Fourthly, the tragic situations under debate are, fortunately, rare. Yet they cause tremendous turmoil and moral agony. The neonatologist who told me 'we want to be sure that we did the right thing' expressed a need for moral confirmation of a medical decision. Debriefing of entire teams after the event may be helpful. However, reinforcement of the decision before its implementation could prevent the need for such debriefing.

Campbell is right when he says that 'to apply modern treatments indiscriminately . . . would be irresponsible' (page 571). Yet, since discernment displayed in current decisions has come more than once under heavy fire, the reasonable thing seems to be to mobilise those moral forces before deciding, rather than facing them after the facts.

Reference

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Effects of oral theophylline and oral salbutamol in the treatment of asthma

Sir,

The negative interaction between salbutamol and theophylline shown in the study by Dawson and Fergusson¹ does not accord with my clinical experience^{2,3} and can be explained by either of the following: (1) The use of an unsuitable oral formulation for the salbutamol-theophylline combination diminished the bio-availability of theophylline, consequently producing lower serum levels and thus less improvement in peak flow. (2) The response to a bronchodilator is dependent on the baseline peak flow value, the poorest response being obtained in both the most mild and most severe forms of asthma. The best way to gauge this response is to measure the percentage improvement over the baseline value. In their study Dawson and Fergusson neither measured baseline values nor did they record the percentage improvement. Although assignment was random the severity of the asthma (mean baseline values) between the two groups could have been significantly different.

For the sake of the record it should be pointed out that the maximum recommended dose of salbutamol is 0.15 and not 0.1 mg/kg.⁴

References

- ¹ Dawson K P, Fergusson D M. Effects of oral theophylline and oral salbutamol in the treatment of asthma. *Arch Dis Child* 1982; **57**: 674-6.
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- ³ Blumenthal I. A comparative trial of slow-release aminophylline, salbutamol, and a half dose combination in the prevention of childhood asthma. *J Int Med Res* 1980; **8**: 400-3.

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Dr Dawson and Dr Fergusson comment:

We regret that the results of our randomised double blind trial do not accord with Blumenthal's experience and, of course, we would welcome a replication of our results. In reply to his specific comments: (1) Whether or not the oral formulations of theophylline and salbutamol used were unsuitable and diminished the bio-availability of theophylline is a matter for further investigation. However, in our trial we used standard oral preparations of Ventolin syrup and Nuelin syrup which are commonly used in the treatment of asthma, and we have little doubt that many patients on combination therapy receive these specific preparations. Our results are thus likely to reflect the effects of typical prescribing patterns. (2) Since the major aim of our trial was to examine the hypothesis of Wilson *et al.*¹ that when used in combination salbutamol and theophylline produced increased serum theophylline levels, measures of peak flow were collected only incidentally during the course of the trial. Therefore, we cannot comment on whether similar effects would be shown with a percentage improvement statistic. However, Blumenthal's comments appear to have missed the major point of our analysis which was not to demonstrate differences in single measures but rather differences in joint, multivariate, distribution of serum levels, peak flow rates, and pulse rates between treatment groups. The compelling aspect of the study is the way in which all three indices behave in similar ways between the two treatments rather than the results for single measures.

Dr Blumenthal's comments 'Although assignment was random . . . the two groups could have been significantly different' betray a misunderstanding of the logical basis of the test of significance applied to a randomised experiment. Statements such as ' $P < 0.05$ ' simply imply that the probability of the observed results is less than 5% under the null hypothesis that there were no differences between the treatment groups. Implicit in this logic is the necessary risk (that is $< 5\%$) that the results could have been due to the way subjects were assigned to treatments. This risk is taken once the null hypothesis is rejected and is part and parcel of the decision theory associated with the significance test. We would add, however, that with respect to pre-trial serum theophylline levels there were no significant differences between the groups. The mean pre-trial level for the theophylline group was 8.46 $\mu\text{mol/l}$, compared with the mean of 7.4 $\mu\text{mol/l}$ for the salbutamol/theophylline groups.

We thank Dr Blumenthal for correcting our impressions of the maximum recommended dosages for salbutamol, although in recent trials it has been customary to use a 0.1 mg/kg dosage.²

References

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