Thorax

Editorials

Salbutamol enantiomers: early clinical evidence in humans

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Salbutamol, like all β_2 agonists used in the treatment of asthma and, indeed, many other drugs and endogenous biologically active compounds, exists in two isomeric forms. These stereoisomers or enantiomers relate to the presence of four different substituents of a particular carbon atom (the stereocentre) within the molecule. This carbon is asymmetrical, resulting in two possible conformations which are "mirror images". If the mirror images are not superimposable then the molecule is chiral (from the Greek *cheir* meaning "handedness"). It will have "right handed" and "left handed" forms. Stereoisomers are distinguished by their ability to rotate the plane of polarisation of light either to the right (+) or the left (-). The dextro (D) and laevo (L) systems have more recently become known as the R-(rectus) and S-(sinister). This refers to the conformation (clockwise or anticlockwise priority of the substituents around the chiral centre) of the molecule and allows the unambiguous description of the absolute molecular configuration of a compound. If a molecule has two chiral centres – for example, ephedrine – then the R-/S- configuration must be defined at each centre. The biologically active β_2 agonist (eutomer) is designated R-(-)-salbutamol while the distomer is S-(+)-salbutamol. All currently available β_2 agonist preparations are racemic mixtures (equal combinations of the two isomers).

However, the production of single stereoisomeric formulations is now a target for new drug development. US, Canadian, and European regulatory authorities require information on individual isomers of new racemic drugs and pressure is growing for chirally pure forms. Until recently the chemistry was complex, time consuming, and expensive. New companies developing single isomeric forms of existing drugs and others producing chiral intermediates for larger pharmaceutical companies to develop further are flourishing.

The simplistic idea of an active eutomer and an inactive distomer is outdated. Stereoisomers can have different properties (the different enantiomers of carvone are responsible for the taste of caraway or dill and spearmint), and the "inactive" enantiomer can have a multitude of effects ranging from antagonism of the "active" enantiomer to toxicity to a different beneficial effect. In addition, enantioselectivity may be important for disposition and metabolism of the drug. The eutomer of the diuretic indacrinone causes retention of uric acid while the distomer is uricosuric. Manipulation of the eutomer:distomer ratio enhances the uricosuric properties.¹ Trimetoquinol is a β_2 agonist where the S-isomer is a bronchodilator while the R-isomer inhibits platelet aggregation. The β_1 selective

agonist prenalterol, which is licensed for use in heart failure, is a single isomer.²

A number of existing drugs are under late phase development as single isomers. These include ketoprofen (where it is hoped that one isomer will be a safer non-steroidal anti-inflammatory and the other has potential in preventing periodontal disease), doxazosin (for benign prostatic hypertrophy), fluoxetine (one isomer is antidepressant and the other is effective in preventing migraine), and laevobupivacaine (as a safer, less cardiotoxic, local anaesthetic).

In this issue of *Thorax* we see the first two full papers reporting the bronchial and extrapulmonary effects of the two enantiomers of salbutamol with some apparently conflicting conclusions. Cockcroft and Swystun³ examined the bronchodilator and bronchoprotective effects of single large inhaled doses of racemic, R-salbutamol, and S-salbutamol in a well designed, double blind, placebo controlled, crossover study in 12 mild asthmatic subjects. R-salbutamol in a dose of 1.25 mg produced equivalent improvement in forced expiratory volume in one second (FEV₁) and protection against methacholine challenge (3.5 fold at 20 minutes and 1.7 fold at two hours) to twice the dose of the usual racemate. Tachycardia and restlessness were related to the R-isomer alone. However, in addition, a marginal but statistically significant positive effect of S-salbutamol on PC₂₀ methacholine was seen at 20 minutes (a 5% increase in FEV₁ was not significant). This may be due to contamination of the S-salbutamol with small amounts of the R-isomer or a weak intrinsic effect of S-salbutamol (a ratio of R-salbutamol to S-salbutamol of 70–300 to 1 in vitro⁴ has been reported). The authors also report a small but non-significant reduction in FEV₁ at three hours, and the implication of this is that S-salbutamol may be responsible for some of the anomalous adverse effects of racemic salbutamol.⁵ A short report by Perrin-Fayolle⁶ suggested that R-salbutamol in a dose of 100 μ g was more effective than 200 μ g of the racemate in reducing methacholine responsiveness while S-salbutamol 100 μ g increased the methacholine response at three hours compared with placebo. However, the shortcomings of the parallel group design and the analysis have been pointed out.³

By contrast, Lipworth *et al*⁷ report that the effects on finger tremor, heart rate, and plasma potassium are completely explained by effects of the R-enantiomer in a study of doubling doses of nebulised R-, S-, and RS-salbutamol in 12 normal volunteers. The effects of S-salbutamol did not differ from placebo. Higher plasma levels of S-salbutamol than of R-salbutamol were found, confirming

previous reports,^{8,9} but there may be some conflict with other authors who report no interaction between the isomers during metabolism.¹⁰ As the authors point out, it will be important to determine whether significant accumulation of S-salbutamol occurs in the lung, but this seems unlikely.⁹

