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THE USE OF KETOCONAZOLE AS AN INHIBITOR OF STEROID PRODUCTION

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KETOCONAZOLE is an imidazole derivative that is chemically related to miconazole (Fig. 1). It is an oral antimycotic agent with broad-spectrum activity and low toxicity.[1-3] The drug is considered to represent an important innovation in the treatment of fungal disease and has been used extensively in clinical practice for the past five years. The development of gynecomastia in some patients treated for mycosis first led to the investigation of the drug's effect on the production of testosterone.[4,5] Thereafter, ketoconazole was shown to be a potent inhibitor of gonadal and adrenal steroid synthesis in vitro and in vivo.[5-10] The finding of its important endocrine effects has aroused a new interest in this agent.[11] Extensive studies have been carried out to elucidate its mechanism of action. In addition, there have been clinical trials to assess its therapeutic potential. Because ketoconazole acts as a steroid inhibitor with differential selectivity, it is a new therapeutic tool in the management of conditions in which it is beneficial to suppress gonadal or adrenal hormone production, such as prostate cancer and Cushing's syndrome, respectively.

MECHANISM OF ACTION

Ketoconazole inhibits the synthesis of ergosterol in fungi and of cholesterol in mammalian cells.[12,13] In addition, it interferes with cytochrome P-450 enzyme systems in several organs — namely, the testis,[5] ovary,[6] adrenal gland,[7] kidney,[14] and liver.[15,16] Like other imidazole drugs, it appears to interact with cytochrome P-450 at the heme iron site.[17,18]

Steroidogenesis

The most sensitive site of action in humans appears to be the C_{17-20} lyase (Fig. 2), explaining the greater suppressibility of testosterone secretion, as compared with cortisol secretion, in humans after a single dose of 200 or 400 mg.[10,19] A similar finding has been reported in male beagle dogs.[20] Inhibition of C_{17-20} lyase has been demonstrated by an increase in ratios of precursor (17α-hydroxyprogesterone or 17α, 20α-dihydroxyprogesterone or both) to product (androstenedione or testosterone) both in vivo[19,20] and in vitro.[18,21-23] All in vitro studies to test C_{17-20} lyase have used testis preparations, but clinical data show that both gonadal and adrenal androgens decrease after ketoconazole administration,[7,9,24,25] indicating interference with adrenal C_{17-20} lyase as well; the extent of this inhibition has not been determined. Since there is evidence that 17α-hydroxylase and C_{17-20} lyase activities reside in a single enzyme, it is not surprising that ketoconazole inhibits 17α-hydroxylase as well (Fig. 2).[21-23,26]

Cholesterol side-chain–cleavage blockade by ketoconazole has been demonstrated in both testicular and adrenal tissue preparations.[14,27,28] In vitro studies in rat testicular microsomes have shown that cholesterol side-chain cleavage has a higher sensitivity to ketoconazole than does C_{17-20} lyase.[27] A species-dependent sensitivity may account for this finding. Adrenocortical steroid biosynthesis is also inhibited at the 11β-hydroxylation[14,29-31] and 18-hydroxylation steps.[31] Ketoconazole is more potent in vitro than metyrapone in the inhibition of both 11β-hydroxylase and cholesterol side-chain cleavage (Fig. 2).[31]

The effects of ketoconazole on estrogen synthesis have not been fully clarified. In contrast to in vitro findings that the agent inhibits rat ovarian[6,32] and testicular[33] and human placental[34] aromatase, in vivo studies have shown that the estradiol:testosterone ratio is increased in men given ketoconazole.[35-37] No data are available on estrogen levels in women during treatment. An inhibitory effect on oversecretion of estrogen by adrenal tumors has been reported.[25,38]

It is of interest that much higher concentrations are required to affect cytochrome P-450–dependent enzymes in mammalian tissues than to inhibit fungal cytochrome P-450.[18,21,28] This may explain why endocrine effects become evident in patients only at high doses. Concentrations 12 times higher than those sufficient for antifungal activity are needed to inhibit androgen synthesis in testis microsomes. Cholesterol side-chain cleavage in testes and adrenals and adrenal 11β-hydroxylase are inhibited at even higher concentrations.[39]

Steroid Transport and Action

In addition to a direct action on multiple enzyme systems in different steroidogenic glands, other mechanisms by which ketoconazole may produce endocrine effects have been described. A glucocorticoid antagonist activity, which acts by occupying glucocorticoid receptors, has been observed in cultured hepatoma cells.[40] Displacement of dihydrotestosterone and, to a greater extent, estradiol from sex-hormone–binding globulin by ketoconazole is observed in vitro at drug concentrations equivalent to those in patients receiving high therapeutic doses.[41] Cortisol binding to corti-

