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(21) Biochemical and Endocrinological Studies on Experimental Iatrogenic Hypercorticism of the Dog

Norihiro KOMIYAMA, Takesi MIKI and Masatosi TAKEISHI

Department of Veterinary Obstetrics and Gynecology,
College of Agriculture and Veterinary Medicine, Nihon University

Abstract

Thirteen beagles were injected intramuscularly with a daily dose of 4 mg of dexamethasone (DXM) for 37 days. After a recess for 120 days, they were again administered with the same dose of DXM by the same route for 65 days.

Eosinophils were reduced in count to 200/mm^3 or less in the dogs 2-4 days after the first and the second series of injections with DXM. Alkaline phosphatase and serum GPT increased in level 5-14 days and 10-14 days after the beginning of the first and the second series of injections, respectively. No significant changes were found in blood urea nitrogen, blood glucose or cholesterol, A/G ratio, or Na, K, or Cl level.

After a series of injections with DXM for 10 days, the plasma cortisol level was lower in the dogs in the first and the second series of injections with this drug than in normal intact dogs. It returned to the pre-injection level in those dogs 27 days after the end of the series of DXM injections.

Introduction

Cases of iatrogenic hypercorticism previously reported are not those induced experimentally but those encountered in the clinical practice and having occurred as the result of treatment by a physician or surgeon. In the present experiment an attempt was made to induce experimental cases of iatrogenic hypercorticism in dogs by injection with a glucocorticoid. The drug used was dexamethasone (DXM), or 9-fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione. The cases of this disorder previously reported had been caused by the treatment with prednisolone in the clinical practice. Therefore, the cases mentioned in the present paper are the first ones in which this disorder has been induced with DXM, instead of prednisolone. In them, biochemical examination was carried out, as well as the adrenal function test. It is characteristic of the present experiment that two periods of long-term administration were set up with a rather long recess in between. The examination and test were performed comparatively in each period.

In 1932, Cushing[1] reported what is now known as Cushing's syndrome (CS) in human beings for the first time. He proposed the term pituitary basophilism for the disorder reported, because he presumed that the etiology of this disorder might consist in the pituitary body. In 1943, Albright[2] suggested that the disorder might be caused by the excess in production of glucocorticoid from the adrenal cortex.

Siegel et al.[3] and Owens and Drucker[4] pointed out that CS had been induced by the excess in secretion of ACTH from the pituitary body or by adrenal tumor in the same manner in dogs as in human beings. Recently, Scott and Green[5] reported cases of CS of iatrogenic origin caused by excessive or long-term consecutive administration with glucocorticoid.

In the present experiment iatrogenic hypercorticism (Cushing's syndrome) was produced artificially in dogs by long-term administration with glucocorticoid. In these dogs changes in blood components and the adrenocortical function were examined with the lapse of time. This paper deals with the results of these examinations.

Materials and Methods

The dogs used had been raised at the arthors' laboratory and regarded as clinically healthy. They were 13, or 8 male and 5 female, beagles 2-10 years old weighing 8-12 kg. They were injected

intramuscularly with 4 mg of DXM, as a glucocorticoid, daily for 37 days. After a recess for 120 days, they were again injected with the same dose of DXM by the same route daily for 65 days. Blood samples were collected from them at intervals of 2 days after the beginning of injection. The plasma level of cortisol was estimated by the RIA method.

Results

Clinical findings

In the untreated control group, no remarkable changes were observed by 3 days of experiment (hereinafter referred to as day 3).

