Metabolism of 6 α -Methyl-17 α -acetoxy-progesterone and 6-Dehydro-retroprogesterone in Human Subject

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The metabolism of two synthetic progestins, 6 α -methyl-17 α -acetoxy-progesterone (MAP) and 6-dehydro-retroprogesterone (DHRP), was investigated in human subjects. Compounds were administered in doses of 100 mg. per day to patients who had undergone extensive radical hysterectomy with salpingo-oophorectomia bilateralis for uterine cancer. Single oral administration of ^3H -DHRP in a dose of 5 mg. was also carried out in two cases. During the experiments, betha-methasone (3 mg./day) was given orally to these patients in order to suppress endogenous steroid excretion.

Throughout the experiments, urine samples were collected every 24 hours and stored in a deep freezer without preservatives. The urine was analysed as soon as possible. The methods of hydrolysis and extraction are listed in Fig. 1.

The crude extracts were adsorbed on alumina and eluted successively with each 100 ml of benzene, 0.1, 0.3, 0.5, 1.0, 5.0 and 30.0% methanol in benzene and then with methanol. In the isolation of MAP metabolites, column chromatography was omitted from the procedure. The radioactivities were determined on a Tri-Carb Liquid Scintillation Spectrometer. Radioactive peaks thus obtained were chromatographed on papers in modified Bush B₅, B_a and B₃ systems. Radioactive peaks or UV absorbing areas were eluted with methanol and further characterized with the aid of the following procedures. 1) INAH reaction. 2) Zimmermann reaction. 3) Acetylation. 4) Saponification. 5) Oxidation. 6) Dehydration. 7) UV absorption. 8) Sulfuric acid chromogen spectrum. 9) Porter-Silber reaction.

Results and Discussion.

1) 6 β , 17 α , 21-trihydroxy-6 α -methyl-progesterone was identified as a main metabolite of MAP (Fig. 6).

2) It was suspected that 6 β -hydroxylation and 21-hydroxylation of MAP took place in vivo in an organ other than the adrenal, probably at the liver.

3) 20 α -hydroxy-9 β , 10 α -pregna-4, 6-diene-3-one was isolated and identified in the glucuronide fraction of urine as a single major metabolite of orally administered DHRP. (Fig. 15, 17.)

4) Increasing urinary excretion of tritium was observed during the first 5 hours after administration of ^3H -DHRP in an estrogen primed rabbit. On the other hand, simultaneous administration of 4- ^{14}C -progesterone to the same animal resulted in maximum urinary excretion of ^{14}C within 2 hours (Fig. 23).

5) The recovery of radioactivities from the first 6 days urine after administration of ^3H -DHRP was culculated as being about 20% (Fig. 7).

6) The radioactivities found in glucuronide fraction were accounted for 75% of the total administered doses, 8-13% in free fraction, 3-9% in sulfate fraction, and 10% in unextractable fraction. (Table 1.)

7) The other urinary metabolites of DHRP also retained the 4,6-dien-3-one structure, but no further critical analysis of the structure could be made.

8) These experimental data suggested that the reduced reduction of Δ^4 -3-ketone system in vivo of these synthetic progestins led them into the other metabolic pathways from that of progesterone. (pp. 900~917)