpyrazone	1	7	8
Having no neurological events in either period	Both	14	8	22
		Total	24	21

* Of the 39 patients analysed 6 had TIAs in both periods.

Factors likely to influence prognosis

Age. The mean age of patients continuing to have TIAs (63 ± 9 years) and with major complications (59 ± 8 years) was similar to that of all patients completing the trial (63 ± 9 years).

Previous TIAs

Patients with a history of having experienced one or more TIAs before the one which led to acceptance into the trial had a rather greater tendency to have recurrences during the trial (5 out of 11) compared with those in whom this had been the first attack (8 out of 24).

Carotid bruits

Bruits were heard over the carotids in 25% of the patients. They were not present in those with a major complication but were present in similar proportion in those with and without recurrent TIAs.

Other factors

The sex ratio remained similar in the sub-groups of those who completed the trial. However all the major complications occurred in men. Blood pressure did not appear to influence outcome. This was not surprising since uncontrolled hypertension (diastolic >110 mmHg) was a bar to entry into the trial.

Follow-up study (Table 3)

Thirty-seven patients were available for follow-up, comprising 35 who completed the 8-month trial

period, and the 2 patients with non-fatal strokes who had previously been withdrawn from the study following this complication. Seven of the 13 patients who had TIAs during the sulphinpyrazone trial had further neurological events, 2 died from a stroke and 5 continued to have TIAs. In contrast, of the 22 patients who had no neurological episodes during the trial, 20 continued free of neurological episodes, although one developed cardiac failure and died, and one patient died after a fall. Only one experienced TIAs for the first time after the end of the drug trial and another had a non-fatal stroke. Thus, the risk of having further neurological events is significantly less ($P < 0.01$) amongst patients who do not have a recurrence during the 6–8 months after the initial episode.

Only 9 of the 37 patients followed-up had continued taking sulphinpyrazone after the initial study. Five of them continued to have TIAs and only 4 had no attacks. Therefore there seems no reason to suppose that long-term treatment affected the outcome.

Of the 2 patients who had non-fatal strokes during the drug study, one had died during the follow-up period while the other continued to have TIAs despite sulphinpyrazone therapy.

Discussion

This study showed that on entering the trial the greatest risk of developing a further neurological episode occurred in the first 4 months (3 out of 4 strokes, and all 13 patients with TIAs). Furthermore

TABLE 3. Relationship between neurological events occurring during follow-up period and during drug study

	Follow-up study	
	Patients having further neurological events	Patients having no further neurological events
Patients who had TIAs during drug study (13)	7 (2 dead)	6
Patients who did not have TIAs during drug study (22)	2	20 (2 dead – 1 CCF) 1 fall

sulphinpyrazone seemed to have little overall effect on the incidence of neurological events since they occurred in 7 out of 16 patients taking sulphinpyrazone and 9 out of 23 on placebo. However, all the 9 patients who started on placebo had neurological events during the first 4 months but only one continued to have TIAs during the second (sulphinpyrazone) period. In contrast, in the 8 patients who started on sulphinpyrazone, the events were more evenly distributed, in that 2 occurred during the first 4 months (one TIA and one death from stroke); one patient died from a stroke on placebo and the remaining 5 patients had TIAs during both treatments.

With small numbers in the groups, the possibility arises that any difference in outcome between the 2 groups was due to some factor characterizing the patients in each group other than their treatment. However, of those factors examined, especially the distribution of patients presenting with a history of multiple TIAs, none showed a bias likely to account for the results.

On reviewing the patients 2 years later, long-term treatment with sulphinpyrazone seemed not to have been beneficial although this was not formally tested. However, this conclusion would be in keeping with that of the Canadian Cooperative Study Group (1978) trial in which no advantage could be detected for sulphinpyrazone treatment of TIA over one year or more, although the effect of the drug over the first 4 months after a TIA was not examined.

A significant influence on prognosis over the 2 years could be detected depending on whether neurological complications had occurred by the end of the 8-month trial period. Twenty of the 22 (90%) free of further neurological events during the 8 months continued so subsequently, as against only 7 of the

15 (47%) who had suffered TIAs or a non-fatal stroke over the first 8 months.

The diagnosis of TIA may not always be correct when based on the clinical history alone. Indeed, 3 patients were withdrawn from the trial because they were subsequently found to have a cerebral tumour, epilepsy and a detached retina respectively rather than TIAs. However, investigation is generally corroborative rather than diagnostic. Electroencephalography, computerized tomography, or isotope brain scans were only carried out where a strong clinical indication existed, and cerebral angiography was not considered necessary in any of the cases. The patients in this study were therefore probably representative of patients presenting clinically with transient cerebral ischaemic attacks.

This study clearly shows that the probability of the recurrence of TIAs is greater in the first 4 months following an attack, but there was little evidence that sulphinpyrazone was of any value in preventing them.

Acknowledgments

We thank Dr M. J. Kendall for his help with the study, and Ciba-Geigy Pharmaceuticals, Horsham, for statistical advice.

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