

Professor Martine Duclos

Full Professor, Hospital Practitioner, Endocrinologist,
Professor of Physiology (Université d'Auvergne), Head of Service: Service de
Médecine du Sport et d'Explorations Fonctionnelles, CHU G. Montpied, Clermont-
Ferrand

Member of the CNOSF Medical Commission

Agence Française de Lutte contre le Dopage: Member of the Commission
Prospective, Member of the Commission Pré-ciblage, Member of the AMA-AFLD list
Committee

AFSSAPS: Clarification of « Utilisation des glucocorticoïdes chez le sportif atteint de
pathologies traumatiques, allergiques, infectieuses ou cutanées: état des lieux et
conduite à tenir », validated by Commission Nationale d'Autorisation de Mise sur le
Marché of 10 April 2008 (group expertise).

Professor Yves Le Bouc

Full Professor, Hospital Practitioner, Endocrinologist, Paediatrician, Professor of
Physiology (Paris IV), Head of Service: Laboratoire d'Explorations Fonctionnelles
Endocriniennes, Hôpital Armand Trousseau, APHP

Director of Equipe 4 "IGF System" du centre de recherche St-Antoine Unité INSERM
U. 938

President of the Conseil d'Orientation Scientifique de l'Agence Française de Lutte
contre le Dopage

Corresponding Member of Académie de médecine.

Doctor Michel Guinot

Rheumatologist and Physiologist

Hospital practitioner CHU de Grenoble

Director of Antenne médicale de prévention du Dopage Rhône Alpes, Unité médicale
Sports & Pathologies, Clinique de Physiologie, sommeil, exercice Pôle Locomotion,
Rééducation Physiologie.

To:

Doctor Armand MEGRET
Fédération Française de Cyclisme
5, rue de Rome
93560 ROSNY SOUS BOIS

20 September 2013

Dear National Federal Doctor, Dear Colleague,

You requested our expertise as to the value of the plasma cortisol measurements, obtained according to the regulations, on competitors concerning the screening of the consequences of the use of glucocorticoids on the adrenal function, the possible health risks for user athletes as well as the medical decisions that may be recommended when biological adrenal insufficiency is noted.

Concerning the screening of the consequences of the use of glucocorticoids on the adrenal function:

The data in the scientific literature clearly shows that, whatever the means of administration of a glucocorticoid (general or local), there is a systemic passage that may provoke a reduction in the physiological secretion of cortisol by the adrenal glands, mainly by a hypothalamic and pituitary feedback mechanism. This effect is most likely proportional to the dose of glucocorticoid administered although there are probably individual susceptibilities accounting for cases of severe suppression of the adrenal function with low systemic passages.

Demonstration of the partial or total blocked secretion of cortisol (adrenal insufficiency) is ideally based on pharmacological stimulation testing of the hypothalamic-pituitary-adrenal axis. For practical reasons, this type of test is not available in symptom-free sportsmen during competition. This is why the simple assay of the plasma cortisol in the morning, when the concentration is physiologically highest, detects the most severe biological adrenal insufficiencies, even if it does not detect all of them.¹ In addition, the figure chosen as abnormally low is below the lower limits of the laboratory (less than 2 standard deviations under the mean).

As regards the sampling conditions, in particular the time of the sample, it should be noted that cortisol is naturally secreted according to a circadian rhythm. The plasma concentration therefore also varies according to a wake-sleep cycle. It is lower at the beginning of the night and maximum when waking up. The interpretation of the cortisol therefore has to take into account the wake-sleep cycle of the subject since the rhythm of secretion may be reversed in athletes who work at night or are time-lagged.

Ideally, the plasma cortisol should be measured when its value is highest. Therefore, the time of sampling recommended² in the regulations of your federation seems to be well adapted for athletes who usually have a "standard" sleep-wake cycle.

Concerning adrenal insufficiency related health risks:

The detection of a cortisol plasma concentration under the standards in the kit used by the laboratory reflects a biological adrenal insufficiency. In the athlete, this results from the administration of a synthetic glucocorticoid, whatever the type of administration and independently of the way it was obtained (with or without a medical prescription)³.

This biological situation corresponds to a situation where the organism is unable to provide an adapted response to major stresses (anaesthesia for surgery, severe sepsis, haemorrhagic shock, major trauma). In fact, these situations require the secretion of an increased amount of cortisol by the adrenal glands, as this hormone is necessary for the metabolic and cardiovascular adaptations for survival.

Indeed a lack or insufficient response (acute adrenal insufficiency) may be life-threatening, even when the subject is *a priori* in good health. The few studies that have colligated these cases revealed a high rate of morbidity or even mortality.

It is difficult to assess the real frequency of post-corticotherapy adrenal insufficiency, since a systematic declaration of this complication is not required in French drug monitoring centres

¹ Figures based on the data in the literature are fully described in the action to be taken in the FFC medical regulations

² 6:30 a.m. to 9:00 a.m.

³ There are other causes of adrenal insufficiency although the incidence is low, in general occurring within a context of a known disease.

and where atypical or attenuated manifestations⁴ likely increase the rate of underestimation. Nevertheless, the incidence is most likely low although glucocorticoids are very often prescribed in general medicine as well as in sports medicine.

Concerning medical decisions with respect of the athlete:

As explained above, the athlete presenting biological adrenal insufficiency risks death in case of added severe cardio-circulatory or metabolic stress, even if this possibility is rare.

Since cycling, in particular road running, is a sport involving a high traumatic risk, with the possibility of haemorrhagic fracture or fracture requiring surgery, it seems advisable for the French Cycling Federation to foresee medical solutions to reduce the risk of acute adrenal insufficiency.

For this reason, the establishment of cortisol assays before departure in competitions or during medical monitoring seems well adapted to detect subjects at risk.

The systematic declaration of recent treatments with glucocorticoids by cyclists or their entourage also seems advisable. We call to mind that when corticotherapy by general route or injection is prescribed, it corresponds to injuries that also requires resting for healing.

Finally, the decision to establish a counter-indication by the federal medical practitioner is one possibility even if other solutions may be proposed in competitions comprising medical assistance.

We hope that we've answered your questions.
Yours truly,



Professor Martine Duclos



Professor Yves Le Bouc



Doctor Michel Guinot

⁴ It is possible that malaise during stress sometimes provoking inexplicable counter-performance or abandon may be the atypical or attenuated manifestations of adrenal insufficiency.