The short-term effects of dexamethasone on the blood concentrations of acute phase proteins (haptoglobin and ceruloplasmin) and trace elements in rats

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SUMMARY

Acute phase response is the non specific reaction of the animal against infection, inflammation or trauma and corticoids may stimulate the expression of most acute phase proteins directly or indirectly. This study aimed to determine the short-term effects of dexamethasone at different dosages varying from 0.1 to 10.0 mg/kg on some acute phase proteins and minor elements in Wistar rats. The 40 male 3 month-old Wistar albino rats were randomly divided into 7 groups: in the group 1 (n = 4), rats served as controls and received physiologic saline while in the other groups (n = 6 in each group), rats were treated by intraperitoneal injection of various doses of dexamethasone: 0.1 mg/kg (group 2), 0.5 mg/kg (group 3), 1.0 mg/kg (group 4), 2.5 mg/kg (group 5), 5.0 mg/kg (group 6) and 10.0 mg/kg (group 7). Haptoglobin and ceruloplasmin concentrations tended to increase whereas albumin concentrations tended to decrease in dexamethasone-treated rats, but these changes were not confirmed statistically because of the great value dispersion except in some groups receiving low (group 2) or moderate doses of drug (groups 4 and 5). A strong positive correlation between the 2 acute phase proteins was evidenced in groups 3-5. No significant variation of zinc and iron concentrations was observed in treated groups although zinc concentrations tended to decrease and iron concentrations to increase when animals received moderate doses of dexamethasone and that zinc and albumin concentrations were positively correlated. By contrast, except for the group 6, mean plasma copper concentrations were significantly higher in treated groups than in controls. These results suggest that the dexamethasone treatment may directly affect the synthesis of positive acute phase proteins and indirectly affect the distribution of some trace elements (copper, iron and zinc) even if the short-term effects are not proportional to the administered dose and that inter-individual dexamethasone response delays would considerably varied.

Keywords: Acute phase response, haptoglobin, ceruloplasmin, dexamethasone, iron, zinc, copper, rat.

RÉSUMÉ

Effets à court-terme de la Dexaméthasone sur les concentrations sanguines des protéines de la phase aiguë de l’inflammation (haptoglobine et ceruloplasmine) et des oligoéléments chez le rat

La phase aiguë de l’inflammation est une réaction non spécifique de l’animal contre une infection, une inflammation ou un trauma et les corticoïdes peuvent stimuler directement ou indirectement l’expression de la plupart des protéines de cette phase. L’objectif de cette étude est de déterminer les effets à court terme de différentes doses de dexaméthasone allant de 0.1 à 10.0 mg/kg sur certaines protéines de la phase aiguë et sur les oligoéléments chez le rat Wistar. Quarante rats mâles Wistar albinos âgés de 3 mois ont été aléatoirement répartis en 7 groupes : les rats du groupe 1 (n = 4) ont servi de contrôles et ont reçu du sérum physiologique tandis que ceux des autres groupes (6 animaux par groupe) ont subi une injection intra péritonéale de dexaméthasone aux doses suivantes : 0.1 mg/kg (groupe 2), 0.5 mg/kg (groupe 3), 1.0 mg/kg (groupe 4), 2.5 mg/kg (groupe 5), 5.0 mg/kg (groupe 6) et 10.0 mg/kg (groupe 7). Les concentrations en haptoglobine et en ceruloplasmine ont eu tendance à augmenter chez les rats traités par la dexaméthasone alors que celles en albumine ont eu tendance à diminuer, mais ces variations n’ont pas été statistiquement confirmées en raison d’une dispersion importante des valeurs exception excepté dans certains groupes ayant reçu une dose faible (groupe 2) à modérée (groupe 4 et 5). Une forte corrélation positive entre ces 2 protéines inflammatoires a été mise en évidence dans les groupes 3, 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5. Aucune variation significative de la sidérémie ou de la zinémie n’a été obtenue chez les rats traités avec des doses de dexaméthasone comparées aux valeurs des contrôles, mais une corrélation positive entre le fer et le zinc a été mise en évidence dans les groupes 4 et 5.

Mots clés : Phase aiguë de l’inflammation, haptoglobine, ceruloplasmine, dexaméthasone, fer, zinc, cuivre, rat.