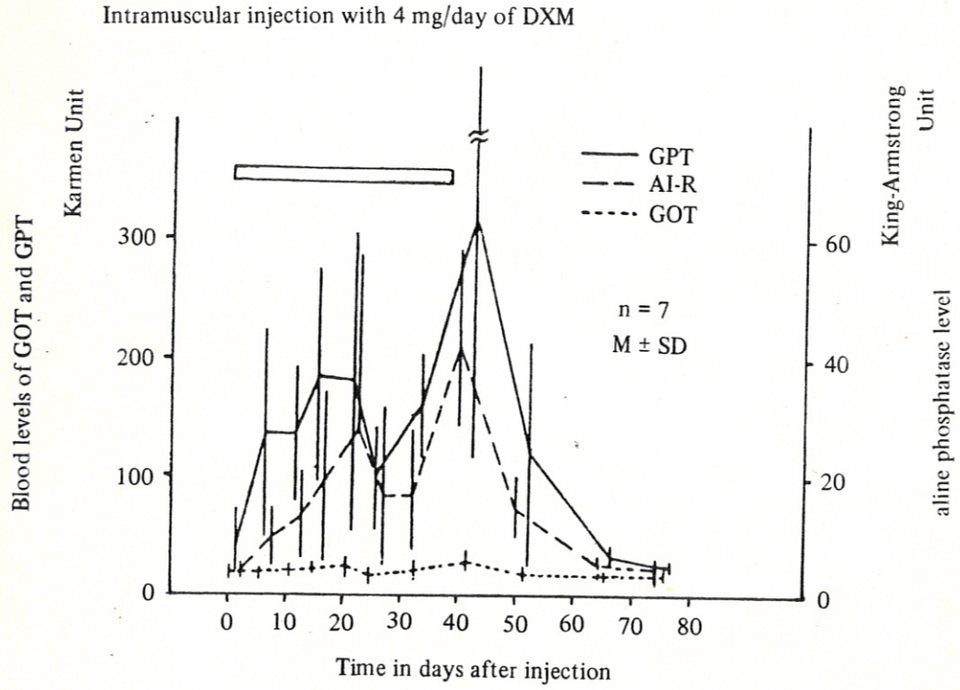
In the treated group, polydipsia, polyuria, and diarrhea occurred on day 5. In addition to these symptoms, the distension of the abdomen was seen 4 days later. Muscular weakness was shown in all the dogs.

Laboratory examination

From 2 to 4 days after each series of injection eosinophils were reduced in count to 200/mm^3 or less in both groups. The DXM was recovered 8-15 days and 10-14 days after the first and second series of injections, respectively. Alkaline phosphatase and GOT increased on days 5-14 in the first series and on days 10-14 in the second series of injections. No significant changes were found in BUN, blood glucose or cholesterol, A/G ratio, or Na, K, or Cl level.

Cortical function test

In the ACTH response test the dogs were injected with 0.125 mg of synthetic ACTH. Blood samples were collected from them an hour after injection. After a series of injections with DXM for 10 days, the plasma cortisol level was lower in both groups than in the normal control group. It returned to a normal level 27 days after the last injection with DXM. It lost its circadian rhythm