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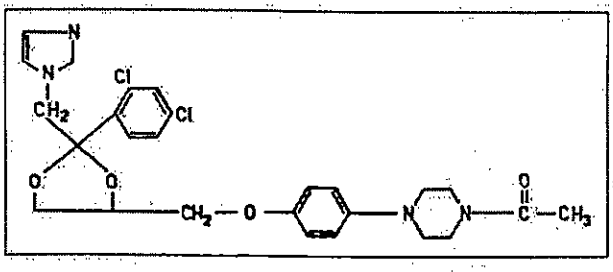

Figure 1. Structure of Ketoconazole.

a significant elevation of the estradiol:testosterone ratio (both total and free hormone) occurs,[35,36] but the percentages of bound and free fractions of both hormones are not significantly altered; thus, the displacement of estradiol from its binding globulin is not relevant in vivo.[8,35,36] The increased estradiol:testosterone ratio may be an important factor in the development of gynecomastia,[42] a principal side effect of the drug.[4,5,8,35]

Ketoconazole seems to have no direct effect at the pituitary level on the secretion of either adrenocorticotropin[43] or luteinizing hormone[26] in rat tissue studied in vivo and in vitro. This is in agreement with clinical findings, as discussed below.

Pharmacology

The hormonal changes produced by the administration of ketoconazole are dose-dependent and fully reversible,[5,7,8,10,19,20,35,41,43] with recovery from steroidogenic blockade 8 to 16 hours after an oral dose.[7,10] A considerable degree of variation in the bioavailability of the drug has been observed in pharmacokinetic studies.[44,45]

In normal subjects given a single oral dose of 200 or 400 mg of ketoconazole, the peak serum concentrations occur at two hours and are 3 to 4 and 5 to 8 μg per milliliter, respectively.[44,46-48] Higher serum levels are found in patients taking 800 to 1200 mg per day.[8,49] At eight hours, the drug is still measurable in serum, but it is undetectable at 24 hours.[35,46,47] Administration immediately after a meal results in lower serum levels than does administration during fasting.[46,48,49] Gastric acidity is required for absorption, which may be impaired by achlorhydria or antacid medication.[48,50]

Serum or plasma levels of ketoconazole have been determined by bioassay[46,49,51] and by more sensitive high-performance liquid chromatographic methods.[52,53] Even at high concentrations the drug does not interfere with hormone radio-

has been found to be biphasic, with an initial half-life of 1 to 3.3 hours[46,49] and a terminal half-life of 8 hours.[48,51] Protein-binding studies have shown a high percentage of ketoconazole bound to plasma proteins, mainly albumin: 99 percent in human whole blood,[47] and 93 and 91 percent in human serum at serum concentrations of 50 and 25 μg per milliliter.[54] The drug is widely distributed in body fluids, with detectable concentrations in urine, saliva, sebum, and cerumen after a 200-mg oral dose.[47] In a patient receiving 400 mg per day, semen ketoconazole concentrations one and three hours after the dose were 0.9 and 0.25 μg per milliliter, indicating penetration into the genitourinary tract.[41] One study found that after an 800-mg dose, ketoconazole was measurable in the cerebrospinal fluid.[55]

Ketoconazole is extensively metabolized into inactive compounds, primarily by the liver.[47,48] Metabolites and unchanged drug are excreted mostly in the feces, with very little excretion into the urine. Although renal impairment does not seem to cause accumulation of the drug, hepatic insufficiency is a contraindication to its use, since the agent is metabolized mainly by the liver and might worsen liver damage by producing a toxic effect.[47,48]

In addition to its hepatotoxicity, ketoconazole's interference with some mixed-function oxidase systems in liver microsomes[15,16,56] may have important nonendocrine clinical effects that result from alterations in the hepatic metabolism of the drug. Possible drug interactions, which are most likely due to interference with enzyme activities in liver microsomes, include potentiation of oral anticoagulants by ketoconazole,[57] markedly diminished serum concentrations of both rifampin and ketoconazole upon simultaneous administration of those agents,[58] a delay in the post-dose peak of ketoconazole concentration during long-term ad-