Introduction

The acute phase response is an early and complex reaction of an animal or men. It is an innate defence mechanism to a variety of challenges [5, 6, 20]. On a global view, the acute phase response is the reaction of the animal disturbance in its homeokinesis caused by bacterial, viral or parasitic infections, mechanical or thermal trauma, ischemic necrosis, neoplastic growth, immunologic disorders and other non-specific stress situations [6]. This response includes the production (up regulation) or on the contrary the suppression (down regulation) of a number of proteins called the acute phase proteins and this reaction primarily aims to limit tissue damage and to promote healing in such conditions [12]. Its main-players are
plasma proteins and include primarily the haptoglobin, ceruloplasmin, serum amyloid A and C-reactive protein [30]. The clinical outcome of an acute phase response is pyrexia and anoxemia. During the acute phase response the pathogens are being isolated and neutralized and the entry of new pathogens is inhibited by the organism. At the same time, the tissue injury will be reduced and homeokinetic mechanisms are regulated by the induction of the tissue repair [5].

Haptoglobin (Hp) is a positive acute phase protein. Haptoglobin is synthesized and secreted during acute phase response caused by conditions such as early inflammation or stress [30]. Its synthesis is regulated by glucocorticoids and cytokines [14]. Ceruloplasmin (Cp) is an α-2 glycoprotein transporting the copper, and it is needed for wound healing and protection of cells and tissues against oxidant compounds [5]. It is also one of the positive acute phase proteins, which are produced primarily in the liver [12].

Cytokines are main inducers of the acute phase response. Corticoids and catecholamines, as the major stress mediators, enhance this induction to various extend. Corticosteroids may stimulate directly the expression of the most acute phase proteins [4] within the first two days [2] and they produce short term versus long term effects (pharmacological or physiological) according to their concentrations [4]. Evidences indicate that immunosuppressive and anti-inflammatory effects of glucocorticoids are linked with the inhibition of adhesion-related processes (inhibitory effect of dexamethasone on lymphocyte adhesion molecule in vitro) [4]. However, the molecular mechanisms of this process are still unknown.

Dexamethasone is a potent synthetic analogue of hydrocortisone, the major endogenous glucocorticoid in many animal species. Different doses of this drug with various administration periods are widely used to treat many physiopathological conditions in veterinary and human medicine. Animal diseases in which dexamethasone are an effective way of treatment include under others inflammation, acetonaemia, non-specific skin diseases, shock and stress [25]. This wide range of therapeutic usage reflects the broad spectrum of pharmacological actions of the corticosteroid hormones. However, if the effects of dose, route of administration and the length of the treatment with glucocorticoids may affect the Hp and Cp concentrations is not well known.

This study aims to determine the effects of dexamethasone on some acute phase proteins (haptoglobin and ceruloplasmin) and trace elements (iron (Fe), copper (Cu) and zinc (Zn)) at different physiological and pharmacological doses in Wistar rats.

Materials and Methods

ANIMALS AND EXPERIMENTAL DESIGN

This study was approved by The Institutional Animal Ethics Committee of Adnan Menderes University, Turkey. Experiments were carried out in a semi-acclimatised room at 22°C, with 50-70% humidity and 12/12-hour light/dark cycle. A total of 40 male Wistar albino rats 3 month-old were used in this study. The mean weight of rats was 216.13 ± 17.07 g. Rats were randomly divided into seven groups. The group 1, served as control (n = 4) while other groups received dexamethasone (Devan, Topkim-Topkapi Ilaç Premix San Tic. A.S.) by an unique intraperitoneal injection at different doses: group 2 (n = 6; 0.1 mg/kg); group 3 (n = 6; 0.5 mg/kg); group 4 (n = 6; 1.0 mg/kg); group 5 (n = 6; 2.5 mg/kg); group 6 (n = 6; 5.0 mg/kg); group 7 (n = 6; 10.0 mg/kg). The control group (group 1) received an equal volume of physiologic saline by intraperitoneal way. Blood was withdrawn from the hearth 48 hours after dexamethasone injection under the ether anaesthesia into heparinized and/or plain tube, clotted at room temperature. Plasma and serum were separated by centrifugation at 1700 g for 10 min. and they were kept frozen -20°C until analysis.

