The effect of Dexamethasone and Prednisolone on Cortisol, Parathyroid and Calcitonin hormones concentrations in male Rabbits

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Abstract:
This study was conducted to investigate the side effects of dexamethasone and prednisolone drugs in a dose of (0.4 mg / kg) on Cortisol, Parathyroid and Calcitonin hormones in the Lepus cuniculua domestica rabbits. Thirty domestic male rabbits were obtained from the Veterinary Hospital of the Ministry of Agriculture - Samarra Agriculture Division, and in rolled in this study. Their age was 7-9 months and their weight was (1250 - 1500 g). The animals were randomly distributed in to 6 groups and each group contains 5 Rabbits. The first group (Control) was the control group where the diet was given with normal drinking water. The second group (A) was given Dexamethasone (0.4 mg / kg) with the diet and regular drinking water. The third group (B) was given prednisolone (0.4 mg / kg) with the diet and regular drinking water, the fourth group (C) given dexamethasone and prednisolone together with a concentration of (0.4 mg / kg. For each one) with the diet and regular drinking water. The fifth group (D) given the drug prednisolone (0.4 mg / kg) and vitamin C with a concentration of (30 mg / kg) with the diet and regular drinking water. The sixth group (E) given dexamethasone (0.4 mg / kg) and vitamin C with a concentration of (30 mg / kg) . The experiment lasted for 21 days for all groups. The results showed a significant decrease in cortisol concentration in all groups when compared to the control group, while it led to a significant increase in parathyroid hormone concentration in all groups except the fourth and sixth group there were a significant decrease in serum compared to the control group , result also showed a significant increase in concentration of calcitonin hormone in all groups when compared to the control group. Dexamethasone and Prednisolone had the ability to significantly low the level of cortisol hormone concentration with significant elevation in Parathyroid hormone and calcitonin hormone concentration.

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المستخلص
أجريت هذه الدراسة لمعرفة التأثيرات الجانبية لدواء الدكسيميثازول و البرينيزولون بجرعة (0.4 ملغ/كمغ) على هرمون الكورتيزول ، جنبي الادراة والكالسيتونين في ذكور الأرانب المحلية. استخدم (30) ذكرًا من الأرانب المحلية التي تم الحصول عليها من المستشفى البيطري التابع لوزارة الزراعة – شعبة زراعة سامراء وثناها في هذه الدراسة. أعمارهم كانت 7-9 أشهر و أوزانهم كانت (1250 – 1500 غم). وزعت الحيوانات عشوائيا إلى (6) مجموعات لكل مجموعة (5) أرانب. كانت المجموعة الأولى (Control) هي المجموعة السيطرة.
Introduction

The artificial glucocorticoids are similar to glucocorticoids normal in pharmacological activity but differ in the ability of the effect of sodium arrest by the doses taken [1]. The artificial glucocorticoids are chemically similar to the synthesis of natural cortisol [2]. These corticosteroids are powerful anti-inflammatory and immunosuppressant, but the side effects of these drugs are difficult to separate from other therapeutic benefits [3]. High doses of corticosteroids for a long period of time will lead to protein decomposition, skin thinning, retardation of children's mental development, increase the ductility of the capillary tubes, muscle weakness, osteoporosis, and bone resorption [4]. Steroid drugs are immunosuppressive agents such hydrocortisone, prednisolone and dexamethasone and are effective by dose and duration of treatment [5]. Dexamethasone is a synthetic glucocorticoid hormone and is similar to the synthesis of hydrocortisone [6]. This drug has a high efficacy of more than three times the effectiveness of natural cortisol, and cortisol which is from natural corticosteroids and is responsible for about 95% of the activities of the crustaceans [7]. Dexamethasone is an obvious cause of osteoporosis by inhibiting the absorption of calcium and bone formation and this leads to bone weakness and ease of fracture [8]. It affects the function and composition of the osteoblast cells [9]. Prednisolone is a synthetic glucocorticoids with a synthetic formula similar to that of the natural cortisol. The drug was first synthesized in 1955 by the microbiological oxidation of cortisol and its chemical formula (C_{21}H_{28}O_{5}) [10]. It is from a corticosteroids used extensively to treat many diseases such as asthma, allergies, cancer, and immune diseases as well [11]. The drug
Prednisolone is used mainly in the treatment of inflammations, including rheumatoid arthritis and also inflammations caused by autoimmune conditions and produces some side effects such as fluid retention in the face and auditory and visual defects [12]. The drugs prednisolone and dexamethasone are among the most steroid drugs used in clinical cases, while the latter has a higher and more activity and is effective in reducing tumor load in patients and also has more serious adverse effects than the other [13]. Calcitonin is a peptide hormone that works in response to a high level of calcium in the blood where it reduces and maintain bone mass by inhibiting osteoclasts [14]. Parathyroid hormone is produced by the parathyroid gland in response to lowering blood calcium levels, which is works on kidneys, bones and intestines to maintain calcium levels in the blood and stimulates osteoclasts to pull calcium from the bones into the blood [15]. This study aimed to know the effect of dexamethasone and prednisolone on cortisol, parathyroid and calcitonin hormones in male rabbits.