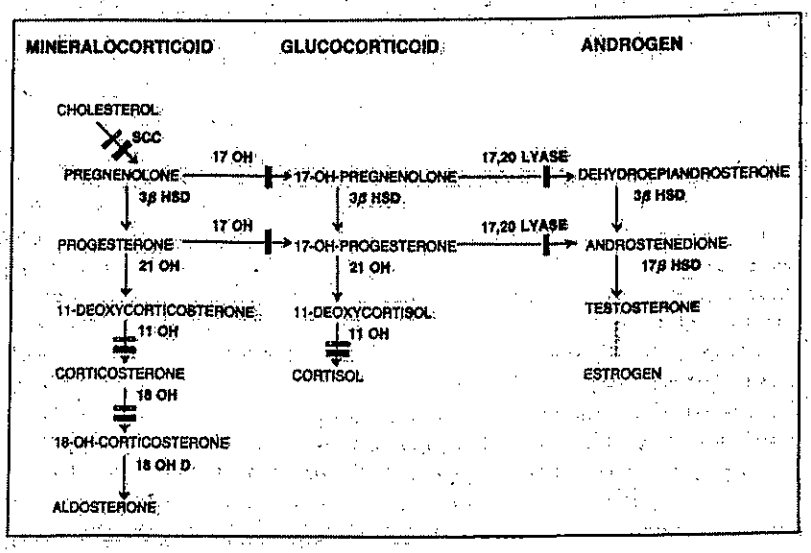

Figure 2. Main Pathways of Adrenal Steroidogenesis.

ministration of phenytoin,[49] accumulation of cyclosporine during ketoconazole therapy,[48] and inhibition of the disposition of methylprednisolone.[59]

Side Effects

The most common side effects at the doses usually employed for fungal infection (200 to 400 mg per day) are gastrointestinal reactions, pruritus, and alterations in hepatic function.[15,47,48,56,60-62] About 10 percent of patients have transient abnormalities in liver function,[60,63] but the incidence of true hepatic injury seems to be very low (0.1 to 1.0 percent).[47,48,60] Fatal hepatitis[64] and anaphylaxis[65] have also been reported. The mechanism of liver damage induced by ketoconazole is still unclear. It seems to involve an idiosyncratic type of reaction that does not depend on the daily dose or the duration of treatment. However, an immune hypersensitivity mechanism could not be excluded in some cases. Biochemical tests and assessment for clinical signs of liver dysfunction at periodic intervals (i.e., biweekly for the first two months and then monthly) are therefore advised. No increased incidence of hepatotoxicity has been reported in patients receiving prolonged high-dose treatment (800 to 1200 mg per day). In patients on a regimen of 200 to 400 mg per day, gynecomastia[4,5] is very rare. At higher doses, endocrine effects, such as impairment of testicular function[8,66] and adrenal insufficiency,[67-69] may occur. It is because ketoconazole produces such effects that it has been used to treat clinical conditions that may benefit from inhibition of either gonadal or adrenal steroid production (see below).

Inhibition of Androgen Production

A substantial decrease in total and free testosterone and androstenedione levels occurs in normal men two hours after a single 200-mg dose of ketoconazole.[5,19] Recovery from suppression begins at 8 hours and is complete by 24 hours. There is a compensatory increase in plasma luteinizing hormone and no change in cortisol levels, as compared with values in persons receiving placebo, suggesting that there is selective inhibition of C_{17-20} lyase at low doses.[19] In patients receiving high or repeated doses on a long-term basis, end-organ effects of diminished testosterone levels become apparent, with marked individual variations. Large differences in mean serum levels of both ketoconazole and testosterone are found among patients receiving the same dosage; yet, an inverse correlation between ketoconazole and testosterone concentrations is consistently observed.[8,37,70,71] During prolonged treatment with 800 to 1200 mg per day in a single dose for progressive systemic fungal disease, testosterone levels are subnormal over 24 hours in some cases, resulting in reduced sperm counts (after four months), azoospermia, decreased libido, impotence, and gynecomastia.[8] Functional hypogonadism appears to be reversible upon drug withdrawal.

Because of its marked effects on the androgen–gonadotropin feedback system in vivo, ketoconazole has been advocated for use in a test of gonadotropin reserve in men.[37] Additional studies are required to verify its feasibility and clinical usefulness. In the first trial, nine normal men received four doses of ketoconazole (300, 600, 900, and 1200 mg per day); each dose was given for one week. The response to luteinizing hormone–releasing hormone was assessed before and after each week. Increases in luteinizing hormone and follicle-stimulating hormone were maximal after the dose of 900 mg per day. However, there was great variability among subjects in the levels of both gonadotropin and testosterone at each dose tested.[37]

Therapeutic Use

The potent inhibitory action of ketoconazole on testosterone synthesis (Fig. 2) has been used with therapeutic benefit in the management of prostate cancer.[70-74] The drug acts very quickly and has the advantage over other treatments currently employed of also decreasing adrenal androgen production.[72-74] At divided doses of 400 mg every eight hours, which prevent androgen levels from returning to base line, castrate values are initially recorded. However, the rise in luteinizing hormone triggered by the fall in testosterone leads to a progressive increase in testosterone levels.[70-72] Nevertheless, striking clinical improvement is seen in many patients; serum levels of prostatic acid phosphatase decrease and considerable pain relief and regression of some lesions occurs, greatly reducing the need for analgesics.[71-74] Indeed, clinical improvement seems to be better than would be expected on the basis of testosterone levels over the long term. However, in addition to impotence and gynecomastia, severe gastrointestinal disturbances[75] and signs of adrenal insufficiency[71,72] may occur, requiring dose reduction and glucocorticoid replacement, respectively. Further hormonal assessment during long-term treatment shows a consistent rise in progesterone, no changes in prolactin and estradiol, and an increased estradiol:testosterone ratio.[35,70-72]