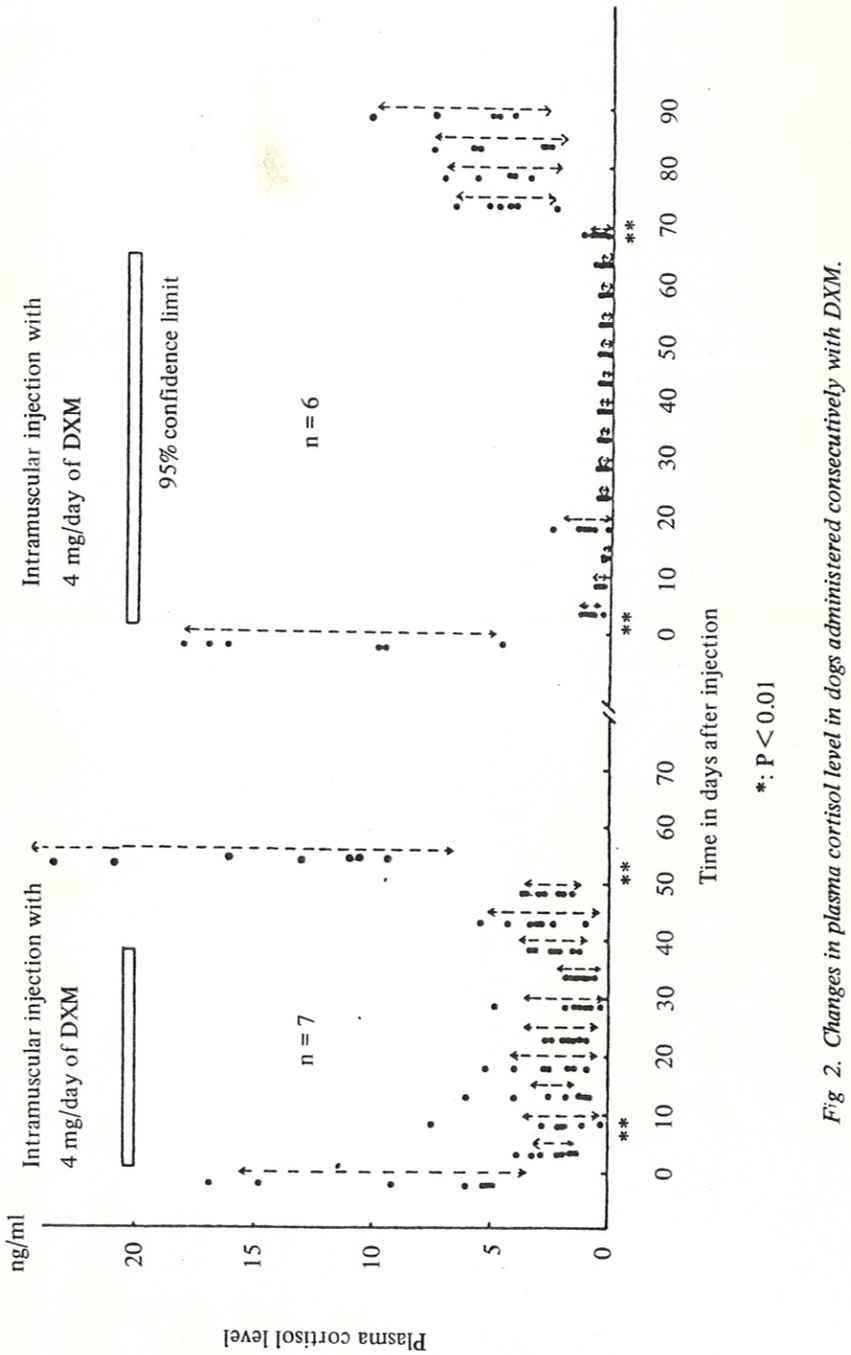


Fig 2. Changes in plasma cortisol level in dogs administered consecutively with DXM.
*: $P < 0.01$

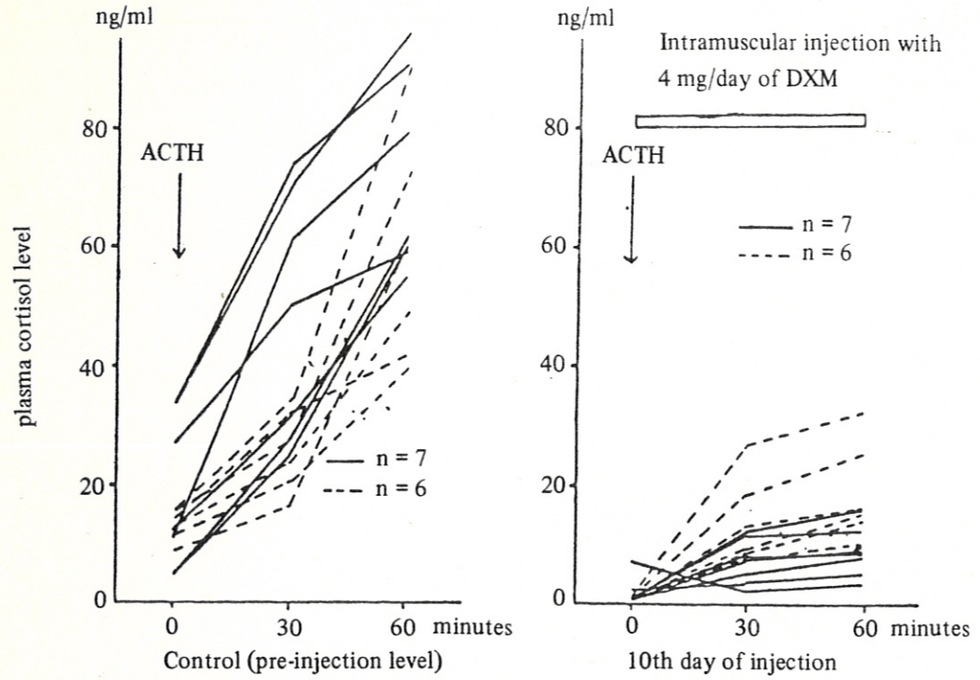


Fig. 3-A. ACTH loading test in dogs administered consecutively with DXM. (Remarks: Intravenous injection with 0.125 mg of ACTH)

