MEDICAL PRACTICE

Clinical Topics

Mortality from ischaemic heart disease among patients using anticonvulsive drugs: a case-control study

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Abstract

Patients who use phenytoin and some other anticonvulsive drugs have been shown to have raised concentrations of plasma high density lipoprotein. As this lipoprotein is known to be inversely associated with the incidence of ischaemic heart disease the causes of death of all patients with epilepsy known to be taking anticonvulsive drugs who died during 1978-80 were studied. Of 1399 deaths of anticonvulsant users, 258 (18·4%) were caused by ischaemic heart disease. This was significantly less ($p<0·001$) than the 382 deaths from ischaemic heart disease (27·3%) observed among paired controls matched for sex, age, and date of death. The total cardiovascular mortality was also lower among patients with epilepsy than among controls ($p<0·02$) despite there being more deaths due to cerebrovascular disease among patients. The difference in mortality from ischaemic heart disease was significant for both sexes and was not accounted for by excess deaths due to any other single cause. Users of phenytoin, carbamazepine, and barbiturates (alone or in combination) showed 29% less mortality due to ischaemic heart disease than respective controls ($p<0·001$).

Introduction

Plasma high density lipoprotein cholesterol and apolipoprotein A I have a strong inverse association with the incidence of ischaemic heart disease.[1-3] As patients using phenytoin or carbamazepine have increased serum concentrations of high density lipoprotein cholesterol and apolipoprotein A I[4-8] patients with epilepsy receiving long term anticonvulsive treatment might be expected to suffer less ischaemic heart disease. Some previous observations have suggested that patients with epilepsy have less myocardial infarction than normal subjects,[9 10] but this has not been confirmed by other studies.[11-13]

We studied the problem further by taking advantage of the fact that in Finland all patients with epilepsy receive their anticonvulsive drugs free of charge and are therefore registered by the treatment they receive in the national drug register.

Patients and methods

The study considered all deaths that occurred during 1978-80 among patients with epilepsy registered at the Social Insurance Institution of Finland. Detailed information about the treatment of each patient was obtained through the drug register of the local office of the Social Insurance Institution. The death certificates were obtained from the Central Statistical Office of Finland. For every patient with epilepsy a control subject matched for age, sex, and date of death (day and month) was randomly selected from the Central Statistical Office's register of death certificates for 1979. The International Classification of Disease codes 410-414 were accepted as causes of ischaemic heart disease, and codes 430-438 were accepted as causes of cerebrovascular disease (stroke). These two groups combined represented the total cardiovascular mortality. McNemar's test of symmetry was used for statistical analysis.[14]

Results

During the study 1399 (915 men and 484 women) registered patients with epilepsy died. The mean age at death was 55·2 and 55·3 years for patients and controls respectively. In both groups there were 497 deaths of subjects under 50, 559 of subjects aged 50 to 69, and 343 of subjects 70 or older. Necropsy was performed in 695 (49·7%) patients and 734 (52·5%) controls.

Table I shows the number of deaths due to major causes. The mortality

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from ischaemic heart disease was significantly lower among epileptics than controls. In contrast, the mortality from cerebrovascular causes was higher among epileptics than controls, a predictable result as epilepsy is often a consequence of cerebrovascular disease. Nevertheless, the total cardiovascular mortality was still significantly lower among patients than controls.

TABLE I—*Number of deaths of patients with epilepsy and controls in selected diagnostic categories*

Cause of death	No of cases/controls		Total No (%) of cases/controls
	Men	Women	
Ischaemic heart disease	190/287***	68/95**	258/382*** (18/27)
Cerebrovascular disease	81/55**	76/33***	157/88*** (11/6)
All cardiovascular disease	271/342***	144/128*	415/470* (30/34)
Neoplasma	214/156***	124/145 n.s.	338/301* (24/22)
Violence	144/210***	32/72***	176/282*** (13/20)

*p<0·02; **p<0·01; ***p<0·001; McNemar's test of symmetry.

