The Effect of Liver Disease on Adrenal Cortical Function

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IT HAS been demonstrated that a number of biochemical modifications of adrenal cortical steroids are made by liver tissue *in vitro*. When cortisol, which appears to be the major secretory product of the human adrenal cortex, is injected intravenously the largest portion of this material, which has been identified, appears in the urine as the hydrogenated derivatives conjugated with glucuronide. There is convincing evidence that these derivatives are formed and conjugated in the liver. One might expect, therefore, that the liver would be an important organ in the regulation of the levels of circulating cortisol in humans.

We have studied the metabolism of cortisol, both endogenous and exogenous, in patients with cirrhosis as well as in subjects with normal liver function. These studies demonstrate that there is altered metabolism of adrenal cortical steroids in patients with liver disease.

METHODS

The methods which were used in the determinations in these studies involved the Porter-Silber reaction. This reaction depends on the formation of colored phenylhydrazine derivatives of cortisol. The reactive group is the 17, 21-dihydroxy-20-ketone side chain. For convenience, the reacting steroids are usually referred to as 17-hydroxycorticosteroids. The color reaction itself is highly nonspecific. It is therefore essential that for detailed studies great purity of the extracts on which the color reaction is performed be attained. This is accomplished by extraction of plasma or urine with various organic solvents, particularly chloroform, which removes many of the interfering substances. In addition, chromatography on a Florosil column is carried out with nearly all of the extracts. In certain circumstances, it is also useful to partition the material between water and benzene, which further eliminates interfering compounds. The final extracts are essentially free of interfering substances.

Among the steroids, those having the typical side chain of cortisol react with this material in indistinguishable fashion. This means that in addition to cortisol, cortisone and 17-hydroxy-11-desoxycorticosterone (Reichstein's substance S) as well as their hydrogenated derivatives, which still contain the typical side chain, undergo the reaction. For practical purposes, in subjects without adrenal dysfunction, and specifically in the normal subjects and patients with liver disease concerned in this manuscript, the material in the plasma which gives this reaction is cortisol. There is also present a considerable amount of hydrogenated compounds; however, these apparently exist entirely as the glucuronides which are not carried through the extraction procedure.

In the urine, there is a small portion of free 17-hydroxycorticosteroid which, under ordinary circumstances, does not exceed 200 mcg per day. The bulk of the urinary 17-hydroxycorticosteroid is present as glucuronide conjugates and consists of reduced steroids which must be released either by

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glucuronidase or extracted with a different solvent. The details of the methods are described in the papers by Nelson and Samuels[1]; Eik-Nes, Nelson and Samuels[2]; and Brown *et al.*[3]

Two types of special procedures have been carried out in evaluating the adrenal cortical function of these individuals. The first is a test which we have designated the "adrenal cortical capacity."[4] It consists of the continuous intravenous infusion of a maximally stimulating dose of adrenocorticotrophic (ACTH) hormone for a minimum period of six hours. This results in a rapid rise in the plasma level of 17-hydroxycorticosteroids and is useful for evaluating the maximal rate of secretion of which the adrenal is capable.

The second technic consists of the determination of the rate at which cortisol is removed from the plasma when large doses are infused.[3] This process proceeds in a logarithmic fashion; that is, the removal rate is proportional to the level attained. The technic consists of the administration of 1 mg per kg cortisol as an intravenous infusion over a period of one-half hour, following which, values are obtained at intervals for eight hours. By evaluation of these two tests, an estimate can be made of the rate of adrenal secretion as well as the rate of removal of the substance from the plasma.[6]

RESULTS

Plasma Levels of 17-Hydroxycorticosteroids and Response to the ACTH Infusion

In a series of 17 patients, the morning levels of 17-hydroxycorticosteroids showed a value of 12.6 mcg ± 4.0 per 100 ml of plasma. This compares to a mean of 13.0 ± 3.0 mcg per 100 ml of plasma in a large series of normal individuals. In six patients with liver disease infusion of ACTH produced a progressive rise in plasma 17-hydroxycorticosteroid level. These values averaged 45 mcg per 100 ml at the end of six hours. In 39 normal subjects, a level of 42 mcg was reached in the same period, and the curves were not significantly different. Thus, these examinations showed no evidence of abnormality in the control levels of 17-hydroxycorticosteroids nor in the plasma response produced by the infusion of ACTH.

Rate of Removal of Hydrocortisone After a Load Dose

In contrast to these observations, when hydrocortisone was infused in the standard fashion, the plasma levels at the end of the first hour were 103 mcg per 100 ml as compared to 76 mcg for a control series of 11 normal patients. In both groups, the steroid was removed in a logarithmic fashion, but the half-time in the normal subject was approximately 100 minutes while that in the patients with liver disease was 200 minutes.[3] It is thus apparent that, although the control values of circulating 17-hydroxycorticosteroids are quite normal, these patients do not remove the material from the plasma at nearly as rapid a rate as do normal individuals. Assuming that this also applies at normal plasma levels, it becomes apparent that less steroid would be required to maintain the plasma level at a normal value and that the actual secretion rate was decreased.

