PROJECT OVERVIEW

"Criteria setting for the misuse of glucocorticosteroids. Study LSDD-Lausanne"

M. Saugy, L. Mateus-Avois (Laboratoire Suisse D'analyse du Dopage, Lausanne, Switzerland)

The aim of this project is to set criteria for the misuse of glucocorticosteroids including synthetic glucocorticosteroids and natural glucocorticosteroids (cortisone/hydrocortisone) and Synacthen as stimulators of the adrenal cortex.

For synthetic glucocorticosteroids, a general methodology has to be established including oral and intra-muscular administration as systemic routes and nasal and/or inhalation administration as local routes, with a high probability of systemic effect. The other local routes are to be considered as having a low probability of systemic action. According to this scheme, a two step study was built.

First, for each test substance, time-related studies will be carried out under well controlled clinical conditions (ie clinical trials) for the systemic routes (oral and IM), as well as for the local routes with a high probability of systemic recovery (nasal and/or inhalation). These results will be used to set preliminary criteria for positivity (part I).

Secondly, for some substances, time-related studies will be performed under ambulatory treatments (uncontrolled conditions) for the other local routes (dermal, intra-articular). These results will be used to confirm the preliminary criteria or to modulate them if necessary (part II).

Moreover, urine indicators of native cortisol metabolism breakdown will be monitored by GC-MS in parallel to the measure of synthetic glucocorticosteroids urinary concentration by LC-MS/MS, whatever the mode of administration (part I and part II of this study). It is expected that these additional results will offer a way to confirm the general authorization for local routes or to modulate their initial status, especially if there is any evidence of a substance-related health risk due to cortico-adrenal gland suppression.

For natural glucocorticosteroids (cortisone/hydrocortisone) the determination of endogenous glucocorticosteroid profiles by GC-MS analysis is also regarded as a key step in this study. Consequently, complementary analyses of the main cortisol metabolites by GC-C-IRMS

and of other native steroid compounds by CC-MS will be performed.

Two anti-doping laboratories (Laboratoire National de Depistage du Dopage, (LNDD), Chatenay-Malabry, France and Laboratoire Suisse D'analyse du Dopage (LSDD), Lausanne, Switzerland) collaborate in this project .

Results and Conclusions

The results obtained after investigations with various glucocorticosteroids (methylprednisolone, triaminolone, triamcinolone acetonide, prednisolone, budesonide, dexamethasone, betamethasone) show great variability depending on the modes of administration, the maximum concentrations eliminated by individuals, the ratio between free and conjugated fractions, and the duration of elimination.
However, in view of the results, it is already possible to distinguish the systemic routes (oral, intramuscular) from other local routes of administration (pulmonary, nasal) according to the urinary concentrations eliminated from the various glucocorticosteroids investigated and their persistence in the patients' urine. Nevertheless, the intra-articular and epidural routes should be re-evaluated because they cannot be differentiated from the systemic routes.

After compiling the results obtained by the laboratories in Paris, Lausanne and Sydney (WADA grant "Improved methodology for detecting and confirming the abuse of glucocorticosteroids"), it will probably be possible to refine the positivity threshold, for different glucocorticoids, making it possible to better regulate the administration of glucocorticosteroids.

On the other hand, it would be interesting to continue and deepen the investigations into intra-articular and epidural injections, and possibly other modes of administration (periarticular, peritendinous, but also ointments, eye drops and other solutions).

In view of the preliminary results, it would be possible by measuring Cortisol to distinguish the systemic route (oral and especially intramuscular) from other local routes of administration, such as pulmonary inhalation. A collapse of urinary cortisol to near zero concentrations could indicate the nature of the administration of the glucocorticosteroid.

Nevertheless, additional analyzes should still be carried out in order to confirm and generalize this observation. In particular, on a larger number of volunteers and especially on samples from intra-articular and other local applications.