Multiple sclerosis

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Calcium antagonists in exercise-induced asthma

Sir,—The report by Dr K R Patel (21 March, p 932) that the calcium antagonist verapamil inhibits exercise-induced asthma is supported by the observations of Cerrina and co-workers,1 who report that nifedipine, another antagonist of calcium influx, also prevents the bronchoconstrictor response to exercise in asthmatics. In discussing the mechanism of exercise-induced asthma both Dr Patel and Cerrina et al suggest that the release of spasmones from lung mast cells may play a role in this condition and that calcium antagonists, in addition to relaxing smooth muscle, may prevent exercise-induced bronchospasm by inhibiting the calcium-dependent release of these spasmones.

In recent studies on the antigen-induced release of spasmones from sensitised fragments of human lung, using well-established techniques2 smooth muscle rather than there is an absolute requirement for extracellular calcium ions in the release processes. However, nifedipine and verapamil at concentrations up to 100 μmol/l failed to inhibit the release of histamine from human lung when the drug was preincubated with the tissue for 30 minutes before challenge. We did observe, however, that verapamil at 100 μmol/l, but not at 10 μmol/l, inhibited the release of slow-reacting substance. In addition, verapamil (500 pmol/l-150 μmol/l) inhibited the spasmogenetic effect of histamine (1 μg/ml) on human superfused bronchial smooth muscle with a concentration effective in 50% of cases (EC50) of 9 μmol/l.

Spasmones derived from mast cells are unlikely to make a major contribution to the bronchoconstrictor response to exercise in asthmatics.8 Even if their contribution is greater than currently believed the results presented here suggest that calcium antagonists exert their inhibitory effects in exercise-induced asthma on the constrictor responses of 90% of cases (EC50) of 9 μmol/l. I have shown on the release of spasmones from mast cells.

Nifedipine was a gift from Bayer UK Limited and verapamil was a gift from Abbott Laboratories Limited.

R Butchers I F Skidmore C J Varey A Wheelon

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Are fibre supplements really necessary in diverticular disease of the colon?

Sir,—What should we do when clinical impressions over a number of years are not confirmed by a randomised, cross-over, double-blind controlled trial? With only an occasional exception patients with symptomatic uncomplicated diverticular disease of the colon report a persisting improvement when they take extra dietary fibre, often without an additional bulking agent. Personally I accept the verdict of my patients and then look doubly carefully at the double-blind trial.

The trial which you report by Mr M H Ornstein and others (25 April, p 1353) surely has an obvious fallacy. I was taught that the mode of a drug is that which has the desired effect without causing side effects, and the same is true for dietary supplements. To give a standard amount, and a small one at that, to every patient irrespective of their real need invites trial disaster. In their subsequent letter (16 May, p 1629) the authors admit that "it is important to give sufficient bran or ispaghula to relieve straining and the amount will vary greatly between patients." This is equally true for other symptoms. With their own words they themselves condemn their own trial, which I believe is meaningless and dangerously misleading, although it appears to be beautifully designed and executed.

I am not alone in thinking that this paper should have been published in a specialist and not a leading world medical journal. This is not the first time that a clinical trial has given a dubious answer and I have shown how to interpret the results in my new series “Statistics in Question” about assessing clinical trials (16 May, p 1605).

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1 Brodribb AJM. Lancet 1977;i:664-6.

Multiple sclerosis

Sir,—Your leading article on multiple sclerosis (14 February, p 502) suggests that in a cross-sectional survey the median duration of the disease can be calculated by doubling the time from onset to prevalence day. The fallacy of this statement can be demonstrated with an extreme but simple example.

Suppose that 80% of patients with a particular disease survive for six months after...
onset, while the remaining 20% survive for six years. Then a cross-sectional study can be expected to contain 25% short-term survivors and 75%, long-term survivors, because of the greater risk of short-term survivors being dead before "prevalence day." Thus, assessing a single cohort incidence, we can arrive at a median interval from onset to prevalence day of two years. The recommended method would therefore estimate the median survival to be four years compared to the true figure of six months.

It is also apparent from this example that an increase in estimated median survival can result from a shortening of life expectancy among those with a poor prognosis.

