The Adrenal Response to Metyrapone in Amitriptyline-Treated Subjects

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Metyrapone is widely used to test “pituitary reserve”, i.e. the ability of the gland to secrete an increased amount of ACTH in response to an appropriate stimulus, in this case a decrease in the concentration of cortisol in body fluids. Metyrapone inhibits the adrenal enzyme 11β-hydroxylase, which is necessary for the conversion of 11-desoxycortisol into cortisol. This is the last step in the biosynthesis of the hormone. As a result the production of cortisol decreases and a negative feedback mechanism in the brain comes into play. The secretion of ACTH is then increased to an extent sufficient to restore cortisol production to normal or near normal, always provided that the enzymatic block is not complete. A large increase in 11-desoxycortisol production occurs at the same time; the magnitude of the increase depends upon the degree of inhibition of the enzyme (COPE et al., 1966).

The simplest method of assessing the pituitary-adrenal response to metyrapone is to measure urinary 17-hydroxycorticosteroids (17-OHCS), which comprise the metabolites of both cortisol and 11-desoxycortisol, before and after metyrapone administration. Normally a sharp rise in 17-OHCS excretion occurs. A rather more direct assessment of 11-desoxycortisol can be made by measuring urinary 11-desoxycorticosteroids (11-DOCS). Provided that the adrenal is able to respond to ACTH, an absent or subnormal response to metyrapone is usually taken to imply pituitary disease or interference with the neuroendocrine feedback mechanism. It may also be due to inadequate inhibition of 11β-hydroxylase. A failure of enzyme inhibition is best shown by simultaneous estimation of the secretion rates of cortisol and 11-desoxycortisol. This method gives a precise measure of the adrenal response and also enables the degree of enzyme inhibition to be calculated (COPE et al., 1966).

GOLD et al. showed that chlorpromazine and other phenothiazines block the adrenal response to metyrapone, a finding confirmed by other workers. One of their subjects was given imipramine and, although it is not explicitly stated, it seems that in this case also the metyrapone response was blocked. It is generally assumed that phenothiazines inhibit
the response by blocking the neuroendocrine feedback mechanism. It was decided to extend the work of GoLD et al. by testing a second tricyclic antidepressant, amitriptyline.

**Methods**

The plan was to begin with a small study in which urinary 17-OHCS and 11-DOCS only were measured. When the first results suggested that amitriptyline did block the metyrapone response, secretion rates of cortisol and 11-desoxycortisol were estimated in later subjects, in an attempt to elucidate the mechanism of the blockade.

The subjects were in-patients in a psychiatric unit who had been treated with amitriptyline in a dose of 150 mg or more daily, for at least two weeks. None of the subjects was more than mildly depressed at the time of testing. 24-hour urine collections were begun at 8 a.m. on each of three successive days. On the second day metyrapone was given by mouth, 750 mg every four hours for six doses; the first dose was given at 8 a.m. Urinary 17-OHCS were measured by the method of PETERSON et al. (1957). The same technique was used to estimate 11-DOCS, except that carbon tetrachloride was used instead of dichloromethane to extract the hydrolysed urine. In later subjects the secretion rate of cortisol was measured on the first and third days, that of 11-desoxycortisol on the third day only. Tritiated steroids (1 μg of each) were given by mouth. The chemical methods were modifications of those of COFFE et al. (1966).

**Results and Discussion**

The results are listed in Tables 1 and 2. A normal response is an increase of at least 100% in 17-OHCS and of at least 7 mg in 11-DOCS on the second or (more usually) the third day in comparison with the first. By these criteria, the first two subjects showed subnormal responses. All subsequent subjects, however, showed normal responses. In the last five subjects, when secretion rate estimations were made, a large secretion of 11-desoxycortisol occurred in each case, while the cortisol secretion rate was almost as great on day 3 as on day 1. These findings indicate that amitriptyline had no effect in subjects 5 to 9 on enzyme inhibition or on ACTH release in response to the consequent fall in cortisol production. Enough ACTH was released to restore cortisol secretion to normal or near normal.

The discrepancy between the first two and the last seven subjects cannot be explained by the data available. There was no change in the chemical techniques or in the batch of metyrapone as the study progressed. There were no obvious clinical or somatic differences in the subjects and certainly nothing to suggest pituitary or adrenal deficiency. Since a subnormal response to metapyrone is sometimes found in healthy