"The influence of exercise and dehydration on the pharmacokinetic and pharmacodynamic profile of beta2-agonists in various human populations"

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Project aims:

No studies have examined the influence of factors such as exercise and dehydration on the pharmacokinetic profile of asthmatic drugs (beta2-agonists). Exercise may modify the metabolism and excretion of drugs, and sweat loss during exercise can result in dehydration, both affecting the urine concentration of the drug. Furthermore, most current pharmacokinetic studies of beta2-agonists have been performed in non-athlete European subjects, and are therefore not representative for neither athletes nor for the most of the human population not being Europeans.

During the recent years WADA have changed the restriction towards beta2-agonists with the introduction of urinary thresholds instead of "therapeutic use exceptions" for the commonly used asthmatic drugs salbutamol, salmeterol and formoterol. A large number of studies have investigated the pharmacokinetic profile of these substances, providing support for the urinary threshold of 1000 ng/mL for salbutamol and of 30 ng/mL for formoterol. However, the background evidence for supporting these thresholds is to some degree still inadequate. Humans from various ethnical backgrounds respond different to drugs.

The genetic variations and impact of exercise and fluid intake are of crucial relevance when it comes to determination of urinary thresholds on the prohibited list. Today, little are known of the pharmacokinetic and pharmacodynamic profile of asthmatic drugs in response to exercise or of genetic variations. It is not unreasonable to assume that therapeutic use of asthmatic medication could result in urine concentrations above the urinary threshold limit of salbutamol, and hence a false positive doping test. If this is the case, the current threshold on the prohibited list may be too low and should be changed.

The purpose of this study is to examine the pharmacokinetic and pharmacodynamic profile of inhaled beta2-agonists in athletes' blood and urine during exercise and dehydration, as well as the variations between ethnical groups.

Results and Conclusions:

The purpose of the research proposal was to investigate the influence of exercise and dehydration on the pharmacokinetics of therapeutic inhaled salbutamol and terbutaline in healthy well-trained men.

In study I, we investigated pharmacokinetics of salbutamol after inhalation of the maximal WADA-permitted dose (8×200 µg) during three conditions: exercise (EX), exercise+dehydration (EXD) and rest (R). Exercise consisted of 75 min cycling at 60% of VO2max and a 20-km time-trial. Fluid intake was 2300, 270, and 1100 mL during EX, EXD, and R, respectively. The 2016 WADA decision limit (1200 ng/mL) for salbutamol was exceeded in 23, 31, and 10% of the urine samples during EX, EXD and R, respectively, when unadjusted for USG. When adjusted for USG, the corresponding percentages fell to 21, 15, and 8%. During EXD, mean urine concentrations of salbutamol exceeded (1325±599 ng/mL) the decision limit 4 h after administration when unadjusted for USG. Our data from study I demonstrated a high risk of AAFs in urine samples of salbutamol the first 6 hours after inhalation during EXD and EX with 28 and 20% samples being above the threshold limit for salbutamol, respectively. Adjustment of samples to a USG of 1.02 g/mL reduced the amount of false positive AFFs. Nine of 13 subjects had urine samples that exceeded the decision limit, hence being false positive. In conclusion, exercise and dehydration affect urine concentrations of salbutamol and increase the risk of Adverse Analytical Findings in samples collected after inhalation of that maximal permitted (1600 µg) for salbutamol. This should be taken into account when evaluating doping cases of salbutamol.

In study II, we investigated pharmacokinetics of terbutaline after inhalation of 8×500 µg as a single dose during three conditions: Exercise in hot ambient conditions (30-35°C)(EXH), exercise in normal ambient conditions (20-25°C)(EX), and rest (20-25°C)(R). Exercise consisted of 130 min at various intensities. When unadjusted for USG, urine concentrations of terbutaline after 4 h were different in the order EXH>EX>R ($P \leq 0.01$). When unadjusted for USG, urine concentrations of terbutaline were 299±151 ng/mL higher ($P \leq 0.001$) after 4 h compared to adjusted concentrations in EXH. In conclusion, exercise in hot ambient conditions results in higher urine concentrations of terbutaline. This should be taken into account when evaluating doping cases of terbutaline.

Our observations from study I & II clearly indicate that dehydration due to insufficient fluid intake or exercise in hot ambient conditions increases urine concentrations of beta2-agonists in urine samples that are unadjusted for USG. While adjustment of urine samples for USG also has some limitations, the present findings suggest that it may be relevant to consider USG of beta2-agonist urine samples in doping control.