The particular interest in S-salbutamol, which was previously considered to be inert, results from work by Morley's group. In a number of studies¹¹⁻¹³ in sensitised guinea pigs they have shown that S-isoprenaline, S-terbutaline and S-salbutamol, as well as the racemates, induce airway hyperresponsiveness to a variety of stimuli including histamine, cholinergic agonists, PAF, bombesin, prostaglandin F_{2α}, and peptidoleukotrienes, as well as antigen. These effects are independent of β₂ receptors, which is confirmed by the fact that they are unaffected by β blockade with propranolol, not associated with β₂ receptor down-regulation, not duplicated by forskolin (which directly stimulates cyclic AMP), but involve the parasympathetic system (being inhibited by vagal nerve section). However, high doses of the compounds are involved, they are usually administered systemically, and not all the work in guinea pigs is in agreement.¹⁴ Direct in vitro stimulatory effects of S-salbutamol on guinea pig bronchial smooth muscle and human basophil histamine release have been reported.¹⁵ A parallel for these non-β receptor mediated effects of S-isoprenaline and S-salbutamol exists in their ability to reduce intraocular pressure.¹⁶ It is suggested that these findings in guinea pigs may translate to an effect of RS-salbutamol to increase bronchial hyperresponsiveness in asthma. So far the direct evidence for an adverse effect of S-salbutamol in asthma^{3,6,17} is thin. The hypothesis that adverse effects of "inactive" S-enantiomers of β₂ agonists contribute to the increased asthma mortality and morbidity which has been associated with regular β₂ agonist therapy is of interest.⁵ However, the evidence that S-salbutamol is

safer than RS-salbutamol is far from conclusive. What is clear is that more work on S-salbutamol is required.

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- 1 Tobert JA. Enhancement of uricosuric properties of indacrinone by manipulation of the enantiomer ratio. *Clin Pharmacol Ther* 1981;29:344-50.
- 2 Morgan DJ. Clinical pharmacokinetics of β-agonists. *Clin Pharmacokinet* 1990;18:270-94.
- 3 Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. *Thorax* 1997;52:845-8.
- 4 Brittain RT, Farmer JB, Marshall RJ. Some observations on the β-adrenoceptor agonist properties of the isomers of salbutamol. *Br J Pharmacol* 1973;48:144-7.
- 5 Morley J. Anomalous effects of albuterol and other sympathomimetics in the guinea pig. *Clin Rev Allergy Immunol* 1996;14:65-89.
- 6 Perrin-Fayoll M. Salbutamol in the treatment of asthma. *Lancet* 1995;345:1101.
- 7 Lipworth BJ, Clark DJ, Koch P, Arbeeny C. Pharmacokinetics and extra-pulmonary β₂ adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997;52:849-52.
- 8 Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996;41:35-40.
- 9 Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. *Clin Rev Allergy Immunol* 1996;14:115-38.
- 10 Walle T, Walle UK, Thornberg KR, Schey KL. Stereoselective sulfation of albuterol in man. Biosynthesis of the sulfate conjugate by HE. *Drug Metab Dispos Biol Fate Chem* 1993;21:76-80.
- 11 Sanjar S, Morley J. Airway hyperreactivity. *Lancet* 1988;ii:160-1.
- 12 Sanjar S, Kristersson A, Mazzoni L, Morley J, Schaeublin E. Increased airway reactivity in the guinea pig follows exposure to intravenous isoprenaline. *J Physiol* 1990;425:43-54.
- 13 Mazzoni L, Naef R, Chapman ID, Morley J. Hyperresponsiveness of the airways following exposure of guinea-pigs to racemic mixtures and distomers of β-selective sympathomimetics. *Pulm Pharmacol* 1994;7:367-76.
- 14 Akers IA, Coleman RA, Johnson M, Nials AT, Vardey CJ. The effect of repeated inhalation of (+)-albuterol on airway reactivity in the guinea-pig. *Am J Respir Crit Care Med* 1995;151(Suppl 2):A274.
- 15 Andersson RGG, Johansson F, Aberg G. Effects on bronchial reactivity and histamine release of the isomers of albuterol. *Am J Respir Crit Care Med* 1995;151(Suppl 2):A273.
- 16 Potter DE, Nicholson HT, Rowland JM. Ocular hypotensive response to β-adrenoceptor agonists. *Curr Eye Res* 1982;2:711-19.
- 17 Blum P, Morley J, Gunawardena KA, Aberg G. Exposure to S-albuterol changes responsiveness of human airways to methacholine. *Am J Respir Crit Care Med* 1995;151(Suppl 2):A273.