PROJECT OVERVIEW

"Criteria setting for the misuse of glucocorticosteroids. Study LNDD-Paris"

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The aim of this project is to set criteria for the misuse of glucocorticosteroids including synthetic glucocorticosteroids, 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) and Synacthen, 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, respectively.

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

Endogenous glucocorticoids

As for many hormones the quantification of hydrocortisone and cortisone in urine by conventional methods (GC / MS, RIA, LC // MS) is not suitable for suspicion or confirmation of doping . To circumvent this, we conducted a population study (made up of men and women of Caucasian origin) based on the determination by GC / MS of the ratios of the concentrations of cortisol on HRT (F / HRT), and of THF on HRT (THF / HRT) in urine. HRT is the metabolite of the precursor cortisol, therefore, it cannot be affected by taking natural glucocorticoids. It is naturally present in all urine. The population study showed that the F / HRT and THF / HRT excretion ratios are sex-related. Excretion studies have confirmed that administration of hydrocortisone and or cortisone increases these ratios, with an acceptable detection window. Via two separate population studies, we established suspicion thresholds corresponding to the mean + 2 standard deviations, then positivity thresholds corresponding to an isotopic depletion of 3 ‰ on the basis of the mean + / - 3 standard deviations. These cutoffs are in agreement with studies of cortisol and cortisone excretion.

These control studies have demonstrated that the interpretation of the ratios THF/THS and F/THS ratios when taken together are generally consistent with the technique.

As our studies are limited to subpopulations of Caucasian origin, the universality of the results should be examined through studies of a multiethnic population.

A variation of the direct oxidation method used for IRMS with separation of cortisol and cortisone metabolites from deoxycortocosterone prior to oxidation improved the specificity of the isotope analysis.

Exogenous glucocorticoids:

Several excretion studies were done using different glucocorticoids and routes of administration in coordination with LSDD. For final results please see summary in "Criteria setting for the misuse of glucocorticosteroids. Study LSDD-Lausanne"