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* Poskanzer et al1 point out (p 236) the statistical problem: "Assuming that there is no change in the pattern of a disease, average duration could be estimated as twice the period from onset to prevalence day. It is therefore assumed that the duration among a group of patients identified on prevalence day will approximate to a normal distribution and that ascertainment of nearly all existing cases will be achieved, especially those cases with a recent onset of the disease. The latter requirement has probably not been fully met in each of the four surveys in the Orkneys and Shetlands. However, the method can be applied by using information discovered later about cases with onset close to prevalence day. The effect of not identifying all cases with recent onset overestimates the average duration. If it is assumed, however, that the error resulting from the exclusion of recent-onset cases is relatively constant over the four surveys, the data can be used to determine if the duration has changed over time but not to determine the actual duration of the disease." Space did not allow us to go into these details about the statistical method in our leading article, but we are grateful to Dr Prescott for writing.—Ed, BMJ.


Trial of folate treatment to prevent recurrence of neural tube defects

Sir.—We have been extremely interested to read the recent papers by Dr K M Laurence and others (13 December, p 1592; 9 May, p 1509) on the relationship of maternal diet and folic acid supplementation to neural tube defect recurrence. Their observations on red cell folate levels support our earlier work1 and their conclusions regarding folate supplemenpt point in the same direction as the results of our supplementation study,2 full details of which will be published shortly.3 We note that the Cardiff group had methodological problems, as we did. We are puzzled by their use of the term "double-blind" in their more recent paper, which can only have applied until six to nine years after that conception, when blood folate levels were estimated and "non-compilers" were identified. The high rate of non-compliance must also have disappointed the authors. We entirely endorse their view that further studies are needed, directed towards the following ends:

1. To provide further confirmation that vitamin prophylaxis is effective. Our own continuing studies remain encouraging, but among the defects in the offspring of fully "supplemented" women in our second cohort are one recurrence of frank neural tube defect (south-east England); one small, skin-covered lesion in a woman with a neurological deficit (Nortn Ireland); and one very large third fontanelle without involvement of brain or meningies (Yorkshire).

2. To define further the role of folic acid and other vitamins. We regret that Dr Laurence and his colleagues chose to describe Pregnanl Forte Fe, a vitamin and iron preparation containing folic acid, as an "expensive blunderbuss preparation". We chose it because our earlier studies demonstrated low first-trimester blood levels of ascorbic acid and riboflavin as well as folic acid in mothers bearing fetuses with central nervous system defects. It is certainly more expensive than folic acid, but should it prove to be more effective the cost (less than 5p daily) would be bearable.

3. To study carefully mothers who are enrolled for supplementation but who comply only in part. The South Wales "non-compliers" may have complied in part, and details of the two who had recurrences are crucial. It is only from this group that we can discover the minimum effective period of supplementation. There is certainly a difference between the two. The medical correspondent of The Times has advocated (8 May) vitamin supplementation on the basis of our series and those of the Cardiff group. It can no longer be assumed that mothers not given vitamin supplements by research workers necessarily have none. There is also a danger of "do-it-yourself" supplementation by mothers obtaining over-the-counter vitamin preparations, none of which contains folic acid.

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Sir,—Dr N Davis (9 May, p 1548) is concerned about drug company sponsorship of an educational programme, organised by the Centre for Medical Education at the University of Dundee, where the company's products are mentioned. I would make the following points:

1. I believe that the pharmaceutical industry does have a role in education of practitioners in the subject areas in which the companies have an interest. Just as clinical trials are done in conjunction with university departments, so also should there be collaboration in the production of educational materials. This is reasonable provided that there is editorial independence and that the names of the companies producing the materials are not mentioned.

2. Therapeutics is an area in which general practitioners express a demand for continuing education. If programmes are to be meaningful and related to day-to-day practice of a general practitioner, it is impossible to avoid reference to individual drugs. It is our experience that many general practitioners prefer reference to be made to the trade rather than to the generic names.

3. Our interest at the Centre for Medical Education is in exploring methods of continuing education in medicine. We have identified some characteristics of programmes which are likely to ensure their success and these are incorporated in the series. The approach seems to be appreciated by many doctors. Of the first 100 doctors replying to a questionnaire we have sent out, 98 expressed a desire to receive a similar series. If this response is any indication of what we might expect, we are at present completing a report evaluating the project in detail.


Masked advertising?

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