## PROJECT REVIEW

### Beta2 adrenoreceptor agonist and elite athletes: Pharmacokinetics, Physiological and Pharmacogenetic Studies

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Asthma is the most common respiratory disorder among adolescents and young adults and the majority (70%) of ATUE certificates in Denmark concerns beta2-agonist.

Asthmatic athletes who request permission to use inhaled beta2-agonist (salbutamol, terbutaline, salmeterol, and formoterol) will be given permission, whereas systemically taken beta2-agonist will never be allowed. Therefore high urine level of beta2-agonist will be considered as doping.

Some cross-sectional studies of blood and urine levels of inhaled beta2-agonists exist, but follow-up studies are needed, taking blood and urine samples concurrently over several hours. Such studies will show the relationship between intakes and out-put of beta2-agonist.

Furthermore, asthmatics using beta2-agonist daily might be better in breakdown beta2-agonist, and therefore have different level in their urine compared with their blood. Moreover elite athletes have not participated in those studies and lastly systemic intake of the drug has not been tested.

Finally, the existence of salbutamol glucuronide in human urine has not been proven or reported in the scientific literature yet. Consequently, an accurate and rapid confirmation procedure will be developed based on direct injection of the urine specimens into the analytical instrument and subsequent determination of concentrations of unconjugated (i.e., free) salbutamol, salbutamol glucuronide and salbutamol sulfate. This is of significant importance for the future doping analysis of beta-agonists

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## Results and Conclusions

**Background and aim:** An increased use of asthma medication is seen among elite athletes due to a high prevalence of asthma, which could result in a permitted therapeutic use or doping. The two aims were A) to compare concentrations of two short $beta_2$-agonists (SABA) after inhalation and systemic intake, and furthermore two long-acting $beta_2$-agonists (LABA) after inhalation only. B) to compare the distribution of conjugated versus non-conjugated salbutamol.

**Material:** All subjects visited the Respiratory Research Unit three times. At the different pharmaceutical studies, different asthmatics and non-asthmatic subjects participated, although an overlap exists. At the first visit, all subjects were diagnosed as asthmatic or non-asthmatic, as well as elite athletes versus non-elite. In total, 10 normal, 10 asthmatics and in the salbutamol study 8 elite athletes with asthma participated.

**Methods:** Blood samples (10 mL) were collected at baseline, 30 min, 1, 2, 3, 4, and 6 h and urine was collected at baseline, 0-4, 4-8, and 8-12 hrs after administration of beta2-agonist. A 30 mL aliquot was stored until analysis. The 12 hr urine sample was collected at home.

**Results:** No differences were demonstrated between normal, asthmatics and elite athletes with asthma in urine or serum levels of beta2-agonist. Urine concentrations peaked in the collecting period 0–4 h after administration of inhaled medication as well as oral salbutamol in all groups. The mean (SD) urine concentration of salbutamol was 356 (162), terbutaline 553 (299), formoterol 7.7 (4.7) and salmeterol 0.37 (0.14) after inhalation and after systemic administration salbutamol values of 2724 (1810) and of terbutaline values of 549 (424) was found. The maximum concentration after inhalation of salbutamol was 742, terbutaline was 1370, formoterol 18.30 and salmeterol 0.62. (ng $mL^{-1}$). Two samples of salbutamol exceeded the threshold value of 1000 ng x $mL^{-1}$ (1082 and 1057 ng x $mL^{-1}$) uncorrected for urine specific gravity, but when corrected values of 746 and 661 ng x $mL^{-1}$, respectively was found. While salbutamol glucuronide was not detected in excretion urine samples after inhalation, 26 out of 82 specimens collected after oral ingestion showed salbutamol glucuronide with a peak value of 63 ng/mL. The

percentage of salbutamol glucuronide compared to unconjugated salbutamol was less than 3 %.

**In conclusion:** Mean values have been established for four $beta_2$-agonists. Uncorrected urine values are higher than values correction for gravity. The excretion of salbutamol glucuronide in urine after administration of salbutamol has been proven and is reported for the first time.