Extrapolmonary effects of fenoterol and salbutamol in normal subjects

Newham et al have attempted the difficult task of trying to dissect relative \( \beta_2 \) and \( \beta_1 \) mediated cardiovascular responses to large doses of salbutamol and fenoterol in normal subjects with a low dose of atenolol (June 1993;48:656–8). There are two issues: firstly, the comparative responses to similar doses of these agents by inhalation and, secondly, their selectivity at the \( \beta_1 \) receptor.

Newham et al showed that salbutamol and fenoterol in doses of 1 mg and 3 mg from metered dose inhalers led to similar increases in heart rate, stroke distance, and tremor, with fenoterol causing a slightly greater fall in serum potassium concentration and a greater rise in systolic blood pressure than salbutamol. Their findings suggest smaller differences between higher doses of salbutamol and fenoterol in extrapolmonary effects than other studies, whether the comparisons have been made in vitro, in vivo, or in different species. Invariably fenoterol has been found to be more potent in large doses than salbutamol. After intravenous preparations have had a 2–4 times greater effect on heart rate with fenoterol, and this has led to a tenfold difference in the concentration of intravenous solutions used routinely (500 mg/ml salbutamol compared with 50 mg/ml fenoterol). The reasons for the different findings of Newham et al are unclear.

The attempts by the authors to dissect relative \( \beta_2 \) and \( \beta_1 \) effects have failed as they have shown that atenolol significantly attenuates the \( \beta_1 \) mediated effect on heart rate, tremor, and serum potassium concentration. Other designs based on studies by Wellstein et al 5 or Hall et al 6 may enable such relative \( \beta_1 \) receptor specificity to be shown.

AUTHORS' REPLY In reply to the letter of Crane et al 7 there are some fundamental issues which, we believe, were not discussed in the paper, require further clarification.

The purpose of our study was not to assess the relative potency of fenoterol and salbutamol, which requires careful extrapolation to asthmatic subjects to ascertain relative bronchodilator and systemic \( \beta_1 \) receptor activity. The 25 mg dose of atenolol in our study was chosen on the basis of it producing relatively selective \( \beta_1 \) blockade. It is, however, well documented that atenolol displays dose related \( \beta_2 \) blockade, 1,2 and so it is not, perhaps, surprising that even a 25 mg dose produced a degree of \( \beta_2 \) antagonism. The important point is that a comparable degree of attenuation occurred with heart rate and potassium responses, both of which have been shown to be \( \beta_1 \) mediated. Indeed, this occurred to the same extent with both fenoterol and salbutamol.

If fenoterol had stimulated cardiac \( \beta_1 \) receptors to a greater degree than salbutamol, one would have predicted atenolol to have antagonised the chronotropic response to fenoterol more than salbutamol. This was clearly not the case, and the percentage attenuation by atenolol at the 4 mg dose being 14% for fenoterol and 16% for salbutamol. The percentage attenuation of the systolic blood pressure was also comparable for both to fenoterol (5%) and salbutamol (8%). Thus, whilst fenoterol may exhibit greater \( \beta_2 \) potency, there is no evidence for it being less selective in terms of relative cardiac \( \beta_1 \)/\( \beta_2 \) receptor stimulation. It is also worth pointing out that in a study from Windom et al 8 in asthmatic subjects there was no difference in either chronotropic or systolic blood pressure responses to fenoterol and salbutamol, in contrast with isoprenaline which produced greater effects, presumably \( \beta_1 \) adrenoceptor mediated.

Our in vivo data are indeed supported by in vitro data in human right atria, 9 showing that the relative \( pA_2 \) values for practolol (\( \beta_1 \) antagonist) and ICI 18 551 (\( \beta_2 \) antagonist) were 5.47 and 8.24 respectively, for antagonism of the inotropic response to fenoterol. Taken together we believe that the body of evidence supports the hypothesis that the effects of fenoterol on the human heart are predominantly stimulated by cardiac \( \beta_1 \) receptors.

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