The Effects of Cortisone and Anabolic Steroids on the Tensile Strength of Healing Wounds

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Anti-inflammatory steroids such as cortisone delay healing in wounds, when given before or during the first few days after operation.[8] These same steroid drugs will, in general, inhibit growth, alter metabolism, and initiate structural changes in connective tissue. Connective tissue resorption, for instance, can be induced within 24 hours by a single injection of cortisol.[6]

Anabolic steroids, on the other hand, have effects which are opposite to those of corticoids. Anabolic steroids stimulate growth and metabolism and counteract some specific corticoid effects. Kowalewski[7] showed that anabolic agents prevent the characteristic collagen structural changes induced by cortisol. Singh and Udupa[9] demonstrated that anabolic steroids prevent anti-inflammatory steroids from affecting bone healing. At one time, patients with Cushing's disease were given testosterone, which resulted in an over-all improvement in their condition.[1, 2]

We recently demonstrated that Vitamin A negates the effects of cortisone on wound healing.[4] Vitamin A is also an "anabolic agent," and has effects on growth which are similar to those of anabolic steroids.

This study was designed to determine whether anabolic steroids also share with Vitamin A the antagonism to corticoid effects on healing.

Method

Male Sprague-Dawley rats, 4 to 6 months old, and weighing 350 to 450 Gm. were placed in separate cages and were given free access to water and Purina Chow. No dietary supplements were given.

The animals were anesthetized with ether and their backs were shaved and cleaned with tincture of iodine. One standard wound, 6 cm. long, was made parallel to and 1 cm. from the spine, using a technic described by Sandberg.[8] Equal numbers of rats were wounded on the right and on the left sides. The wounds were closed with a running suture of 4-0 silk. Immediately after wounding, the rats were placed in collars to prevent damage to the wounds. The rats were divided into four groups.

Group I: Controls. Ten rats were wounded and received only intraperitoneal saline injections in the postoperative period.

Group II. Anabolic steroids (intramuscular) were given to 18 rats which also received intraperitoneal injections of saline

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TABLE 1.

No.		Group	No. of Animals	Mean Tensile Strength (Gm.)	Standard Deviation (Gm.)
I.		Control	10	367	79
II.	A.	Testosterone Alone	6	360	48
	B.	Durabolin® Alone	6	361	49
	C.	Bolmantalate® Alone	6	354	45
III.		Cortisone Alone	10	284	52
IV.	A.	Cortisone Plus Testosterone	6	362	67
	B.	Cortisone Plus Durabolin®	6	381	82
	C.	Cortisone Plus Bolmantalate®	10	372	56

daily, starting with day 0 and continuing to day seven.*

Sub-group A: Six rats received intramuscular injections of 5 mg. testosterone propionate daily. *Sub-group B:* Six rats received 5 mg. of Durabolin® ** daily. *Sub-group C:* Six rats received 5 mg. of Bolmantalate® *** daily. Each rat was given a total of 30 mg. of an anabolic steroid intramuscularly, starting with day 0 and continuing to day five.

Group III. Ten rats received cortisone alone. Each rat was given intraperitoneal injections of 10 mg. of Cortone® acetate daily, starting with day 0 and continuing to day seven. An injection of 0.1 ml. of sterile peanut oil was also given intramuscularly each day from day 0 to day 5.

Group IV. Twenty-two rats were divided into 3 subgroups. All 22 animals received 10 mg. of cortisone intraperitoneally starting on day 0 and continuing to day seven.

Sub-group A: Six rats received 5 mg. testosterone propionate intramuscularly. *Sub-group B:* Six rats received 5 mg. Durabolin® intramuscularly. *Sub-group C:* Ten rats received 5 mg. of Bolmantalate® intramuscularly. *Sub-group C:* Ten rats received 5 mg. of Bolmantalate® intramuscularly. Each rat received a total of 30 mg. of anabolic steroid, concurrently with 80 mg. of cortisone, over a 7-day period, starting with day 0 and continuing to day five.

The tensile strength of the wounds was measured in all four groups, 7 days after wounding. The procedure has been described previously.[4]

All animals were weighed on day 0 and day seven.

