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Increased Creatine and Creatinine Excretion after 17α-Ethyl-19-Nortestosterone.* (24136)

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Among biological processes, the rate of creatine synthesis in mammals is remarkable for its constancy. Creatine is formed in the liver by methylation of guanidinoacetic acid (1). It then diffuses freely throughout the body: concentration of free creatine in various cells and body fluids is approximately equal. Creatine, particularly in muscle, is phosphorylated to form the labile phosphocreatine, thus concentration of total creatine in cells is higher than that of free creatine(2). There is a renal threshold for creatine(3), and under normal circumstances very little appears in the urine. Creatinine, the end product of creatine metabolism, arises from creatine or phosphocreatine by non-enzymatic dehydration(4). At closely regulated pH and temperature of body, its rate of formation appears to depend only on concentration of creatine. In man, about 1.64% of the creatine body pool is converted to creatinine each day (5). Creatinine does not enter into any metabolic reactions and ultimately is completely excreted in the urine. While fluctuations in excretion in consecutive short term collections are known to occur, creatinine content of successive 24 hour collections is quite uniform (6,7). Since a steady state of formation and excretion is established, even in illness, the measure of combined creatine and creatinine chromogen in urine is also a measure of creatine synthesis. The factors which regulate rate of synthesis of creatine are not well known. Changes in peripheral requirements for creatine do not seem to modify its production(8). However, Wilkins, Fleischmann and Howard(9) found that methyltestosterone, but not testosterone, increased markedly the formation of creatine. This communication reports a similar, perhaps more profound increase in creatine synthesis as judged by excretion of total creatinine chromogen after oral administration of 17α-ethyl-19-nortestosterone.

Materials and methods. Six apparently healthy adults were given 30 mg 17α-ethyl-19-nortestosterone (Nilevar) daily by mouth. A 24 hour urine collection was obtained prior to and after 6 weeks of drug administration for determination of creatine, creatinine, total creatinine chromogen and uric acid. Subjects were placed on a creatine-free diet for 4 days before urine collections were obtained. Creatine was determined by the method of Anderson, *et al.*(10), creatinine was measured by the method of Owen, *et al.*(11), and uric acid was determined by the method of Brown(12).

Results. Increase in excretion of creatine and total creatinine chromogen was observed in all subjects. Mean daily excretion of creatine was 81.4 mg before and 473.3 mg after 6 weeks of drug with a mean increase in creatine excretion of 393.7 mg. Mean daily excretion of total creatinine chromogen was 1.58 g before and 2.35 g after 6 weeks of drug

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TABLE I. Urinary Creatine and Creatinine Excretion before and after 6 Weeks of 30 mg. 17 α-methyl-19-nortestosterone daily.

Age, sex, wt (kg) of subject	Creatine, mg/24 hr	Creatinine, g/24 hr	Total creatine chromogen, g/24 hr	Uric acid, g/24 hr
36, ♀, 59.1	27.8	1.10	1.13	.43
	612.4	*1.20*	*1.82*	*.42*
30, ♂, 82.7	98.8	1.85	1.95	.66
	612.0	*3.27*	*3.89*	*.81*
27, ♂, 74.6	74.2	1.65	1.72	.46
	122.8	*2.12*	*2.25*	*.48*
25, ♂, 77.3	103.0	1.78	1.88	.63
	422.2	*2.01*	*2.43*	*.75*
32, ♂, 78.2	129.6	1.76	1.88	.59
	153.3	*1.93*	*2.08*	*.59*
27, ♀, 66.0	55.2	.87	.93	.20
	917.0	*.72*	*1.62*	*.36*
Mean increment	393.7	.36	.77	.07

Values after drug are in italics.

with a mean increment of 0.77 g. The results are given in Table I.

It is difficult to reconcile these results with an effect of 17α-ethyl-19-nortestosterone on the kidney. While it is conceivable that increase in filtration of creatinine might occur or change in renal "threshold" for creatine might occur, a new steady state of synthesis and excretion would be quickly established and excretion of total creatinine chromogen would be again limited by, and a reflection of, the rate of creatine synthesis.

The mechanism whereby 17α-ethyl-19-nortestosterone acts to increase excretion of creatine and creatinine, and therefore synthesis of creatine, is not clear. Both this drug and methyltestosterone, which produces creatinuria, cause a positive nitrogen balance and an increase in muscle mass and tone(13). Perhaps the alteration of creatine metabolism which has been observed is a part of the general anabolic effects of these steroids. Increasing creatine synthesis may be a generic effect of 17-alkylated androgens.

Summary. A mean increase of 393 mg in daily excretion of creatine and an increase of 0.77 g in daily excretion of total creatinine chromogen has been observed in 6 subjects after oral administration of 30 mg 17α-ethyl-19-nortestosterone daily for 6 weeks.

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