

Summary:

Oral dosing of salbutamol is known to lead to beneficial performance effects in athletes and is banned, however, it is allowed to be delivered by inhalation with some restrictions for use in athletes with asthma. The drug is usually used as the racemic mixture consisting of active R- and inactive S-enantiomers (non-superimposable mirror image molecules) which have a different time course in the blood and urine. These differences are further amplified by whether the drug is taken orally or by inhalation. To date, anti-doping strategies have not capitalised on this difference in how enantiomers are eliminated from the body. Furthermore, studies have not adequately investigated the effects of repeated dosing of both inhaled and oral salbutamol over several days on urine levels in a doping control context. We will apply our advanced analytical technique that can measure both R- and S-salbutamol in urine, to samples from patients treated with either oral or inhaled therapy over the course of a week. The project will validate the benefits, namely increased sensitivity and reduced risk of false positives and false negatives, of measuring R- and S-salbutamol enantiomers. This will allow to better discriminate between oral and inhaled salbutamol.

Background: Salbutamol is a chiral drug, consisting of non-superimposable mirror image molecules called enantiomers (R- and S- salbutamol). Salbutamol is usually administered as a 1:1 racemic mixture of these enantiomers. The body metabolises and eliminates R- and S- salbutamol differently over time (called enantioselective pharmacokinetics).

Objectives: The primary objective of this project was to improve discrimination between prohibited oral and permitted inhaled dosing by using ratios of salbutamol enantiomers in spot urine samples collected over one week of treatment duration with high doses.

Results: As predicted, the S:R ratio was greater in oral versus inhaled dosing but the difference was not a reliable overall determinant of route of salbutamol administration, with significant intra- and interpatient variability. Enantiomer ratios offered modest improvement over the current urine threshold in diagnostic capability. During the trial, several subjects exceeded the current urine threshold of 1000 ng/ml after administering salbutamol via inhalation in a permitted manner, both in one week of treatment (800 microgram daily), as well as after an acute dosing regimen within 24 hours (2x 800 micrograms 12 hours apart). Some individuals appeared to have a higher likelihood of exceeding the threshold and more work is required to understand these determinants. A secondary finding of the study was that use of urine specific gravity (USG) normalisation to 1.020 for all samples to account for hydration improved diagnostic performance (mainly sensitivity), compared to both correction for concentrated samples only (as per TD2018DL) and uncorrected concentration.

Conclusions: Salbutamol S:R ratio is different between oral and inhaled delivery, but the ratio only provided a modest increase in diagnostic performance over existing approaches. The 1000 ng/ml urine threshold is an imperfect classifier of prohibited dosing with potential for some individuals to exceed the threshold using permitted inhalation high and repetitive dosing. USG normalisation for all samples improves the performance of the salbutamol urine threshold