All these differences were significant in both sexes. Neoplasms were more often the cause of death in patients with epilepsy than controls. The difference in mortality from ischaemic heart disease in favour of patients, however, did not change after all pairs in which either patient or control had died from a neoplasm (another possible cause of epilepsy) had been eliminated. The difference in the number of violent deaths also did not explain the results as violent death was less prevalent among patients than controls. There was no other single cause of death that could explain the lower mortality from ischaemic heart disease among epileptics.

Reliable information about the kind of anticonvulsive drug used was obtained in 763 cases. This cohort was divided into subgroups according to treatment received (table II). The mortality from ischaemic heart disease

TABLE II—*Number of deaths among patients with epilepsy classified by treatment received and respective controls*

	No of cases/controls		
	Phenytoin as only drug	Phenytoin, carbamazepine, or barbiturate	Other anticonvulsive drug
Ischaemic heart disease	54/65	140/196***	15/13
Cerebrovascular disease	28/15	80/44**	5/2
All cardiovascular disease	82/80	220/240	20/15
Total No of pairs	215	686	59

*p<0·02; **p<0·01; ***p<0·001; McNemar's test of symmetry.

was 17% lower in patients using phenytoin alone than in their paired controls, but because of the relatively small number of cases in this category the difference was not significant. On the other hand, the number of deaths from ischaemic heart disease was significantly lower among patients who had received phenytoin either alone or in combination with another anticonvulsant (114 of 549) than among their respective controls (160 of 549, p<0·01). Also among the patients receiving phenytoin, carbamazepine, and barbiturates (singly or in any combination) the risk of death from ischaemic heart disease was 29% lower in patients than controls. In contrast, the patients who had been treated with any other anticonvulsant did not show any differences in mortality from cardiovascular causes compared with controls.

Discussion

Previous reports contain little data on the incidence of or mortality from ischaemic heart disease among patients with epilepsy receiving long term anticonvulsive treatment. Indeed, two reports suggesting an unusually low prevalence of ischaemic heart disease in patients with epilepsy were only anecdotal without any data.[9 10] Annegers *et al* have since published three papers on a follow up study of a small cohort of patients with epilepsy.[11-13] For patients with idiopathic epilepsy they could not show any reduction in the standardised mortality ratio for heart disease or in the incidence of ischaemic heart disease compared with that for the white population in the United States, which was not defined. They did find, however, that the proportion of deaths due to ischaemic heart disease was low compared with all deaths in the United States.[13] This finding was interpreted as resulting from competitive causes of death among patients with epilepsy, but no data were presented in support of this hypothesis. Moreover, the total number of deaths due to ischaemic heart disease in that cohort of patients was only 48,[13] while in this study it was 258.

In the present study the causes of deaths of patients registered by their use of anticonvulsive drugs were compared with those of randomly selected paired controls. The drug register covers all patients who were receiving anticonvulsive drugs, although evidence of regular and continuous use of defined drugs could be obtained in only 763 (55%) of cases. Of these patients, 686 (90%) were taking anticonvulsants known to modify plasma concentrations of lipids or lipoproteins. Changes in treatment therefore occurred mainly between phenytoin, carbamazepine, and barbiturates. Ischaemic heart disease as the cause of death was significantly more prevalent among the controls than the patients. In contrast, cerebrovascular disease as a cause of death was more prevalent among patients than controls, as might be expected, stroke often being the cause of secondary epilepsy. In these cases the anticonvulsive treatment (which may raise high density lipoprotein concentrations) was started only after cerebrovascular disease had been identified clinically and therefore could not have had any preventive effect.

When divided into subgroups according to the anticonvulsive drug prescribed, the regular users of phenytoin, carbamazepine, and barbiturates, singly or combined, showed significantly lower mortality from ischaemic heart disease than the controls. A similar trend was also present among patients using phenytoin as single treatment, but the difference did not reach statistical significance owing to the small number of cases. Neither was there a significant difference between patients using carbamazepine or barbiturates alone and controls.

