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ANDROGEN METABOLISM: EFFECT OF 5 α-REDUCTASE INHIBITORS.

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The effects of 4-hydroxy-4-androsten-3,17-dione (4-OH-A), a steroid previously shown to inhibit the aromatization of androgens into estrogens, and of 17 β-N,N-diethylcarbamoyl-4-aza-5α-androstan-3-one (4MA), a compound previously shown in experimental animals to be an inhibitor of the 5α-reduction process, were investigated "in vitro" on the enzymes (5α-reductase and 3-hydroxysteroid-dehydrogenases) involved in the conversion of testosterone (T) into DHT and the diols. The epididymis and the prostate of normal rats and human BPH tissue have been used. When 4-OH-A is added in concentrations ranging from 10^{-7} to 10^{-5} M to the incubation media containing either rat prostatic or epididymal tissue and labelled T, the steroid prevents the transformation of T into DHT and the diols. 4-OH-A does not influence directly the conversion of labelled DHT into the diols. 4-OH-A and 4-MA (10^{-8} to 10^{-6} M) cause also a significant decrease in the formation of DHT and the diols, when incubated with human BPH tissue and labelled T. These data suggest that: 1) 4-OH-A is able to interfere with the process of 5α-reduction in the rat epididymis and prostate as well as in the human BPH tissue; 2)this steroid may be considered simultaneously an inhibitor of the aromatase and of the 5α-reductase; 3) the human BPH tissue is more sensitive than the rat prostate to the inhibitory action of the molecules tested. 4-OH-A might represent a new therapeutical approach for the treatment of BPH and for male contraception.(Supported by the CNR through "Oncologia" Contract n.84.00664.44.115. 02503, and "Medicina Preventiva e Riabilitativa"Contract n.84.02467.56.115.08178).

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TREATMENT OF ANDROGENIZED WOMEN WITH ANTIANDROGENS: ENDOCRINOLOGICAL AND PHARMACOLOGICAL ASPECTS.

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In the treatment of androgenized women only two compounds, cyproterone acetate (CPA) and spironolacton (SL), have proved to be efficient so far. In addition to their inherent antiandrogenicity, they are efficient inhibitors of gonodal androgen secretion either directly by interfering at the gonodal level (SL) or indirectly via suppression of hypophysial gonadotropin release (CPA). Drugs with only peripheral antiandrogenic or androgen production inhibiting properties are disappointing in this respect. Whereas the clinical usefulness of CPA is unanimously acknowledged, the respective therapeutical role of SL is still a matter of discussion.

CPA, which is also a potent progestogen, exerts considerable depot effects even after oral intake. At high dosages it must be administered along with estrogens according to the "reverse sequential regimen", i.e. 50-100 mg of CPA daily from day 5 to 14 and 40 µg ethinyl estradiol from day 5 to 25 of the cycle, in order to avoid bleeding irregularities. The justification for this empirically developed therapeutical scheme was provided by pharmacokinetic studies only recently. Thus, the half lives of the first and second disposition phases of CPA were found to be as long as 5.2 and 36 h, respectively. In the course of the "reverse sequential regimen" CPA blood values reach maximum around day 15 of the cycle. Fourteen days after the last CPA intake often appreciable CPA blood levels are still present; this is especially true for obese women.
Intramuscular administration of 300 mg of CPA given once per cycle along with daily oral estrogens proved to be effective even in women who failed to respond to the oral treatment. The superiority of parenterally to orally administered CPA cannot be explained by differences in the bioavailibility of this antiandrogen. In fact, the "area under the curve" is directly proportional to the amount of CPA given per treatment regardless of the route of application.

15ß-hydroxy-cyproterone acetate (15-CPA) is the main metabolite of CPA. After oral as well as vaginal administration its blood levels are at least twice as high as those of the parent compound. Pharmacokinetic studies after intramuscular administration are presently conducted. According to animal experiments, 15-CPA has both antiandrogenic and progestational properties. These two endocrine activities are obviously better balanced in the metabolite than in the parent compound with its heavy progestational preponderance. The use of 15-CPA as a drug for the treatment of androgenized women should be considered.