
Conference report

β Agonists in asthma—state of the art: report on a Royal Society of Medicine seminar

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The last few years have seen the development of longer acting β_2 agonist drugs, new information on the structure and function of the β receptors derived from the use of molecular biology techniques, and more recently controversy regarding the safety of β_2 agonists in the treatment of asthma. It was therefore timely for β_2 agonists to be reviewed in a seminar organised by the recently formed respiratory section of the Royal Society of Medicine on 16 February 1992.

The seminar opened with a review of the molecular pharmacology of β receptors by Professor P J Barnes. Four β receptors have been identified as G-proteins (β_1 is neuronal, β_2 is hormonal, β_3 is metabolic and β_4 is possibly found in brown fat). The first three have been cloned. In the lung β receptors are widely distributed, with fewer β_2 receptors in the airway smooth muscle and more at or beyond the terminal bronchioles. Airway smooth muscle contains large amounts of β receptor mRNA, but less β receptor, which suggests a rapid turnover of the receptor, making desensitisation of the receptor less likely. The reverse is true in the alveolar walls, where a lower concentration of β receptor mRNA suggests that β receptor turnover is low and down regulation is possible. Regulation of mRNA may be at the transcriptional or post-transcriptional level and down regulation occurs through a reduction of mRNA stability. Corticosteroids increase receptor density and reduce down regulation. Professor Barnes suggested that any reduced effect seen with regular β_2 agonists could be due to receptor modulation and uncoupling in the presence of inflammatory mediators.

The interaction between β_2 agonists and the mast cell was reviewed by Dr C Page. He suggested that inhibition of mast cell mediator release after allergen challenge did not necessarily confer benefit. Heparin and heparin like compounds might produce important effects by inhibiting neutrophil chemotaxis and T cell activation. They were also free radical scavengers and able to neutralise cationic proteins. Dr Page proposed that heparin had protective effects and that salbutamol and other β_2 agonists, by inhibiting their release from mast cells, might be counterproductive. The inhibitory effect of β_2 agonists on mast cell mediator release was, however, lost after four weeks of treatment and heparin might be proinflammatory.

The seminar went on to discuss the non-bronchodilatory actions of β agonists. Dr M Johnson focused on the newer agents salmeterol and formoterol. Salmeterol is more lipophilic and its longer duration of action is probably due to binding on a lipophilic site within the β_2 receptor. Animal data suggest inhibition of acute inflammation with salmeterol but the only human data showed a reduction in chemiluminescence of alveolar macrophages after four weeks of salmeterol treatment. Dr P Howarth then reviewed two studies with salmeterol, looking at the effect on inflammation. In the first there was inhibition of the early and late response to inhaled allergen, and a small reduction in bronchial responsiveness by comparison with placebo. In the second study in chronic asthma the salmeterol group, but not the placebo group, had an improvement in symptoms and peak flow. There was, however, no evidence of an effect on chronic inflammation as judged by airway cell profile, markers of lymphocyte activation, and mediator levels in bronchoalveolar lavage fluid or by numbers of eosinophils and mast cells in bronchial biopsy specimens.

The effect of β_2 agonists on bronchial responsiveness was reviewed by Professor A Tattersfield. Some studies have shown a small increase in bronchial responsiveness, but others no change with regular β_2 agonist treatment. Dr J Morley suggested that the increase in bronchial responsiveness seen in a guinea pig model was unrelated to occupancy of β_2 receptors. Bronchodilatation with β_2 agonists was offset by an increase in responsiveness, shortening the time of bronchodilatation and possibly resulting in rebound spasm.

The seminar continued with a consideration of recent studies suggesting a deleterious effect of β_2 agonist treatment in asthma. Dr M Sears proposed that regular use of β_2 agonists in chronic asthma made patients worse. The Wellington study of regular versus "as required" fenoterol used a ranking scheme of symptoms and peak flow to assess individual patients and found that those having regular treatment had reduced clinical control and slightly worse lung function. In the discussion that followed, however, Dr Sears stated that the difference in peak flow with "as required" use of fenoterol was only 2.5%.

Dr W Spitzer discussed the findings of the Saskatchewan case-control study of β agonists, a nested matched case-control study.¹ The

population of Saskatchewan (1.1 million) has a computerised health data base. Cases and controls were selected from 12 301 subjects prescribed antiasthmatic drugs on at least 10 occasions during 1977–87. The primary hypothesis was that there was a relation between the use of β_2 agonists and death or near death from asthma, and a secondary hypothesis was that there was a relation between the use of fenoterol or salbutamol and the risk of death or near death. Concurrent drugs were used as an indicator of comorbidity. The controls and cases were not ideally matched as asthma was less severe in the controls. The use of fenoterol or salbutamol was associated with an increased risk of death or near death from asthma, the risk rising with the number of canisters used per month, and this risk was greater for fenoterol than for salbutamol. Inhaled corticosteroids appeared to be protective but the numbers studied were small. Dr Spitzer's conclusion was that there existed a gradient of risk of asthma death or near death with both salbutamol and fenoterol, present at recommended doses, but that it was not possible to say whether use of β_2 agonists was a marker of disease severity or a cause of death.

Dr R Beasley questioned the relation between β_2 agonists and asthma morbidity and mortality. The first epidemic of asthma deaths in New Zealand in the 1960s was attributed to the use of isoprenaline forte aerosols. During the second, in the 1980s, there was a continued rise in sales of β_2 agonists as mortality began to fall, and the rise in fenoterol sales paralleled the rise in mortality and began to plateau as the

mortality fell. In New Zealand mortality fell sharply in the second half of the 1980s and fell again when fenoterol was withdrawn. In the New Zealand case-control studies, where hospital patients matched for severity of asthma were used as controls, the relative risk of death for patients with severe asthma using fenoterol was increased, but there was no increase with salbutamol. One possible explanation was that, dose for dose, fenoterol had greater effects on the heart than salbutamol, and that these effects were exacerbated by hypoxia.

Dr R Fuller took the opposite view that both short acting and long acting β_2 agonists reduced the number of exacerbations over time. In patients with severe asthma there was a sustained improvement in FEV₁ (250 ml) over one year with salmeterol, no decline in function with salbutamol, no increase in bronchial responsiveness after stopping the salmeterol, and no evidence of tachyphylaxis. There was no evidence to support the view that long acting agents should not be used and good evidence for their benefit.

No conclusion was reached on the possible deleterious effects of β_2 agonists in asthma. At the end of the meeting most delegates considered that the use of β_2 agonists was more a marker of undertreated asthma than a cause of death in itself but that further research was warranted.

1 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, *et al.* The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326:501–6.