Consultant views on the use of aspirin in acute cerebrovascular disease: implications for clinical trials

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Summary: A questionnaire was sent to all 155 consultant physicians and geriatricians in the Yorkshire region who routinely admit patients with acute stroke in order to ascertain: (a) current opinion regarding the prescription of aspirin to patients with various manifestations of cerebrovascular disease, in particular the timing of initial treatment; and (b) the perceived role of computed tomography (CT) scans in relation to such therapy.

The response rate was 81% (126/155). Aspirin was reported to be prescribed routinely by 75% (95/126) of physicians for patients with completed stroke. Amongst those prescribing aspirin, treatment was reported to be initiated routinely within 48 hours of the onset of symptoms by 63% (60/95). Only 10% (6/60) of these physicians reported that they would withhold aspirin therapy until the result of a cranial CT scan was known, although 43% (26/60) thought a CT scan was desirable.

Our survey, which for logistical reasons is one of opinion rather than actual practice, suggests that aspirin is probably being prescribed acutely (less than 48 hours) after stroke to a significant number of patients and often without a pretreatment CT scan. As with patients who have had a CT scan, the balance of risks and benefits of this practice are unknown. We conclude that it would be ethical for acute treatment trials to allow randomization to aspirin without prior CT scan.

Introduction

Although it is less than 20 years since the first large clinical trial reported a beneficial effect of aspirin in cerebrovascular disease, it did not become widely accepted as an effective method of secondary stroke prevention until after the publication of a meta-analysis of 25 trials of anti-platelet therapy in patients with symptomatic vascular disease.¹

In most of these studies, aspirin was started as long as 3 months after the index event, although few details of this delay are usually published. It is possible that the potential benefit of aspirin in this context has been underestimated since epidemiological studies suggest that the occurrence of a first stroke after a transient ischaemic attack (TIA)² or of stroke recurrence³ is greatest in the first month after the index event. This provides some logic for the early use of aspirin but, equally, it is possible that the risks of aspirin therapy, particularly those related to intracranial haemorrhage (ICH), might be greater when given closer to the acute event.

On the other hand, although many of the trials of secondary stroke prevention included patients with 'minor' stroke, for this group, as well as for those with 'major' stroke, the possibility that aspirin may

have a role in acute 'damage limitation' also exists. In the acute phase, aspirin may have a role in reducing ischaemic damage by preventing the propagation of thrombus and, logically, the sooner the treatment is given the more chance it has of being effective. There is much speculation, but little firm evidence, that aspirin prescribed *after* the event results in an increase in the rate of ICH, although amongst those patients in primary prevention studies having a stroke whilst taking aspirin, there is probably a greater proportion with ICH. Withholding treatment until a CT scan has been performed will prevent aspirin being given to patients with ICH but, because of the inevitable delay, it may significantly reduce the possible benefit of the therapy to the large majority of stroke patients who have infarcts.

Interest in using aspirin acutely has undoubtedly been stimulated by the result of the ISIS-2 study which showed that the acute use of 150 mg aspirin daily produced a highly significant reduction in 5 week vascular mortality in patients suffering acute myocardial infarction as well as reducing non-fatal re-infarction and non-fatal stroke.⁴ However, extrapolation from the cardiac trials is not only complicated by the fact that 10–15% of all strokes (and a greater proportion of those admitted to hospital) are due to ICH⁵ but also that spontaneous

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Accepted: 16 September 1993

haemorrhagic transformation may occur in up to 40% of cerebral infarcts, although not always with clinical deterioration.⁶ The impact of aspirin on this process is also unclear but it is *possible* that in acute stroke, unlike in secondary prevention, the risks may outweigh the benefits.

Large multinational clinical trials are now being established which will address the question of the overall value of using aspirin acutely after ischaemic stroke. It has been suggested that it would be unethical to use simple anti-haemostatic agents acutely after stroke without mandatory pre-randomization CT scan because of the *potential* risks of exacerbating deficits due to ICH or haemorrhagic transformation. On the other hand, the necessity for a CT scan would inevitably delay initiation of a treatment whose benefit might be restricted to a very narrow time window. Furthermore, even if the results of a purely CT scan-controlled trial demonstrated that the intervention was beneficial, in areas where CT scan facilities remain sparse, physicians would be faced with a major dilemma about how they should manage their patients. It seems highly improbable that a completely separate trial would be performed simply to address this question. Even in areas where CT scan was not as restricted but perhaps transport to hospital would take several hours, it would also leave a question mark against the relative value of emergency treatment in the community by general practitioners or even by the patients themselves.

Aspirin is already being prescribed 'acutely' after stroke outside clinical trials. Therefore, as part of a larger survey of current consultant opinion on the management of cerebrovascular disease, we sought their views on the use of aspirin in the immediate aftermath of a stroke.