The Effect of Surgery on Circulating 17-Hydroxycorticosteroid Levels and Its Relation to the Liver

In a series of 23 patients with major surgery lasting more than two hours, the plasma levels rose spontaneously to a mean of 40 mcg per 100 ml during the six hours following the surgical procedure.[5] It will be noted that this value is essentially identical with that obtained on maximal stimulation of the adrenal cortex over a similar period of time with ACTH. However, when the individual values are observed, the variation is considerably greater. Particularly, values greatly in excess of the maximum level produced in normal individuals by even prolonged ACTH infusion were frequently observed. The administration of ACTH during this period produced an additional marked rise in the plasma levels of 17-hydroxycorticosteroids over the level which had been obtained spontaneously. These values frequently exceeded the maximal values observed after ACTH infusion in normal individuals or in the same patients under control

circumstances. When hydrocortisone was infused in such postoperative surgical patients, higher levels were achieved than those observed in normal individuals or the same patients under control circumstances. There was a tendency for the high levels to persist well beyond the time that was observed in the control studies. When such postoperative patients were studied for their ability to excrete bromsulfthalein, there was a significant correlation between the magnitude of the spontaneous rise in plasma 17-hydroxycorticosteroid level and the increase which occurred in bromsulfthalein retention as a result of the surgical procedure.[6]

DISCUSSION

In the patients with chronic liver disease, it would appear that the adrenal secretion of cortisol was modified because of a reduced rate of removal of hydrocortisone from the plasma. In these patients, the level of 17-hydroxycorticosteroid was quite normal, but less secretion was required to maintain this level than was required in normal subjects. Similarly, in patients undergoing surgical treatment impairment of hepatic blood flow and hepatic function probably contributed to the rise of 17-hydroxycorticosteroid levels. This was particularly evident in those patients in whom very high levels were observed, which were frequently outside of the range which could be induced by exogenous ACTH. It would appear also that some endogenous stimulation was present in these patients postoperatively.[5]

The observations in the patients with cirrhosis would seem to indicate that the plasma level of cortisol, itself, exerts some controlling influence on the rate of adrenal steroid secretion, probably mediated through the pituitary. However, the apparent stimulation of adrenal secretion by the surgical procedure, even in the presence of elevated levels, indicates that other mechanisms can operate acutely to modify the chronic regulatory system. If we look at the situation in simplified terms, we see that the plasma level or pool is furnished by the secretion by the adrenal cortex. This pool is then removed in a logarithmic fashion by the liver, where the material is degraded to inactive compounds, conjugated with glucuronide in part, and this material is then excreted through the kidney. A very small portion, under ordinary circumstances, of the free circulating steroid also appears in the urine.

Such description of the metabolism of hydrocortisone ignores the fact that this material is a biologically potent one exerting many effects in various tissues. In the light of this fact, there must be an exchange between the plasma pool and the tissue; however, the nature of this tissue phase of the metabolism of cortisol is as yet an obscure one. We have attempted to study the levels in extravascular fluids, where they are nearly always less than in the plasma, unless there is marked inflammation present in the area.[7] With inflammation, these rise to approximately the same as the plasma level. Attempts to analyze for the material in tissue, *per se*, have been fraught with some difficulties, but apparently valid determinations would seem to indicate that even less is present in the intracellular material than is present in the interstitial fluids of the body.

There may also be effects of hepatic dysfunction on the tissue phase of the metabolism of cortisol which is, in reality, the most important phase because it determines the effect on the various metabolic processes of the body. However, at the present time there is no information by which we can critically evaluate this phase of the situation. No gross evidence of excess or deficient adrenal cortical functions as regards hydrocortisone is apparent from the ordinary clinical study of the metabolic processes in the patient with liver disease.

SUMMARY

Study of patients with cirrhosis of the liver has demonstrated that the plasma levels of 17-hydroxycorticosteroid are normal. However, there is a reduced rate of removal of cortisol from the plasma and therefore less secretion is required to maintain these normal levels.

In the postoperative patients the 17-hydroxycorticosteroid levels rose strikingly. It appears that this change was mediated in part

by hepatic dysfunction and in part by stimulation of the adrenal to secrete 17-hydroxycorticosteroids at sub-maximal rates.

In the evaluation of adrenal cortical function, it is important that the status of hepatic function be considered.

REFERENCES

1. NELSON, D. H., and SAMUELS, L. T.: A method for the determination of 17-hydroxycorticosteroids in blood, 17-hydroxycorticosterone in the peripheral circulation. *J. Clin. Endocrinol.* 12:519, 1952.
2. EIK-NES, K. NELSON, D. H., and SAMUELS, L. T.: Determination of 17,21-hydroxycorticosteroids in plasma. *J. Clin. Endocrin.* 13:1280, 1953.
3. BROWN, H., WILLARDSON, D. G., SAMUELS, L. T., and TYLER, F. H.: 17-hydroxycorticosteroid metabolism in liver disease. *J. Clin. Investigation* 33:1524, 1954.
4. EIK-NES, K., SANDBERG, A. A., NELSON, D. H., TYLER, F. H., and SAMUELS, L. T.: Changes in plasma levels of 17-hydroxycorticosteroids during the intravenous administration of ACTH: I. A test of adrenocortical capacity in the human. *J. Clin. Investigation* 33:1502, 1954.
5. SANDBERG, A. A., EIK-NES, K., SAMUELS, L. T., and TYLER, F. H.: The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man. *J. Clin. Investigation* 33:1509 1954.
6. TYLER, F. H., SCHMIDT, C. D., EIK-NES, K., BROWN, H., and SAMUELS, L. T.: The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery. *J. Clin. Investigation* 33:1517, 1954.
7. SANDBERG, A. A., EIK-NES, K., NELSON, D. H., and TYLER, F. H.: Levels of 17-hydroxycorticosteroids in body fluids. *J. Lab. & Clin. Med.* 43: 874, 1954.