

## **“Impact of intense exercise on pharmacokinetics and pharmacodynamics of budesonide and methylprednisolone in relation to doping analysis”**

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### **PROJECT OVERVIEW**

Glucocorticoids are widely used among athletes in treatment of acute inflammation and in chronic inflammatory diseases such as asthma. However, glucocorticoids may be misused to increase recovery and performance during competition, and several former Tour de France cyclists have admitted use of glucocorticoids as performance-enhancing agents during races. The current prohibited list allows glucocorticoids to be applied as a skin cream or inhaled from an inhalator, whereas injections and intake of pills are prohibited. In order to distinguish between prohibited misuse and therapeutic use, and to establish urinary thresholds, it is necessary to investigate differences in urine concentrations between the different administration forms. The aim of the current study is thus to investigate differences in the urine concentration of the two most common glucocorticoids following different routes of administration during exercise.

### **Results and Conclusions:**

While the pharmacokinetics of methylprednisolone is well established in untrained individuals at rest, no studies have, to our best knowledge, investigated the pharmacokinetics of methylprednisolone during simulated competitive exercise applicable to real life sport settings in highly trained individuals. In a randomized open-label crossover study, we investigated urine pharmacokinetics of methylprednisolone after oral, intramuscular (vastus lateralis and erector spinae muscles), and intravenous administration (16 mg for each route) in conjunction with exercise in 16 endurance-trained men [aged  $25 \pm 4$  years with a  $VO_{2max}$  of  $63 \pm 4$  (mean  $\pm$  SD)]. After administration of methylprednisolone, subjects performed 3 hours of cycling exercise at 55-60%  $VO_{2max}$ . Urine samples were collected prior and 0-24 hours following administration and were analysed for concentrations of unchanged methylprednisolone using HPLC-MS/MS. Urine excretion rate of unchanged methylprednisolone followed an exponential decline for the intravenous and intramuscular injection routes, peaking within the first 1½ hours and reaching values close to zero 12–24 hours following injection. For the oral route, excretion rate peaked 1½–3 hours after ingestion, reaching values close to zero 12–24 hours following ingestion. Urine concentrations of methylprednisolone displayed substantial inter-individual variability. Following intravenous or intramuscular injection, urine concentrations peaked 1½ and 3 hours following administration and declined rapidly, displaying low concentrations 8–12 hours following injection. Urine concentrations were

lower following oral ingestion during the first 1½ hours after administration, but slightly higher than the other routes 8–24 hours after administration. These observations indicate that urine spot sampling cannot discriminate different systemic routes of methylprednisolone administration based on the concentrations of unchanged methylprednisolone.