Project Review

“The Pharmacokinetics of repetitive doses of inhaled Salbutamol, Terbutaline and Formoterol and cardiorespiratory side effects of high doses of beta-agonists”

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Asthma has been found with a particularly high prevalence in elite athletes. According to the World Anti-Doping Agency (WADA) the use of beta–agonists in elite athletes with asthma is limited to inhalation of terbutaline, salbutamol, formoterol, or salmeterol, some of which require a Therapeutic Use Exemption (TUE). Despite the granting of any form of TUE, a urinary concentration of salbutamol (free plus glucuronide) greater than 1000 ng.mL-1 in a doping test is considered as adverse analytical finding. Salbutamol is the most extensively examined beta-agonist in doping research, whereas the knowledge of inhaled terbutaline and formoterol is very limited. Lastly all the present studies available when examining elite athletes assume that the uptake and decomposition is following a linear distribution, as none of the study to date are examined in situation similar to daily life situation. Especially during competition repetitive doses with salbutamol, terbutaline and formoterol are used throughout a day or several days. The dose taken in the morning might not contribute substantial whereas those taken later might result in accumulation of the drug.

Lastly, some athletes have been taking around 40 inhalation during one day, which is supratherapeutic intake. To date there is very little knowledge on effects and especially cardio-pulmonale side effects of high doses (8 mg) inhaled salbutamol. Existing studies have focused on therapeutic doses (0.2 – 0.8 mg). High doses of 8 mg, probably might be health damaging, and furthermore it exceed the maximum allowed doses of 4 puffs per day.

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Results and Conclusion

Part I and II:

Asthma and respiratory symptoms have been found with a particularly high prevalence in elite athletes. The high prevalence of asthma in elite athletes has resulted in frequent use of anti-asthmatic medications such as ß$_2$–agonists.

Drug	Single dose (s) (µg)	Max mean level after single inh administration	Repetitive administration Every 2nd (R) hour (µg)	Max mean level after repetitive inh administration
Procaterol	40*	4.4 ng/mL		
Salbutamol	800	340 ng/mL	4x400	599 ng/ml
Terbutaline	2000	688 ng/mL	4x1000	692 ng/ml
Formoterol	18	7.4 ng/mL	4x18	16.35 ng/ml

*nebulised

Repetitive doses, revealed a maximum value of urine concentration, during the day of < 600 ng/mL (corrected for the urine specific gravity (USG)) for salbutamol. This indicates that taking the doses during the day which is more true to the way asthma patients are taking their medication, did it most cases result in urine concentrations below the current threshold of 1000 ng/ml for salbutamol. Repetitive inhalation of 36 microg formoterol every 2nd hour resulted in urine concentrations well below the current threshold for formoterol of 45 ng/ml. When corrected for the USG, the inter-individual variability of the urine concentrations decreased.

Part 3:

Different surveys have examined performance-enhancing effects of inhaled and oral salbutamol. We examined this issue after administration of very high doses of inhaled salbutamol, 40 puffs (8 mg), and measured any effect on oxygen uptake and oxygen uptake kinetics. We observed no effects of salbutamol on any aerobic parameter and no differences in time to exhaustion during incremental exercise. The study was a double-blinded and placebo-controlled cross-over study.