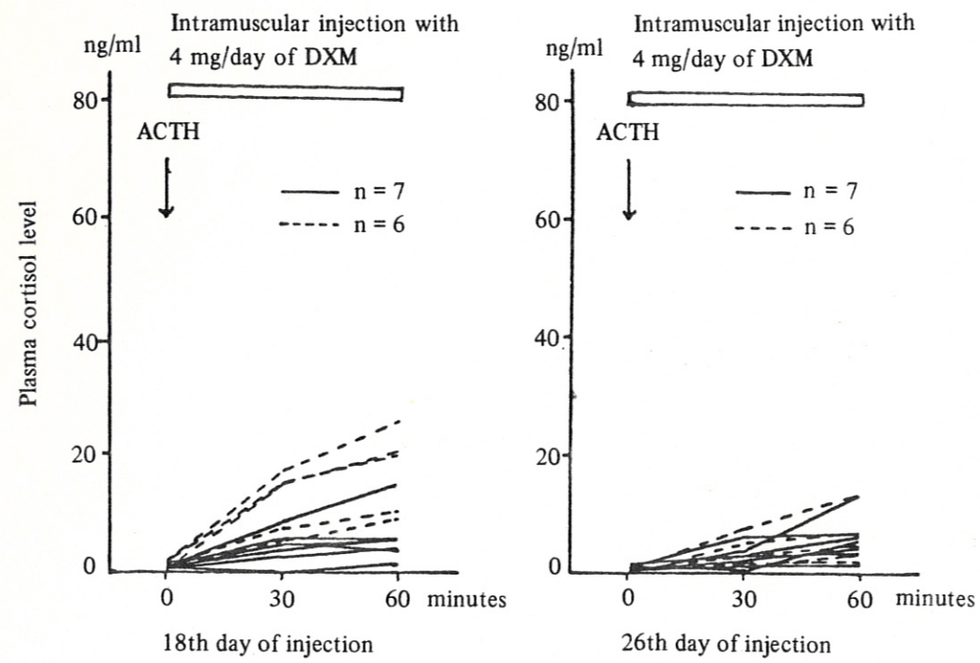


Fig. 3-B. ACTH loading test in dogs administered consecutively with DXM.

