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Effects of ketoconazole on ACTH-stimulated adrenal steroidogenesis in orchiectomized prostatic cancer patients.

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The effects of ketoconazole high dose therapy (H.D., 400 mg every 8 h) on adrenal steroidogenesis were investigated in 5 patients with advanced prostatic cancer who no longer responded to orchiectomy. Two ACTH-challenges were performed, before and after 14 days of treatment. The basal plasma levels of the androgens (testosterone, androstenedione, DHA and DHAS) were lowered by 50-85 % and their stimulation was almost completely inhibited, whereas both basal and stimulated plasma 17α-hydroxyprogesterone and particularly progesterone increased. Basal cortisol and aldosterone were not affected, but ketoconazole H.D. therapy blunted their response to ACTH. Both basal and stimulated plasma 11-deoxycortisol, 11-deoxycorticosterone and to a lesser extend, plasma corticosterone increased more markedly after ketoconazole than after placebo. These results confirm the block by ketoconazole of the conversion of progestins into androgens and the partial inhibition of the 11-hydroxylase in the adrenals.

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Molecular basis for ketoconazole's antifungal and anti-androgen activities

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Ketoconazole, an orally active imidazole derivative, gets antifungal activity from interaction with cytochrome P-450 in yeast and fungal microsomes.

At a 12 times higher concentration ketoconazole also interacts with cyt. P-450 in testis microsomes leading to the accumulation of for example 17,20 diOH pregnenolone, 17-OH pregnenolone and pregnenolone. This results in a decreased androgen synthesis. Ketoconazole also inhibits the cyt. P-450 dependent androgen biosynthesis in adrenal cortex microsomes. From the interactions with these cytochromes P-450 ketoconazole's use in prostate carcinoma may result.

The mitochondrial cyt. P-450 dependent cholesterol side chain cleavage in testes and adrenals is inhibited at higher ketoconazole concentrations as is the 11-hydroxylation in adrenal cortex mitochondria and the 19-hydroxylation in testes microsomes.

This study indicates great differences in the sensitivity of members of the cyt. P-450 family to ketoconazole.

These differences open possibilities to use ketoconazole not only as an antifungal but at higer doses against androgen dependent tumors too.

Part of the research has been funded by IWONL.