BIOCHEMICAL ANALYSES

Hp concentrations were determined to spectrophotometrically as the haemoglobin binding capacity in plasma samples ad modum BATCHELOR et al. [3]. This method is based on the principle that cyanmethemoglobin is protected from acid denaturation when it is complexed to haptoglobin. Serum Cp concentrations were estimated in serum ad modum SUNDERMAN and NUMATO [24]. A coloured oxidation product is formed from ceruloplasmin and p-phenyldiamine and the rate of formation this product is proportional to the concentration of serum ceruloplasmin. The concentrations of albumin (Biomedical Systems®, Barcelona, Spain) in serum, and iron (Biomedical Systems®, Barcelona, Spain), copper and zinc (Randox®, Antrim, UK) in plasma were determined using commercial test kits according to the manufacturer’s protocol. These measurements were carried out a UV-spectrophotometer (Schimadzu, UV-1601).

STATISTICAL ANALYSIS

The data were analyzed by using analysis of variance, and Duncan test was used as post hoc. Differences were considered as significant when p values were less than 0.05. Simple correlation analysis was performed.

Results

The mean concentrations of Hp, Cp and albumin in serum, and those of Fe, Cu and Zn in plasma of animals were given in Table 1. The mean serum haptoglobin mean concentrations were increased in dexamethasone-treated groups except into the group 5 (2.5 mg/kg) but because of the great dispersion of individual values observed in treated animals, differences were not statistically significant. Moreover, the enhancement of the mean haptoglobin concentrations was not proportional to the injected dexamethasone dose. Similarly, increases of the mean serum ceruloplasmin mean concentrations were evidenced in all dexamethasone-treated groups but only differences between the control group and the group 2 (0.1 mg/kg) or the group 5 (2.5 mg/kg) were significant. Individual values presented a great dispersion. Maximal mean ceruloplasmin concentrations were recorded in groups receiving 0.5 mg/kg until 2.5 mg/kg of

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dexamethasone (groups 3, 4 and 5) and the groups 2 (0.1 mg/kg), 6 (5 mg/kg) and 7 (10.0 mg/kg) gave comparable results. On the contrary, mean serum mean albumin concentrations were lower in all assay groups compared to the control group, but the differences were not significant except for the group 4 (1.0 mg/kg) in which this parameter was the lowest. The mean plasma iron and zinc concentrations were quite comparable between the control and treated groups except that slight but not significant decreases of zinc concentrations were observed in the groups 4 and 5 (dexamethasone: 1.0 mg/kg and 2.5 mg/kg respectively) and that iron concentrations tended to increase in groups 3 (0.5 mg/kg) and 4 (1.0 mg/kg). By contrast, except for the group 6 (5.0 mg/kg), mean plasma copper concentrations were significantly increased in dexamethasone-treated group and were similar whatever the injected dose, ranged from 1.91 ± 0.47 to 2.00 ± 0.14 mg/L.

Moreover, some significant correlations were evidenced among the biochemical markers (Table 2). The Hp and Cp concentrations were positively correlated in controls and dexamethasone-treated rats (r = 0.366, p < 0.05, Y = -0.3860 + 0.0341 X). This correlation was more evident in the population of the treated rats (r = 0.398, p < 0.05, Y = -0.5058 + 0.0385 X) and particularly in the groups of rats receiving moderate doses of dexamethasone (groups 3 – 5) (r = 0.519, p < 0.05, Y = -0.8081 + 0.0465 X), but this correlation disappeared in high dose groups (groups 6 and 7) (dexamethasone: 5 and 10 mg/kg). There was also a significant positive correlation between serum Zn and albumin concentrations in controls and dexamethasone-treated rats (r = 0.364, p < 0.05, Y = 60.7825 + 62.0017 X). However, the correlation between these variables could not be confirmed statistically for dexamethasone treated groups (r = 0.321, p = 0.056). There was also a negative correlation between Cp and Fe concentrations in low dose group (group 2) (r = -0.939, p < 0.01, Y = 49.8642 - 0.2546 X). Besides, serum Cp concentrations tended to correlate (although not confirmed statistically) with albumin (r = 0.553, p = 0.078), Fe (r = 0.555, p = 0.076) or Zn concentrations (r = 0.548, p = 0.081) in high dose groups (groups 6 and 7). A tendency to correlate was also noticed for iron or zinc and albumin concentrations (r = 0.550, p = 0.080 and r = 0.519, p = 0.05 respectively) in high dose groups (Table 2).