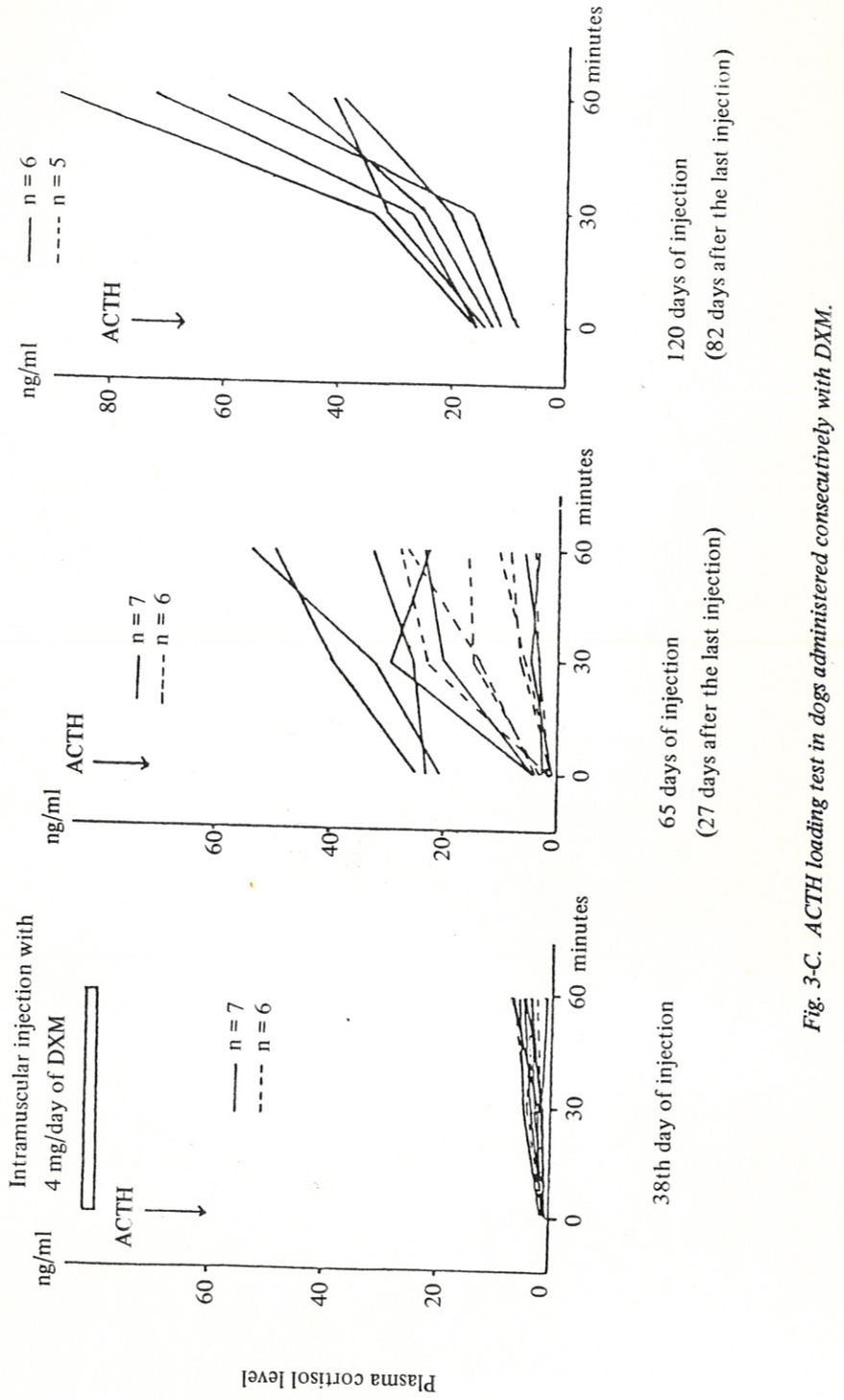


Fig. 3-C. ACTH loading test in dogs administered consecutively with DXM.

10 days after each series of injections with DXM.

Discussion

Scott and Greene[5] mentioned that the clinical symptoms of iatrogenic hypercorticism were essentially the same as those of spontaneous hypercorticism, and that they varied with the type of glucocorticoid used, the duration of administration, and the individual difference in response to the side effects of glucocorticoid. Owens and Drucker[4] pointed out that the distension of the abdomen and muscular weakness were induced by the dissimilation of protein by glucocorticoid.

The eosinophil count remained to be less than 200/mm^3 in the first series of injections and less than 50/mm^3 in the second series of injections. There was a significant difference in it between the two series ($P>0.01$).

Schechter et al.[6] observed a distinct increase in alkaline phosphatase and a mild or moderate increase in GPT and cholesterol level in the case of spontaneous hypercorticism. Davidson and Henry[7] presumed that alkaline phosphatase, GPT, and cholesterol increased in level in this case, probably because the excess in production of intrinsic glucocorticoid caused the deposition of fat in the liver, the obstruction of bile ducts, the fatty infiltration of the liver, and the injury of hepatic cells. In the present experiment alkaline phosphatase, GOT, and GPT increased in level, but cholesterol did not.

Schechter et al.[6] reported that plasma cortisol level became low in the case of iatrogenic hypercorticism. Lorenz[8] mentioned that since extrinsic glucocorticoid inhibited the secretion of intrinsic ACTH, the adrenal cortex became atrophic and the secretion of plasma cortisol was reduced. The present experiment gave the same results as obtained by Schechter et al.,[6] demonstrating a low plasma cortisol level. In it, this level remained to be lower that 4 ng/ml in the first series of injections with DXM and less than 1.9 ng/ml in the second series. There was a significant difference in plasma cortisol level between the two series of injections.

Lorenz[8] and other investigators reported that plasma cortisol level was reduced by a long-term administration with glucocorticoid. No previous authors, however, studied chronological changes in this level in one and the same dog administered with glucocorticoid for a long time. In the present experiment plasma cortisol level was lower in the second series of injections than in the first. This is probably because the adrenal gland showed a more sensitive reaction to DXM in the second series of injections than in the first.

In brief, there was a more remarkable decrease in the hepatic and adrenocortical function in the second series of injections with DXM than in the first. As has been clarified recently, manual antibody of small lymphocytes could recognize the drug injected in the first series of injections with this drug. As a result, the animals were assumed to have manifested a more distinct reaction to the drug in the second series of injections than in the first.

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