

β_2 -Agonist enantiomers: is there a glitch with the chiral switch?

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Current guidelines for the treatment of chronic asthma emphasize the use of anti-inflammatory medication and indicate that short-acting β_2 -agonists should only be taken on an as-needed basis [1]. This approach has been adopted because of the inflammatory nature of asthma and because, somewhat controversially, regular use of short-acting β_2 -agonists at best confers no distinct benefit on overall asthma control [2], and at worst may cause a deterioration [3].

A number of possible mechanisms have been proposed to explain the adverse effects of chronic short-acting β_2 -agonist therapy [4], but the debate continues. One possible explanation currently under consideration is related to the fact that β_2 -agonists are chiral and are administered as racemic mixtures of a pharmacologically active eutomer (e.g. *R*-salbutamol) and an inactive distomer (e.g. *S*-salbutamol). The possibility that the distomers are selectively responsible for the toxic effects occurring during chronic treatment with racemates (e.g. *R,S*-salbutamol or *R,S*-fenoterol) has been extensively discussed [5, 6], although no firm conclusions have been reached. In animal studies, the administration of racemates and distomers has been shown to enhance bronchial hyperresponsiveness [7, 8], but this has not yet been demonstrated in human subjects during chronic dosing.

The paper by SCHMEKEL *et al.* [9] in this issue of the Journal contributes to the debate by providing further data related to the pharmacokinetics of salbutamol enantiomers. The results confirm earlier findings [10–12] that an oral dose of *R,S*-salbutamol is subject to extensive stereoselective first pass metabolism which leads to a high *S*:*R* ratio in the plasma, and to exposure to the more slowly cleared distomer in the absence of the eutomer. In addition, it is shown that salbutamol administered by inhalation is also subject to stereoselective metabolism, and that multiple dosing by inhalation at clinically relevant time intervals leads to an increase in the *S*:*R* ratio as steady state is approached. Since there is some evidence that *S*-salbutamol acts as a functional antagonist to the active enantiomer [12], the potential for exposure to high levels of *S*-salbutamol provides an attractive alternative to tolerance to explain the reduction in bronchodilator efficacy during chronic dosing with racemic drug.

The fact that salbutamol delivered by inhalation undergoes similar enantioselective first pass metabolism to that given orally is not surprising since inhalation of dry powder inevitably involves considerable oral ingestion. It also seems likely that lung metabolism of inhaled salbutamol may be stereoselective, as suggested by *in vitro* studies [13] and by the results reported by SCHMEKEL *et al.* [9]. Endotracheal aerosol administration resulted in higher plasma concentration of *S*-salbutamol but, in the absence of a comparative intravenous study in the same group of patients, it is difficult to quantify pre-systemic metabolism by the lung. In fact, the slow rate of absorption after endotracheal aerosol administration is surprising and leads to the speculation that extrapulmonary metabolism is largely responsible for the stereoselectivity observed. This would explain the results of another recent study [14] which showed that relative exposure to *R*-salbutamol after inhaled racemic drug, with charcoal given orally to prevent gastrointestinal absorption, is similar to that following an intravenous dose. However, irrespective of whether pre-systemic enantioselective lung metabolism occurs, drugs administered by inhalation are absorbed systemically and, during chronic dosing, the lungs will be exposed to the toxicological effects of high levels of *S*-salbutamol.

The debate has now widened to include the possible benefits of formulations containing the therapeutically active *R*-enantiomers only, the so-called "chiral switch". Clearly this is predicated upon the availability of pure eutomers and their configurational stability. In the case of salbutamol, acid catalysed (non-enzymatic) racemization of enantiomers is chemically predictable and readily demonstrable in the laboratory. There is also evidence that oral delivery of *R*-salbutamol leads to acid catalysed racemization in the stomach, leading to exposure to *S*-salbutamol, albeit at low concentrations [12]. No evidence of this has been found after nebulized drug administration [15], despite the fact that a large proportion of nebulized drug is swallowed. Nevertheless, if *R*-salbutamol is to replace the racemic drug, its configurational stability needs to be established.

The deleterious effects of short-acting β_2 -agonists on asthma control include impairment of protection against nonspecific bronchoconstrictors and allergens, increased bronchial hyperresponsiveness, and rebound bronchoconstriction with a fall in baseline airway calibre [16]. The possibility that these effects are due to the distomers of β_2 -agonists has been addressed in a recent clinical study by NELSON *et al.* [17]. In a placebo-controlled parallel group study, these investigators compared equivalent doses of *R*- and *R,S*-salbutamol given regularly by nebulizer over a

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four week period, and found evidence of a detrimental effect on the forced expiratory volume in one second (FEV₁) with the racemate, which they attributed to the presence of the distomer. The validity of their findings and their clinical relevance has been debated [18]. More germane to the current question is the suggestion that the reason for any toxic effects attributable to β_2 -agonists is the longer half-life of the distomers, allowing them to exert negative effects in the absence of the mitigating actions of the bronchodilating eutomers [8, 17]. Unfortunately, this argument is weakened by the fact that salbutamol is unique among the β_2 -agonists in undergoing more rapid enantioselective first pass metabolism of the eutomer. Other β_2 -agonists such as terbutaline and fenoterol undergo faster clearance of their distomers so that exposure to the distomers in the absence of the eutomers does not occur [19, 20].

