# Inhibition of the Urinary Excretion of 17-Ketosteroids by Caronamide. (17505)

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(Introduced by David K. Miller)

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The renal excretion of penicillin has been effectively inhibited by the concomitant administration of the drug, Caronamide (4'-Carboxyphenylmethanesulphonanilide)(1). Caronamide does so by inhibiting the transport mechanism responsible for the tubular excretion of penicillin.(2) It has been demonstrated that caronamide inhibits also the excretion of paraaminohippurate and phenolsulphonphthalein but has no effect on the glomerular filtration rate, the Tm of glucose or arginine, or the clearance of urea or sulfonamides.(3) It was thought to be of interest to study the effect of this compound on the urinary excretion of 17-ketosteroids in man.

*Material and methods.* The subjects studied were hospitalized ambulatory patients receiving the routine hospital diet. At no time during the study was any patient under any unusual "stress." Twenty-four-hour urine collections were checked for accuracy by creatinine determinations. Determination of creatinine was by the method of Folin(4) and of 17-ketosteroids by the method of Fraser *et al.*(5)

*Exp. 1.* After a control period of 2-3 days, during which 17-ketosteroid levels were determined, 1 female and 3 male patients received 24 g of caronamide* in divided doses per 24 hours. The female received the drug only 2 days; the males for longer periods. Each male had some degree of gastric distress toward the end of the drug period. Each subject had a sharp drop in the 17-ketosteroid level in the urine during the administration of drug, followed by a return to normal after a slight lag period (Fig. 1). This "lag" is probably due to continued elevated levels of caronamide due to accumulation of the drug, but since no blood caronamide levels were performed it is impossible to prove this point.

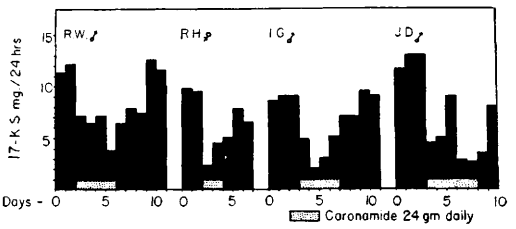


FIG. 1.

The inhibition of 17-ketosteroid excretion by the administration of caronamide. The sudden rise in steroid excretion in the case of Patient J.D. on day 6 of the study was apparently due to the patient's forgetting to take all his drug on this day, which he admitted on questioning.

*Exp. 2.* The injection of testosterone into the human is accompanied by an immediate increased excretion of 17-ketosteroids.(6) An experiment was devised to attempt to determine whether this increased excretion could be modified by caronamide administration.

Patient I.G., a eunuchoid male who had been studied in Exp. 1, was given a single injection of 80 mg of crystalline testosterone in aqueous suspension† after a 48 hour control period (Fig. 2). This was followed by a sharp increase in 17-ketosteroid output. Five days later, after the patient's steroid excretion

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4. Folin, O., *J. Biol. Chem.*, 1914, v17, 469.

* Caronamide (Stataein) was kindly supplied by Dr. W. P. Boger, Sharpe & Dohme Co., Glenolden, N.J.

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† Kindly supplied by Dr. George Hazel, Abbott Laboratories, North Chicago, Illinois.

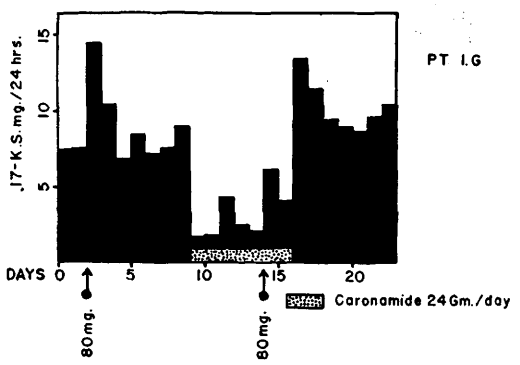


FIG. 2.

The modification of the expected sharp rise in 17-ketosteroid excretion following the intramuscular injection of testosterone by concomitant administration of caronamide.

became stabilized again, he was given 24 g of caronamide in divided dosage per 24 hours for 7 days. On the fifth day of this period he was given another injection of 80 mg of testosterone. The excretion of 17-ketosteroids following the injection of testosterone while the patient was receiving caronamide was distinctly less than that following the previous injection when the subject was not receiving the drug. However, when caronamide was discontinued 48 hours following the second injection, there was an immediate increase in steroid excretion.

*Discussion.* The data in Exp. 1 would seem to indicate that in sufficient dosage, caronamide will inhibit the excretion of endogenously manufactured 17-ketosteroids. The apparent absence of any "rebound" after the discontinuance and elimination of the drug might suggest increased degradation of these substances to non-17-ketosteroid derivatives when their natural avenue of excretion is blocked, or their alternate elimination by some other excretory route.

In reference to Exp. 2, it should be stated that in data not herein presented, we have evidence that caronamide must be given in sufficient dosage to effectively block renal tubular function if the excretion of administered testosterone is to be modified effectively. This has been shown true for penicillin also.(7) It is of some interest that the immediate, expected sharp rise in 17-ketosteroids following the injection of testosterone during the drug period was modified considerably, but that such an increase did occur following the cessation of the drug 48 hours later. This might suggest that the degradation products of administered testosterone are not further degraded rapidly when their natural pathway of excretion is blocked, and that renal tubular excretion may possibly represent their selective excretory route. It would also seem logical to assume from Exp. 1 and 2 that 17-ketosteroid excretion involves a renal tubular mechanism very similar to that for para-aminohippurate, phenolsulphonphthalein and penicillin. Further data must be obtained to substantiate these theories.

*Conclusions.* Caronamide (4'-carboxyphenylmethanesulphonanilide) has been found to inhibit the excretion of 17-ketosteroids in man. In effective dosage it will likewise apparently modify the expected rise in 17-ketosteroids following the intramuscular injection of testosterone.

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