"Evaluation of alternative glucocorticosteroid metabolites for the discrimination between legal and forbidden administration routes"

Rosa Ventura, Jordi Segura, Xavier Matabosch, Oscar Pozo, Rosa Berges Casas, Nuria Monfort (Fundació Institut Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain)

Project Overview

Glucocorticosteroids are widely used in sports medicine for the treatment of conditions such as asthma and acute injuries. The use of glucocorticosteroids by oral, intravenous, intramuscular and rectal routes is forbidden, and their use by other routes is allowed. Since some glucocorticosteroids are marketed in different administration forms, the distinction between different routes of administration through the analysis of urine samples is needed. A reporting level of 30 ng/mL for glucocorticosteroids and their metabolites has been established by WADA to detect corticosteroid misuse. Unfortunately, this reporting level is not suitable to distinguish therapeutic use from forbidden administration for all corticosteroids and the investigation of more effective criteria of discrimination is needed.

The aim of the project is to elaborate analytical strategies to be used in the effective differentiation between legal and forbidden administration routes for synthetic glucocorticosteroids. A comprehensive study of the metabolic pathways of corticosteroids will be performed using liquid chromatography coupled to tandem mass spectrometry. Both phase I (including saturated A-ring and acidic metabolites) and phase II (including conjugates with sulphate and cysteine) metabolism will be studied in several excretion studies already available in our lab for triamcinolone acetonide, betamethasone, prednisolone, methylprednisolone and budesonide.

Differences between responses of every metabolite detected in the different administration routes will be evaluated. Potential markers will be selected based on these results. Selectivity and sensitivity of these potential markers will be compared with current reporting level.

Results and Conclusions:

The objective of the project was to evaluate the current WADA criterion to detect glucocorticoid (GC) misuse. The urinary profiles of budesonide (BUD), triamcinolone acetonide (TA) and betamethasone (BET) were studied in clinical studies were they were administered by allowed and forbidden administration routes in order to look for the best discrimination markers for each GC.

For BUD, the metabolite 6β-hydroxy-BUD was confirmed to be the best the marker to detect BUD misuse. However, high 6β-hydroxy-BUD concentrations were found after high-dose inhaled treatments and, for this

reason, a reporting level of 40 ng/mL is proposed to discriminate allowed from forbidden administrations.
For TA, a reporting level of 30 ng/mL of TA did not allow the detection of intramuscular administration. A reporting level of 5 ng/mL for TA was proposed to detect intramuscular use, and to discriminate topical and intranasal from intramuscular administrations. Concentrations obtained after intraarticular and periarticular administrations, which are currently regarded as allowed administration routes, need be taken into account before proposing a definitive reporting level to discriminate allowed from forbidden administrations of TA.

For BET, a reporting level of 40 ng/mL for BET is proposed to discriminate topical and intranasal from oral and intramuscular administrations. However, concentration values after intraarticular and periarticular administrations are similar to those obtained after intramuscular administrations.

The results of the present project demonstrate the need of studying the metabolism of each GC after allowed and prohibited administration routes in order to establish the best discrimination criterion for each GC.

Publications

- Coll S, et al. Budesonide use and misuse in sports: elimination profiles of budesonide and metabolites after intranasal, high-dose inhaled and oral administrations. Drug Test Anal 2019: dta.2678. https://doi.org/10.1002/dta.2678