"Pharmacokinetics of inhaled salmeterol alone or in combination with fluticasone and investigation of the role of CYP3A4 and P-gp polymorphisms"

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Project Overview

Aims:
The main aim of the present study was to contribute to the development of a urinary threshold level to allow anti-doping organisations to differentiate between the permitted therapeutic use of salmeterol and its misuse in sport.

Methodology:
Twenty-four male, healthy Caucasians who exercise three or more times a week were recruited in the study. Each participant was administered by inhalation 100 μg of salmeterol xinafoate (Phase A) and a week later 100 μg of salmeterol xinafoate combined with 500 μg fluticasone proprionate (Phase B). Blood samples were collected from each participant at baseline, 30 minutes, 1, 2, 3, 4, 8 and 12 hours after administration of salmeterol. Urine samples were collected at baseline, 2, 4, 8, 12, 24, 36, 48, and 72 hours after administration of salmeterol and participants were also instructed to collect any urine to be produced throughout this 72-hour period of the study.

Results and Conclusions:

Results:
As part of the study, liquid chromatography – mass spectrometry (LC-MS) methods for the determination of salmeterol, its metabolite α-hydroxysalmeterol and fluticasone in human urine and plasma were developed and validated. In urine, the Limit of Detection (LOD) was 0.05 ng/mL for salmeterol and fluticasone, and 0.50 ng/ml for α-hydroxysalmeterol, while the Limit of Quantification (LOQ) was 0.10 ng/mL for salmeterol and fluticasone and 1.00 ng/mL for α-hydroxysalmeterol.

At Phase A, the highest observed individual urine concentration of salmeterol when not normalised for specific gravity was 0.56 ng/mL. When all urine concentrations were normalised, the highest concentration observed was 0.61 ng/mL and when only those samples with a specific gravity higher than 1.020 g/mL were normalised the highest concentration observed was 0.53 ng/mL. At Phase B, the highest observed individual urine concentration of salmeterol was 0.91 ng/mL when not normalised for specific gravity, 1.06 ng/mL when all urine concentrations were normalised for specific gravity and 0.79 ng/mL when only those samples with a specific gravity higher than 1.020 g/mL were normalised. No statistically significant differences were found between the concentration of salmeterol at Phase A and Phase B. The

reported urinary concentrations of salmeterol represent the free parent compound, only.

At Phase A, the highest observed individual urine concentration of α-hydroxysalmeterol when not normalised for specific gravity was 5.55 ng/mL. When all urine concentrations were normalised, the highest concentration of α-hydroxysalmeterol observed was 6.94 ng/mL and when only those samples with a specific gravity higher than 1.020 g/mL were normalised to a urine specific gravity of 1.020 g/mL, the highest concentration of α-hydroxysalmeterol observed was 5.55 ng/mL. At phase B, the highest observed individual urine concentration of α-hydroxysalmeterol when not normalised for specific gravity was 3.42 ng/mL. When all urine concentrations were normalised, the highest concentration of α-hydroxysalmeterol observed was 11.4 ng/mL and when only those samples with a specific gravity higher than 1.020 g/mL were normalised the highest observed individual urine concentration of α-hydroxysalmeterol was 3.42 ng/mL. No statistically significant differences were found between the concentration of α-hydroxysalmeterol at Phase A and Phase B.

Conclusions:
We propose establishing a threshold for salmeterol and α-hydroxysalmeterol high enough to prevent any adverse analytical findings from the administration of salmeterol up to the maximum therapeutic dose yet able to detect those athletes who use salmeterol in excess doses. Based on the findings of the present study, the data that are available in the literature from other excretion studies and the analysis of routine doping control samples and a possible accumulation rate of 1.3, a urinary threshold concentration of 2.0 ng/mL for salmeterol can be supported.