Results

Control wounds had a mean tensile strength of 367 Gm. (Table 1). The Group II wounds which were divided into three subgroups had a mean tensile strength of 360 Gm. in sub-group A (testosterone alone); 361 Gm. in sub-group B (Durabolin® alone); and 354 Gm. in sub-group C (Bolmantalate® alone). Groups I and II were statistically indistinguishable, which indicates that anabolic steroids did not stimulate normal healing.

* The day of wounding is referred to as day 1. Day 0 is the day before wounding.

** Durabolin: Nandrolone Phenpropionate donated by Organon Inc., West Orange, New Jersey.

*** Bolmantalate: (19-nortestosterone-17 beta-adamantoate). A new synthetic anabolic steroid donated by Eli Lilly and Company, Indianapolis, Indiana.

The wounds from Group III (rats that received cortisone alone) had a mean tensile strength of 284 Gm. which was statistically different from the controls at 0.01 level.

Group IV (rats treated with cortisone and anabolic steroids) had mean tensile strengths of 362 Gm. in sub-group A (testosterone plus cortisone); 381 Gm. in sub-group B (Durabolin® plus cortisone); and 372 Gm. in sub-group C (Bolmantalate® plus cortisone). Group IV was significantly different from Group III (cortisone alone) at the 0.001 Student T-test level. This statistical difference between Group III and Group IV indicates that the dose of anabolic steroids which was insufficient to stimulate normal healing did return healing to normal in spite of large doses of cortisone. Group IV was statistically indistinguishable from Groups I and II.

The average gain in weight for rats in Groups I and II (controls and anabolic steroids alone) was 7 Gm. at the end of the postoperative period. There was a mean body weight loss of 48 Gm. for Group III (cortisone alone) and a 46 GM. loss for Group IV (cortisone plus anabolic steroids). This similarity in weight loss in both of the groups that received cortisone indicates that the anabolic steroids were unable to overcome the weight loss attributed to cortisone. This also indicates that the cortisone and anabolic steroids excited independent actions and did not chemically interact.

Discussion

In a previous study we postulated that the antagonism between cortisone and Vitamin A might be mediated through the lysosomal membrane.[4] Cortisone stabilizes the lysosomal membrane, while Vitamin A labilizes it. The present study was done to test that hypothesis, since testosterone is also a lysosomal labilizer.[3] If anabolic steroids were to antagonize the cortisone effect as did Vitamin A, the lysosomal theory of action would be implicated through "guilt by association."

On the other hand, it might be postulated that Vitamin A exerts its effect through the enzyme ATP sulfurylase of which the Vitamin A is a known cofactor.[10] Presumably, this effect would be mediated through sulfated mucopolysaccharide synthesis. Anabolic steroids have not been shown to be a cofactor of ATP sulfurylase. Hence, the fact that anabolic steroids also antagonize cortisone in healing does not support the supposition that the cortisone-Vitamin A antagonism is directly related to sulfate metabolism.

It is possible that Vitamin A and anabolic steroids act through independent mechanisms, since the fact that the end result of both is identical does not constitute absolute proof of an identical mechanism.

Singh and Udupa [9] postulated that anabolic steroids aid bone healing in the presence of cortisone through a "nitrogen-sparing effect." This seems a logical conclusion but unfortunately, the concept of "nitrogen sparing" has little meaning in terms of known processes of healing. *Protein depletion* resulting in the loss of 20% to 30% of body weight depresses healing.[5] However, the relatively small nitrogen losses in rats treated with cortisone (11% weight loss) does not affect healing.[8] Furthermore, anabolic steroids returned the healing process to its usual rate without affecting the weight loss.

The question also arises whether the interaction demonstrated here is local (in the wound), systemic, or both. Yet unpublished data demonstrate that local application of Vitamin A also stimulates healing retarded by cortisone without producing a detectable systemic effect. Presumably therefore, the major action of anabolic steroids is also at the wound.

The mechanism of the cortisone-Vitamin A-anabolic steroid interaction remains unproved. The lysosome theory is frequently criticized for being "too facile." However, this theory led to the performance of these experiments and has successfully predicted the results in each case.

Summary

Anabolic steroids such as testosterone, and synthetics such as Durabolin® and Bolmantalate®, restored healing to normal despite the concurrent administration of depressive doses of cortisone. Anabolic steroids did not accelerate normal healing.

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