All of the above considerations remain clinically relevant despite changes in prescribing patterns for short-acting β_2 -agonists since many patients, particularly those with severe asthma, continue to use these drugs frequently for relief of uncontrolled symptoms. Further investigations comparing eutomers and racemates of short-acting β_2 -agonists are required not only to resolve the role of the distomers in causing adverse effects, but also to establish whether administering single active enantiomers is justified. The answers will only be provided by long-term studies over a period of at least 24 weeks in which the most important end-point will be the frequency of exacerbations rather than surrogate measurements such as forced expiratory volume in one second and bronchial hyperresponsiveness.

References

1. The British Thoracic Society. The British guidelines on asthma management 1995 review position statement. *Thorax* 1997; 52 (Suppl. 1): S1–S21.
2. Taylor DR, Town GI, Herbison GP, *et al.* Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol. *Thorax* 1998; 53: 744–752.
3. Sears MR, Taylor DR, Print CG, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; 336: 1391–1396.
4. Taylor DR, Sears MR, Cockcroft DW. The beta-agonist controversy. *Med Clin North Am* 1996; 80: 719–748.
5. Morley J. Sympathomimetic enantiomers *in vivo*: pre-clinical pharmacology. In: Costello JF, ed. *Sympathomimetic Enantiomers in the Treatment of Asthma*. London, The Parthenon Publishing Group, 1997; pp. 71–90.
6. Handley DA, McCullough JR, Crowther SD, Morley J. Sympathomimetic enantiomers and asthma. *Chirality* 1998; 10: 262–272.
7. Galland BC, Blackman JG. Enhancement of airway reactivity to histamine by isoprenaline and related β -adrenoceptor agonists in the guinea pig. *Br J Pharmacol* 1993; 108: 1016–1023.
8. Mazzoni L, Naef R, Chapman ID, Morley J. Hyperresponsiveness of the airways following exposure of guinea-pigs to racemic mixtures and distomers of β_2 -selective sympathomimetics. *Pulm Pharmacol* 1994; 7: 367–376.
9. Schmekel B, Rydberg T, Norlander B, Sjosward KN, Ahlner J, Andersson RGG. Stereoselective pharmacokinetics of S-salbutamol after administration of the racemate in healthy volunteers. *Eur Respir J* 1999; 13: 1230–1235.
10. Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. *Clin Rev Allergy Immunol* 1996; 14: 115–138.
11. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; 41: 35–40.
12. Boulton DW, Fawcett JP. Pharmacokinetics and pharmacodynamics of single oral doses of albuterol and its enantiomers in humans. *Clin Pharmacol Ther* 1997; 62: 138–144.
13. Eaton EA, Walle UK, Wilson HM, Aberg G, Walle T. Stereoselective sulphate conjugation of salbutamol by human lung and bronchial epithelial cells. *Br J Clin Pharmacol* 1996; 41: 201–206.
14. Ward JK, Milleri N, Mackie AE, Ventresca GP. No evidence of enantioselective lung metabolism following inhaled salbutamol in man. European Respiratory Society Annual Congress Geneva, 1998. *Eur Respir J* 1998; 12: Suppl. 28, 324s.
15. Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, Jusko WJ. Pharmacokinetics and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998; 38: 1096–1106.
16. Sears MR, Taylor DR. The beta 2-agonist controversy. Observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994; 11: 259–283.
17. Nelson HS, Bensch G, Pleskow WW, *et al.* Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998; 102: 943–952.
18. Jenne JW. The debate on S-enantiomers of β_2 -agonists: tempest in a teapot or gathering storm? (Editorial). *J Allergy Clin Immunol* 1998; 102: 893–895.
19. Nyberg L. Pharmacokinetics of beta₂-adrenoceptor-stimulating drugs. In: Pauwels R, O'Byrne PM, eds. *Beta₂-Agonists in Asthma Treatment*. New York, Marcel Dekker Inc., 1997; pp. 87–130.
20. Borgström L, Chang-Xiao L, Walhagen A. Pharmacokinetics of the enantiomers of terbutaline after repeated oral dosing with racemic terbutaline. *Chirality* 1989; 1: 174–177.