**Discussion**

Corticoids and cytokines participate as cofactors in the regulation of the acute phase response, but their role differ between animal species and the considered APP (acute phase protein) [18]. Corticoids may directly stimulate the most APP expression. Moreover they together with cytokines, evoke strong synergistic enhancement for most APPs [4]. Studies in rats and humans beings have shown that glucocorticoids significantly stimulate the synthesis of positive APPs, but they are not capable of eliciting a full-scale hepatic acute phase response contrary to the treatment with turpentine [17]. Their stimulatory effects differ from the inflammatory pattern of hepatic proteosynthesis [19]. Glucocorticoids are essential factors for hepatocellular microenvironment and proteosynthesis during both rest and inflammatory period [19].

Hp is an iron-binding protein and its synthesis increases in infections or neoplasms also increase its production [5, 6, 7, 19]. Various non specific stressors such as pregnancy, starvation, infections or neoplasms also increase its production [5, 6, 7]. During the infections to prevent Fe loss and to decrease the iron contents potentially used by bacteria for growth [7].
In the rat haptoglobin gene, glucocorticoid and interleukin-6 responsive elements are included [14]. HIGUCHI et al. [14] showed that dexamethasone increased the haptoglobin synthesis in liver parenchyma cell culture, but had no effect on total protein and albumin concentrations. Similarly, KURASH et al. [15] reported that the acute phase protein synthesis was increased in differentiated hepatocytes cell culture (AR4J-B13) by dexamethasone. Dogs with hyperadrenocorticism or those treated with steroids exhibited higher serum Hp concentrations than healthy normal dogs [7]. In the same way, elevations of the Hp production were evidenced in cows treated with dexamethasone (0.1 mg/kg) [30]. In the present study, although differences with the control group were not significant because of the great value dispersion, serum Hp concentrations tended to increase 48 hours after dexamethasone injection in healthy rats (without any antigenic or inflammatory challenge). Similarly, SILVERA and LIMAUS [22] reported that dexamethasone induced a strong acute phase revealed by high concentrations of Hp and fibrinogen, however, these effects was abrogated when rats were co-treated with metopyren, a specific inhibitor of corticoid hormone synthesis.

Cp is a copper-dependent oxidase, involved in the regulation of iron metabolism and that participates to the inflammatory acute phase response and to antioxidant systems. Although the Cp gene was identified, the molecular mechanisms regulating its expression are not fully understood [9]. Physical stress had no effect on circulating concentrations of Cp and Cu in men, while Zn concentrations were reduced [21]. However, transport stress induced an increase of Cp concentrations in calves on day 3 [1] and intravenous administration of synthetic glucocorticoids increased plasma Cu and Zn concentrations in men [31]. By contrast, the Cp concentrations were not affected in healthy dogs receiving methylprednisolone acetate or prednisolone [18]. In the present study, although the ceruloplasmin concentrations greatly varied from 8.76 to 49.77 mg/L, in dexamethasone-treated rats, mean concentrations were increased compared to the control group and were

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<th>Hp</th>
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<tr>
<td>In low dose group (0.1 mg/kg)</td>
<td>0.366*</td>
<td>- 0.550</td>
<td>0.022</td>
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<td>In moderate dose groups (0.5 to 2.5 mg/kg)</td>
<td>0.398*</td>
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<td>In high dose groups (5 to 10 mg/kg)</td>
<td>0.512*</td>
<td>0.436</td>
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<td>In all rats</td>
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<td>In low dose group (0.1 mg/kg)</td>
<td>0.519*</td>
<td>0.013</td>
<td>0.154</td>
<td>0.162</td>
<td>0.106</td>
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<td>In moderate dose groups (0.5 to 2.5 mg/kg)</td>
<td>0.188</td>
<td>- 0.170</td>
<td>- 0.148</td>
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Table 2: Coefficients of correlations between serum concentrations of acute phase proteins (haptoglobin and ceruloplasmin), albumin and plasma concentrations of trace elements (iron, copper and zinc) in Wistar rats treated intraperitoneally by dexamethasone (0.1; 0.5; 1.0; 2.5; 5.0 and 10.0 mg/kg) or by NaCl 0.9% (control).