Methods

All consultant physicians and geriatricians in the Yorkshire Region under whose care patients with acute cerebrovascular disease are admitted were identified from staff lists provided by the personnel departments at the Regional Health Authority and NHS Trust hospitals. Each was sent a single page questionnaire with an accompanying explanatory letter and pre-paid return envelope. The questionnaire was designed for ease of completion to maximize the response rate.

Amongst other questions, respondents were asked to indicate: (a) whether they prescribed aspirin routinely to patients with stroke (either 'minor' or 'major'); and, if so, (b) at what time after onset did they usually initiate treatment; (c) did they consider that a cranial CT scan was desirable before starting treatment; and, if so, (d) would they

withhold treatment until a CT scan had been performed. For some analyses the responses for 'minor' and 'major' stroke were combined under the term 'completed stroke' (see discussion).

Results

The response rate was 81% (126/155). For patients with 'minor stroke', 75% (95/126) routinely prescribed aspirin, 63% (60/95) within 48 hours of the onset of symptoms. For patients with a 'major stroke', 35% (44/126) routinely prescribed aspirin, 30% (13/44) within 48 hours of the onset of symptoms. All physicians who reported prescribing aspirin within 48 hours of a 'major stroke' also used aspirin after 'minor stroke'.

Amongst those physicians prescribing aspirin within 48 hours of onset of a 'minor' stroke, 43% (26/60) thought that a prior CT scan 'was desirable' but only 10% (6/60) reported withholding treatment until the result was available. The figures for patients with 'major' stroke were 92% (12/13) and 33% (4/12) respectively.

Discussion

With this type of postal survey there will always be a trade-off between the amount of detail obtained and the response rate. We recognize that our questions represent a gross simplification of the complex decisions taken by physicians in everyday practice and, because of variations in practice, the exact figures are likely to vary from region to region. However, our intention was simply to gain a broad view of consultant opinion so that ethical issues arising in the course of clinical trials can be considered in the context of current everyday practice. We consider that the 81% response rate allows this to be done and it seems likely that aspirin is currently being prescribed within 48 hours of onset of a completed stroke by a substantial proportion of physicians.

Any subclassification of completed stroke which is based on the duration of symptoms such as that suggested by the Royal College of Physicians⁷ is of limited value in the context of acute stroke treatment where the therapeutic time window is likely to be hours rather than days. We included the terms 'minor' and 'major' stroke on the questionnaire (although we did not state specifically how they should be distinguished) because the majority of secondary prevention trials which included patients with completed stroke classified them as 'minor' stroke. We suspect that the terms were interpreted as measures of severity rather than duration of the deficit (although the two are correlated). Our questionnaire did not examine

whether the greater reluctance to use aspirin after what was perceived as a 'major' stroke and the greater desire to have the result of a CT scan reflects a conscious awareness that the presence of clinical features such as an early depressed level of consciousness do increase the likelihood of the stroke being due to a cerebral haemorrhage. Although clinical scoring systems such as that reported by Allen⁸ do not predict all cases of cerebral haemorrhage, they may still be a useful means of screening out a significant number of such cases and thereby reducing the risk that aspirin is given unwittingly to cases of cerebral haemorrhage.

Our survey suggests that at present almost 50% of physicians consider it acceptable to give aspirin acutely, that is within 48 hours, to at least some patients with completed stroke and that the majority of them would do so without having a CT scan.

We consider that the following conclusions can be drawn from this survey.

Firstly, there is an urgent need for large, randomized trials of aspirin in acute stroke to establish the risk-benefit ratio, otherwise a *potentially* dangerous treatment may rapidly become widely used, and as with carotid endarterectomy, subsequent attempts to place such therapy on a sound scientific basis will become increasingly difficult. All physicians who manage patients with acute

stroke should consider participating in trials such as the International Stroke Trial (IST)* so that this important management issue can be clarified as soon as possible.

Secondly, that it would be ethical for such trials to allow randomization of patients without prior CT scan, since our survey suggests that a substantial proportion of physicians currently consider this to be acceptable practice. As is the case with the IST, a data monitoring committee should specifically monitor this subgroup and advise if a major difference in outcome was occurring. A major potential advantage of such a policy would be that a single trial would not only be able to address the question of overall efficacy but, should this favour the use of aspirin, at the same time it would be possible to give guidance to physicians in the regrettably large number of hospitals who still do not have ready access to CT scans. Furthermore, cautious extrapolation could be made to the potential use of aspirin by general practitioners and even patients themselves as a means of reducing the time from onset to treatment.

*Details of the IST can be obtained from Dr P. Sandercock, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK.

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