**Materials and Methods**

**Experimental Animals and Design :**

The study included 30 male *Lepus cuniculua domestica* rabbits obtained from the Veterinary Hospital of the Ministry of Agriculture - Samarra Agriculture Division, aged 7-9 months and their weights ranged 1250 - 1500 g these rabbits were randomly assigned in to 6 groups, 5 rabbits per group, Control group: That recieved standard diet with drinking water, Group A: Dexamethasone (0.4 mg / B.W) with standard diet and drinking water, Group B: recieved Prednisolone (0.4 mg /B.W) with standard diet and drinking water, Group C: recieved Dexamethasone (0.4 mg / B.W) and prednisolone (0.4 mg / B.W) with standard diet and drinking water, Group D: recieved Prednisolone (0.4 mg / B.W) with vitamin C (30 mg / B.W) with standard diet and drinking water, Group E: received Dexamethasone (0.4 mg / B.W) with vitamin C (30 mg / B.W) with standard diet and drinking water. The experimental lasted for 21 days for all groups. Doses were taken supposition according design experience.

**Drugs used in the study:**

* Dexamethasone: The drug was used in the form of pills and was manufactured by Samarra company for the manufacture of medicines and medical supplies - Samarra / Iraq, available in local pharmacies, the concentration of this drug 0.5 mg . The pills were well milled and dissolved with distilled water mediated by Gavage tube on a daily basis .
* Prednisolone : The drug was used in the form of pills and was manufactured by Samarra company for the manufacture of medicines and medical supplies - Samarra /
Iraq, available in the local pharmacies and the concentration of this drug 5 mg. The pills were well milled and dissolved with distilled water mediated by Gavage tube on a daily basis.

* Vitamin C: The vitamin was used in the form of pills 500 mg available in local pharmacies, and manufactured by company: Basic Nutrition United Arab Emirates. The pills were well milled and dissolved with distilled water and then orally injected by Gavage tube daily.

**Blood sampling:**

After 21 days of experimentation, the animals were kept for 20 hours and then anesthetized with chloroform. The blood samples were then obtained directly from the heart via cardiac puncture, and 8-10 ml of blood. Were obtained and placed in test tubes free of anticoagulants left for about a quarter of an hour at room temperature (25°C), then placed in the centrifuge at 3000 / rpm for 15 minutes and serum were collected in new clean plastic tubes and kept at (-20°C) until required hormones tests were carried out.

**Study hormones:**

* Cortisol Hormone was estimated using ELISA Kit (Sunlong) according to manufacturer instructions [16].
* Parathyroid and Calcitonin Hormones were estimated using ELISA Kits (Sunlong) according to manufacturer instructions [17].

**Statistical analysis:**

The results were statistically analyzed using the Minitab program. In order to extract the differences between the experimental groups with emphasis on these differences by extracting the standard error (Stand Error) SE Statistical analyzes were conducted according to Duncan were identified the probability level (P≤0.05).

