

“The Influence of Gender and Race on the Ergogenic and Pharmacokinetic Impact of Inhaled and Oral Terbutaline”

G. Whyte, J. Dickinson, N. Chester, J. Burniston (Liverpool John Moores University, UK)

PROJECT REVIEW

In 2002 The International Olympic Committee – Medical Committee (IOC-MC) established the requirement for athletes using asthma medication (short acting 2-agonists) to present evidence of current asthma, exercise induced asthma (EIA), exercise-induced bronchoconstriction (EIB) or airway hyperresponsiveness (AHR) through the therapeutic use exemptions (TUE) process. The World Anti-Doping Agency (WADA) introduced the IOC-MC policy on inhaled short acting 2- agonists in January, 2009. In January, 2010 WADA withdrew the requirement for an objective airway challenge for inhaled Salbutamol and Salmeterol. In contrast, other commonly used short acting 2-agonists including Terbutaline remained on the restricted list.

The inclusion of inhaled 2-agonists on the WADA list is based upon health concerns rather than anti-doping concerns with limited evidence available to support an ergogenic effect. To date, the vast majority of available data has been undertaken with inhaled Salbutamol in Caucasian, male athletes with limited knowledge of the ergogenic effect or pharmacokinetics of other short-acting 2-agonists (i.e. Terbutaline), across gender or ethnicity.

Accordingly, the proposed study aims to quantify Terbutaline limits in the urine after oral and inhaled routes of administration (Study 1) and investigate the ergogenic effect of inhaled Terbutaline on 5 km running performance (Study 2). Both studies will include male and female participants from Caucasian, Asian and Afro-Caribbean communities.

The proposed studies will assist in the implementation of regulations on the use of inhaled Terbutaline and assist in the resolution of contested doping violations. Ultimately the project will provide more clarity for the use of inhaled Terbutaline by athletes with various forms of asthma and will result in improved quality of care for the athlete.

RESULTS and CONCLUSIONS

THE IMPACT OF INHALED TERBUTALINE ON 3km RUNNING TIME-TRIAL PERFORMANCE

Whyte, G., Molphy, J., Chester, N. J., Dickinson, J. W., Loosemore, M.

Elite athletes have a higher prevalence of Exercise-induced bronchoconstriction (EIB) than the general population. Treatment for EIB and asthma includes inhalation of short-acting β 2-agonists which act to reverse the bronchoconstriction of the airways. The majority of athletes treat symptoms of EIB through the use of salbutamol however, other β 2-agonists, such as terbutaline, are available which are longer acting and have fewer side-effects. In contrast to salbutamol, salmeterol and formoterol, therapeutic doses of the inhaled short-acting β 2-agonist, terbutaline still requires a TUE. Limited research exists examining the ergogenic effect of terbutaline. Accordingly, aim of the present study was to examine the effects of 2 mg and 4 mg inhaled terbutaline on exercise performance during a 3km running time-trial.

Participants (8 males; age: 24.3 ± 2.4 years; weight: 77.6 ± 8 kg; height: 179.5 ± 4.3 cm, and 8 females; age: 22.4 ± 3 years; weight: 58.6 ± 6 kg; height: 163 ± 9.2 cm) completed three 3km time-trial in a randomised, single blind, repeated measures design with a minimum of 7 days between trials. Prior to the test participants were assigned to one of three groups:

- (1) 8 inhalations of non-active inhalant (placebo);
- (2) 4 inhalations of non-active inhalant plus 4 inhalations of terbutaline (2mg); or
- (3) 8 inhalations of terbutaline (4mg).

In addition to performance variables, urine concentrations of terbutaline were measured following each trial. There was no significant difference in completion time between trials in either males or females following 2 mg or 4 mg of inhaled terbutaline.

There was no difference in urine concentration following either 2 mg inhalation or 4 mg inhalation in males or females. There was a high individual variation in urine concentration of terbutaline with a maximum value of 1250 ng/ml-1 following the inhalation of 4 mg of terbutaline. In conclusion, terbutaline, when taken in therapeutic doses (2 mg or 4 mg), does not improve 3 km running time-trial performance in males or females.

URINARY CONCENTRATIONS OF SINGLE AND MULTIPLE ADMINISTRATION OF INHALED AND ORAL TERBUTALINE: INFLUENCE OF GENDER AND RACE

Whyte, G., Molphy, J., Chester, N. J., Dickinson, J. W., Loosemore, M.

Elite athletes have a higher prevalence of Exercise-induced bronchoconstriction (EIB) than the general population. Treatment for EIB and asthma includes inhalation of short-acting β_2 -agonists which act to reverse the bronchoconstriction of the airways. In contrast to salbutamol, salmeterol and formoterol, therapeutic doses of the inhaled short-acting β_2 -agonist, terbutaline still requires a TUE. Accordingly, the purpose of the present study was to measure the urine concentrations of terbutaline following single and repeated doses of oral and inhaled terbutaline in Caucasian males, Caucasian females, Afro-Caribbean males and Asian males to allow for comparisons between gender and race.

Twenty-two male and eight female subjects (8 male Caucasian, 8 female Caucasian, 6 male afro-Caribbean, 6 male Asian) provided written informed consent and were recruited for the study. All participants were free from asthma, EIB and AHR confirmed by no history of disease and a negative eucapnic voluntary hyperpnoea (EVH) challenge. Participants were assigned to one of four groups in a cross-over design:

1. Single Oral Administration (SOA): single dose of 5 mg oral terbutaline (Bricanyl, AstraZeneca, UK),
2. Single Inhaled Administration (SIA): 4 inhalations of 0.5 mg terbutaline (Bricanyl Turbohaler, AstraZeneca, UK) totalling 2mg inhaled;
3. Repeated Inhaled Administration (RIA): repeated doses of 1 mg (2 x 0.5 mg inhalations) of terbutaline at 08:00h, 12:00h, 16:00h and 20:00h for 2 days;
4. Repeated Oral Administration (ROA): repeated doses of 5 mg oral terbutaline at 10:00h and 18:00h for 2 days.

Following the final dose of terbutaline during each trial, participants were required to provide urine samples at 1h, 3h, 6h and 12h time-points. Urine samples were frozen at -80°C for later analysis of terbutaline.

The present study demonstrates that both inhaled and oral terbutaline administration results in the presence of terbutaline in urine. Of note, significant differences in urine concentration of terbutaline following inhaled and oral administration were observed. The study identified upper thresholds following oral and inhaled administration which could be used to identify the use of supra-therapeutic doses of terbutaline. The highest urine concentration of terbutaline following inhalation was $1,500 \text{ ng}\cdot\text{ml}^{-1}$ and for oral administration was $2,000 \text{ ng}\cdot\text{ml}^{-1}$. Gender differences existed between male and female Caucasians following multiple oral administration however; further research including both female Asians and female Afro-Caribbean's is required to fully elucidate any gender differences. Ethnic differences were identified between male Caucasians and male Asians following single inhaled administration. Future research should also examine urine concentrations following a minimum therapeutic dose of inhaled terbutaline versus

oral terbutaline and also establish differences in enantiomers in the urine associated with mode of administration.