Salbutamol enantiomers: early clinical evidence in humans

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Salbutamol, like all β₂ 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 at 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 β₂ agonist (eutomer) is designated R-(−)-salbutamol while the distomer is S-(+)salbutamol. All currently available β₂ 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The simplistic idea of an active eutomer and an inactive distomer is outdated.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 β₂ agonist where the S-isomer is a bronchodilator while the R-isomer inhibits platelet aggregation. The β₁ 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 anti-depressant 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 vitro³ 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.⁴ A short report by Perrin-Fayolle⁵ suggested that R-salbutamol in a dose of 100 μg was more effective than 200 μg of the racemate in reducing methacholine responsiveness while S-salbutamol 100 μg 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.⁶

By contrast, Lipworth et al⁷ 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, but there may be some conflict with other authors who report no interaction between the isomers during metabolism. 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.

The particular interest in S-salbutamol, which was previously considered to be inert, results from work by Morley’s group. In a number of studies 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 F2α 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. Direct in vitro stimulatory effects of S-salbutamol on guinea pig bronchial smooth muscle and human basophil histamine release have been reported. A parallel for these non-β receptor mediated effects of S-isoprenaline and S-salbutamol exists in their ability to reduce intraocular pressure. 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 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. 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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