As this type of study records each individual cause of death only as a proportion of all deaths we must consider the possibility that the lower mortality from ischaemic heart disease among patients using anticonvulsive drugs might be accounted for by an excess of competing causes of deaths. Apart from cerebrovascular diseases and neoplasms no single category of cause of death appeared to explain the difference in mortality from ischaemic heart disease between patients and controls.

All the major anticonvulsive drugs—phenytoin, carbamazepine, and barbiturate—have been reported to raise plasma concentrations of high density lipoprotein cholesterol and induce liver microsomal enzymes.[4-8 15] As high concentrations of high density lipoprotein cholesterol are associated with a decreased risk of ischaemic heart disease in the general population[1 2] and in certain subsections—for example, regular users of moderate amounts of alcohol or physically active people—reduced mortality from ischaemic heart disease observed in epileptic patients is also probably related to their high mean concentrations of high density lipoprotein cholesterol. There are, however, other factors that may contribute to protecting these patients from coronary heart disease. Phenytoin is known to inhibit the secretion of insulin and decrease the response of plasma insulin to glucose.[16 17] This might be advantageous for patients with epilepsy as hyperinsulinaemia is an independent positive risk factor for ischaemic heart disease.[18 19] Moreover, phenytoin may inhibit fatal cardiac arrhythmias. We do not really know the reason for the lower mortality from ischaemic heart disease in the present study. There may be reasons other than those mentioned above, but the reduced mortality from ischaemic heart disease in patients with epilepsy was confirmed by the fact that the diagnoses were verified in half of the patients at necropsy.

In a recent study we showed that the low concentrations of high density lipoprotein cholesterol often found among patients with

transient ischaemic attacks could be increased with low doses of phenytoin.[20] This suggests that the possibility of increasing low concentrations of high density lipoprotein cholesterol with safe doses of anticonvulsants should also be considered in patients who run a high risk of coronary heart disease.

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Epidemiology

Comparison of response rates to a postal questionnaire from a general practice and a research unit

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Abstract

A postal questionnaire study was carried out in an urban general practice to determine the effect of the introductory letter being sent by the participants' own general practitioner compared with that from a letter sent directly from a research unit. By sequential sampling 409 individuals aged between 40 and 59 were assigned to one of two groups. The people in one group were written to by their own general practitioner and those in the other by a doctor from a research unit. Husbands and wives were paired and were always sent the same letter. A second letter was sent to non-responders after one month.

The response rate to the general practitioner was significantly higher than that to the doctor in the research unit (85% compared with 75%) and differed by age and sex. The results have important implications for other research workers and suggest that general practitioners are in a key position in the conduct of medical and epidemiological research.

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Introduction

Questionnaires are in widespread use as a tool in medical research for the collection of data. In most study designs it is important to obtain a high response rate from the selected study population to avoid bias. The results of some studies have shown important differences between responders and non-responders.[1,2] Thus responders in a study with a low response rate are unlikely to be representative of the study population. Studies therefore require high response rates or need information about the non-responders so that the nature of the bias may be determined.

As part of a series of pilot studies in preparation for a large, national study of coronary heart disease in Scotland, the Scottish Heart Health Study, a postal questionnaire was sent to individuals aged between 40 and 59 years. The aim was to test a questionnaire design and to investigate the nature and size of the effect of the participant's own general practitioner sending the introductory letter compared with the effect of the letter coming directly from a research unit.

Methods

The participants were selected from the patients who were registered with an urban general practice that has been described.[3] The names and addresses of all patients aged 40 to 59 were obtained from a computer listing from the Tayside master patient index.[4] Twenty six patients were excluded because the general practitioners considered them unsuitable for the study on the grounds of limited knowledge of the English language or mental or physical illness.

The 409 patients who were identified were assigned by sequential sampling to one of two groups. One group was written to by the general