**Results and discussion:**

**Cortisol hormone:**

The results of the present study, as shown in Figure (1), showed a significant decrease (P≤0.05) in the concentration of cortisol in groups A, B, C, D, E (63.60 ± 2.3), (56.40 ± 3.6), (47 ± 2.2), (36.40 ± 1.1), (36.60 ± 2.4) ng / ml respectively compared to control group (70.40 ± 3.5) ng / ml.
Cortisol is a hormone produced from cholesterol and excreted from the adrenal glands by the secretion of corticotrophin (CRH) from the hypothalamus, which in turn stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland and in turn produces cortisol in the adrenal gland. Steroid drugs used to inhibit inflammation. Decreased secretion of cortisol by inhibiting the hypothalamic-pituitary-adrenal gland (HPA). Drugs, such as dexamethasone and prednisolone, may reduce the levels of cortisol from the normal level according to the negative feedback mechanism and work to develop adrenal insufficiency, diabetes, high blood pressure and osteoporosis [18-19-20]. Van der Goes et al noted that the use of these steroid drugs for a long period of time and high doses leads to the reduction in secretion of corticotrophin hormone responsible for the secretion of cortisol and in turn leads to reduced levels of cortisol in the zona reticulum of the adrenal gland [21]. Steroid drugs may increase oxidation of vitamin C and steroid drugs work with vitamin C synergistically [22-23]. As the researcher Teng et al have pointed out in a new study to the role of vitamin C in maintaining levels of cortisol in the body [24]. Since vitamin C has the highest amount in the adrenal gland and its role in maintaining levels of cortisol If steroid drugs are used, which in turn reduces the level of cortisol [25-26].

Parathyroid hormone:
The results of the current study, as in Figure (2), showed a significant increase (P≤0.05) in the concentration of Parathyroid hormone for groups A, B,D (95.30 ± 2.4), (95.02 ± 1.1), (125.44 ± 3.4) pg / ml respectively compared to control group (92 ± 1.6) (pg / ml) and a significant decrease (P≤0.05) for both C, E
That steroid drugs do not have a direct effect on the level of parathyroid hormone Parathyroid regardless of the doses or duration [27]. Steroids such as dexamethasone and prednisolone have a direct effect on calcium metabolism, prevent absorption of calcium in the intestines and increase calcium secretion in the urine, leading to increase parathyroid hormone levels that inhibit osteoblasts and stimulate Osteoclast cells this leads to osteoporosis and excessive parathyroid hormone secretion [28]. This increase in the secretion of this hormone is the result of maintaining the levels of calcium in the blood and thus withdraws calcium from the bone and may lead to osteoporosis [29]. There is no effect of vitamin C on the Parathyroid hormone [30]. The role of vitamin C is synergistic with steroid drugs, increasing the uptake of the drug inside the intestine and transferring it intracellular [22]. Steroidal drugs may induce Parathyroid hormone secretion directly by reducing the amount of secretion [31].

**Calcitonin hormone :**

The results of the current study, as in Figure (3), showed a significant increase (P≤0.05) in the level of the calcitonin hormone for groups A, B, C, D, E (154.60±3.3), (161.84±5.4), (127.94±5.1), (205.76 ±3.9), (156.84±6.7) pg / ml Respectively when compared with control group (28.97 ± 0.9) pg / ml.
Fig. (3): Calcitonin hormone concentrations in the studied doses compared with control group.

Calcitonin secretion is stimulated by increased calcium levels in the serum, which in turn protects against the development of hypercalcemia and works to prevent the loss of bone mass by inhibiting the action of osteoclasts [32-33]. Therapeutic steroid drugs when used in high doses and long-term have side effects that prevent absorption of calcium in the intestine and increase the expression of receptor activator of nuclear factor-kB ligand and prevent the formation of osteoprotegerin, which leads to stimulate bone resorption and thus increase the level of calcium in the blood, which stimulates the secretion of calcitonin hormone to regulate its level in the blood and reduce the loss of bone mass and until the return of calcium to its normal level [28]. Another study suggests that there is a synergistic effect between steroids and calcitonin, which reduce the side effects caused by these drugs [34]. The role of vitamin C is synergistic with steroidal drugs and the increased secretion of the hormone calcitonin acts to increase the consumption of vitamin C to compensate for the lack of bone mass caused by steroid drugs [22].

Conclusions:

This study shows the obvious side effects on concentrations of hormones studied and that the high dose and excessive use of these drugs is a clear cause of loss of control of these hormones and generate other diseases in the body in addition to reducing levels of hormone cortisol and increase levels of thyroid hormone and
calcitonin, and thus hampering their functions within the body.

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