Hp: Haptoglobin; Cp: ceruloplasmin; Alb: albumin; Fe: iron; Cu: Copper; Zn: Zinc, *p < 0.05
significantly enhanced in the group 2 and 5 (0.1 and 2.5 mg/kg respectively). Surprisingly, they were not directly proportional to the administrated dose since maximal mean concentrations were obtained in the groups 3 (0.5 mg/kg), 4 (1.0 mg/kg) and 5 (2.5 mg/kg) and not in the group 6 (5.0 mg/kg) and 7 (10.0 mg/kg). Similarly marked and significant increases of plasma Cu concentrations were evidenced in dexamethasone treated groups (p<0.05) except for the group 6. As Cp is a Cu-binding protein, variations of Cu concentrations were probably linked to increased synthesis of this APP. Nevertheless, no positive significant correlation between Cu and Cp concentrations was obtained (r = 0.016, p > 0.05).

It was reported that plasma Zn and Fe concentrations decreased during the acute phase response in different animals, limiting the Zn/Fe dependent growth bacteria [26, 28] in this way. The down regulation of the trace metal concentrations is mediated through production and release of cytokines such as IL-1 and IL-6 [26, 28]. It was previously suggested that the administration of dexamethasone had no effect on plasma Fe and Zinc concentrations in rats [31]. Similarly, no effect of dexamethasone on serum Fe concentrations could be found by VOYVODA et al. [27] in sheep and by MADDUX et al. [16] in goats. By contrast, dexamethasone induced increases of blood Fe concentrations in horses [23] and in dogs [13], while this parameter was reduced in corticoid treated-cows [29]. During stress, serum Fe concentrations decreased [8] or were not affected by stress in men [10]. FUHR and SCHEINERT reported that corticoid therapy caused a reduction of Fe concentrations whereas stress had no effect [11]. The observed increase of Fe concentrations in horses and dogs could directly result from the inhibition of the release of lactoferrin from neutrophil membranes and indirectly to the increase of neutrophil number [23]. In cows, the mechanism by which dexamethasone induced hypoferremia remained unknown. In the studies on cows and small ruminants neutrophil counts were not evaluated in parallel. Consequently, the effects of dexamethasone on iron concentrations would vary according to the animal species. In this study, no significant effect of the parenteral injection of dexamethasone on the plasma Fe and Zn mean concentrations was evidenced in rats.

In this study, serum albumin concentrations tended to decrease in the most dexamethasone-treated groups compared with the control group. The weak reduction of albumin concentrations would be related to the relative increase of APP production. Indeed albumin concentrations were negatively correlated with haptoglobin concentrations in dexamethasone-treated rats (r = - 0.55). However, this effect remained minor since no statistically significant difference was obtained with control values except for the group 4. In humans, there has been debate on balance between nutritional and production of negative APP's [5]. The recent hypothesis is that the acute phase response has a stronger effect than the nutritional plane on concentrations of albumin and other negative APP [5]. During the acute phase reaction, synthesis of positive APP was associated with a relative decrease of albumin synthesis in liver [5, 12, 14]. But, HIGUCHI et al. [14] reported that dexamethasone had no effect on total protein and albumin concentrations in liver parenchyma cell culture.

In the present study, no relationship with dose effect was evidenced for acute phase protein and trace element concentrations probably because of the great dispersion of the biochemical marker values. Indeed, the delay of response to corticoid would extensively vary between animals and the maximal variations of the biochemical markers could be observed between 24-72 hours after dexamethasone treatment according to the animal and to the drug distribution into the organism (particular drug accumulation in liver). Consequently the time of sample collection may interfere with analysis of these parameters and would explain why variations of concentrations of albumin, Hp, Cp and trace element (Fe, Cu and Zn) were only evidenced or suspected in groups treated with moderate doses of dexamethasone (ranged from 0.5 to 2.5 mg/kg). On the other hand, higher doses of this corticoid (5 and 10 mg/kg) would probably alter more precociously (within 24 hours) the APP and trace element concentrations. A detailed evaluation according to time seems to be necessary for a more accurate analysis of inflammatory markers induced by corticoids.

References


