Protein binding of warfarin

Chan et al. [1], in comparing the results of their study of plasma protein binding of warfarin with one of ours [2], stated that in our study 'no check of radiochemical purity was reported'. That is incorrect. We were the first to point out the importance of assay specificity for plasma protein binding determinations with \(^{14}\text{C}\)-warfarin [3] and used post-dialysis thin layer chromatographic methodology to separate warfarin from its metabolites and degradation products in all our studies with radiolabeled warfarin. This is evident via reference 18 in our report [2] in which it is clearly stated that warfarin concentrations were determined by scintillation spectrometry following extraction and thin layer chromatography. We reported in .976 in a publication not cited by Chan et al. [1] a statistically significant negative correlation between the serum free fraction of warfarin and serum albumin concentration in normal subjects [4]. The absence of a significant correlation between serum free fraction and serum protein concentration in our study of patients [2] is likely to be due to concomitant medication and disease state, and not, as Chan et al. [1] have implied, to deficient methodology.

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Improving patient recruitment in clinical trials: lessons from one multicentre study in asthma

Information regarding recruitment in clinical trials is not often formally reported and is therefore limited, most data referring to large multicentre trials [1, 2]. We report the results of a study aimed at assessing different recruitment strategies from four Spanish centres who were participating in an international trial. This was an 8 week randomized, double-blind, placebo-controlled, Phase II, dose ranging study of a new drug for the treatment of mild to moderate asthma and was performed over a 3 month period. Several criteria for selecting patients could be expected to affect the ease with which suitable patients could be identified, e.g. FEV\(_1\) and FEV\(_1\)/FVC ratio (Tiffenau index) to fail within a defined range; symptomatic asthma to be present; previous drug therapy for the asthma especially with regard to inhaled steroid; and the need to exclude women of childbearing potential. The workload for the patients enrolled was considerable—several pulmonary function tests (PFTs) at each of eight visits, blood sampling at many of them and twice daily recording of symptoms and medication in diary cards.

All investigators, who had experience with similar types of trials, were asked to complete a form in order to collect the following data: total number of medical records reviewed; number of patients appointed for a screening visit; listing of all patients attending a screening visit; reason for non-enrolment where applicable. We considered that a patient was enrolled in the trial after informed consent had been obtained, thus ending recruitment activity [2]. The participating centres were all hospital based. Centre A was a Department of Allergy and Centres B, C and D were Departments of Respiratory Medicine. Centres A and B were less than 500 beds and Centres C and D were more than 1000 beds. The strategies for searching adult patients were as follows: Centre C (the control centre) just screened asthma patients who were otherwise attending the Out Patient Clinic for a standard visit—the 'wait and see strategy'; Centres A, B and D searched hospital files for asthmatic patients to make a preliminary assessment based on data available in the patients' records, and invited those patients who fulfilled selection criteria to a screening visit. Further-
more, Centre D only selected and invited to a screening visit patients for whom a recent PFT print out was consistent with the requirements of the protocol. All three disregarded female patients of potentially fertile age as well as patients living too far from the investigating centre.

The methods used to invite the selected patients to a screening visit varied. In Centre A patients were telephoned by a nurse who asked the patients to attend a standard visit (not mentioning a clinical trial at this stage). In Centre B patients were telephoned by the study co-investigator (up to four calls were tried) and the message included an invitation to participate in some 'clinical trial with a new drug'. In Centre D candidate patients were approached by mail using a standard letter which clearly referred to a 'study' about the use of 'a new drug for the treatment of asthma' and invited the patient to call back to a specific telephone number where an appointment would be arranged. This letter was signed by both the investigator and the co-investigator.

Results are shown in Table 1. The percentage of patients attending the screening visit from those invited to do so was remarkably different between centres: 100%, 58% and 29% for Centres A, B and D respectively. The proportion of patients enrolled from those attending the screening visit was 25%, 27% and 45% in Centres A, B and D respectively. In the control Centre C the proportion of patients enrolled was only 13% and this is statistically different from Centre D (P < 0.05; \( \chi^2 = 5.62 \)) and no statistical difference was found when comparing centres A or B with Centre C, probably due to the small number of patients involved in these Centres. It is worth mentioning that no patients were excluded at Centre D because of a refusal to give informed consent, whereas 21–31% of patients from the other Centres refused to give consent.

Considering the time and effort spent by the investigating team at each screening visit, our results show that it is worth using alternative methods to the 'wait and see' way of trying to enrol patients in a trial. This study clearly shows that recruitment rates could be enhanced by sending letters to patients who appear eligible for entry to a trial from an examination of their hospital records. Further studies are needed to confirm whether telephoning preselected patients could also significantly enhance recruitment. Published data suggests that in large therapeutic trials it is reasonable to expect a 20% enrolment amongst screened patients [2].

It seems advisable in future Phase II placebo-controlled trials in similar populations and settings that a letter to preselected patients inviting them to participate in the clinical trials should be considered at the planning stage. Since it is common to experience delays in the recruitment process and these delays result in increased costs for the trial [1, 3], we should encourage investigators to collect and publish data of this kind in order to add to a sparse literature [1, 2]. This is relevant not only for trials sponsored by research-based companies but for any clinical investigation of new therapies in asthma (and other chronic diseases).

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