PROJECT REVIEW

"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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In accordance with the 2012 Prohibited List all 2-agonists are prohibited in sport, in- and out of-competition, except salbutamol, formoterol and salmeterol when administered by inhalation in accordance with the manufacturers' recommended therapeutic regime. Whereas for salbutamol and formoterol thresholds differentiating the therapeutic use from misuse are indicated in the List, such threshold for salmeterol has not yet been established and existing data seem inconclusive.

Cytochrome P450 3A4 (CYP3A4) is an enzyme that plays a central role in the metabolism of a wide variety of drugs. P-glycoprotein 1 (P-gp), a protein encoded by the ABCB1 gene, is responsible for the regulation of the distribution of drugs. The activity of CYP3A4 and the expression of P-gp may be responsible for the inter-individual variability of pharmacokinetics (PK) of drugs using these substrates for their metabolic pathway and distribution, respectively. This can be explained due to the genetic polymorphisms of both CYP3A4 and P-gp among individuals and/or drug-drug interactions in the case of co-administration of drugs using CYP3A4. Salmeterol and fluticasone are using the same enzyme isoform CYP3A4 and corticosteroids appear to induce the activity of this enzyme.

This study aims to establish the PK profiles of inhaled salmeterol administered alone or in combination with fluticasone proprionate to healthy volunteers and type the genetic variations of the genes encoding for CYP3A4 enzyme and P-gp transporter protein in the participants of the study. This will allow determining the threshold level of the maximum therapeutic dose of inhaled salmeterol administered alone or in combination with fluticasone and to investigate the role of inhaled corticosteroids as potential masking agents when co-administered with salmeterol. Finally, the study will provide preliminary data on the possible association between genetic polymorphisms of the CYP3A4 and the ABCB1 genes with the PK and excretion profiles of inhaled salmeterol in healthy volunteers.