The proposal to use ketoconazole as a "sole treatment" for prostate cancer[72] has been questioned because of several problems that have arisen in some studies: sustained reductions in testosterone levels cannot be maintained, large diurnal fluctuations in serum testosterone occur in most patients, and compliance with a high-dose regimen and strict eight-hour timing of doses is somewhat difficult to obtain.[70,71,75] Nevertheless, good results are generally reported, especially in patients previously castrated or with castrate testosterone levels produced by administration of gonadotropin-releasing hormone analogues. In such patients, ketoconazole, by suppressing adrenal androgen output, brings about further objective or subjective remissions.[71,75] Indeed, a rationale for combined treatment with ketoconazole and superactive analogues of gonadotropin-releasing hormone in this disease has been suggested by the more pronounced androgen suppression obtained with both drugs than with either alone, in studies in both humans[75,76] and

animals.[77] Improvement has been reported in some patients in whom the combination drug treatment was introduced after other treatment methods had been used.[75] However, it has not been proved that the combined treatment is more effective than ketoconazole alone, and further evidence is needed before it can be recommended.

Successful therapy with ketoconazole for up to 12 months has been reported in three children (3.3 to 3.9 years old) with precocious puberty and autonomous Leydig-cell hyperactivity with low basal and gonadotropin-releasing hormone–stimulated gonadotropin levels.[78] Divided doses (up to 600 mg per day) were employed, with striking behavioral and clinical improvement. The growth rate and skeletal maturation were both reduced, and low levels of testosterone and adrenal androgens were maintained in the presence of high levels of 17α-hydroxyprogesterone. Basal cortisol levels were in the normal range for age. Similar results have been obtained in another child (4.2 years old), with gonadotropin-independent precocious puberty and tuberous sclerosis, who was also successfully treated for six months with ketoconazole (600 mg per day).[79] In three older children (5.0 to 7.4 years of age), an "escape" phenomenon occurred after one to three months of continuous treatment with 600 mg per day, probably because of the onset of puberty-like pituitary function. In these children, combined treatment with ketoconazole and a gonadotropin-releasing hormone analogue restored hormonal levels to the prepubertal range.[80] No signs of liver dysfunction or other side effects occurred in any child. In these preliminary studies, ketoconazole was a safe and effective inhibitor of testosterone overproduction in children. However, the long-term safety of high-dose treatment with the agent in children needs to be established.

Finally, because of its selective inhibition of androgen production at low doses,[19] ketoconazole might be useful in the management of hirsutism. However, no clinical data on this issue are available at present, except for reports of a few patients who had regression of their hirsutism while receiving ketoconazole for Cushing's syndrome[38,81] and one patient with hirsutism and polycystic ovary syndrome who had a striking improvement two months after starting ketoconazole therapy (200 mg twice daily).[82] On the other hand, the effects on estrogen production are still controversial, and it is not known whether the drug affects hormonal cyclicity. Thus, the possible interference of ketoconazole with the human menstrual cycle should be evaluated.

Inhibition of Cortisol Production

When ketoconazole is administered to subjects with normal function of the hypothalamic–pituitary–adrenal axis, the plasma cortisol response to adrenocorticotropin is blunted for up to eight hours after a single dose of 400 or 600 mg.[7,8,68,71,83] However, basal cortisol levels are not affected or are only slightly (up to 1200 mg per day).[7,70,72,78] Signs of adrenal insufficiency are uncommon,[58,67-69,71] probably because of a compensatory rise in adrenocorticotropin levels.[8,70,72]

Therapeutic Use

Because ketoconazole is a potent inhibitor of cortisol production, through the inhibition of both adrenocortical 11β-hydroxylase and cholesterol side-chain cleavage (Fig. 2), it has been used in clinical trials of palliative treatment of Cushing's syndrome. Drug control of hypercortisolism is suitable for patients undergoing surgery, as well as for those treated with external pituitary radiation and those in whom more definitive treatment is delayed.[84]

In patients with an adrenal tumor or pituitary-dependent Cushing's disease, plasma cortisol levels are suppressed and the cortisol response to adrenocorticotropin is blunted after administration of ketoconazole; inhibition of cortisol production by the drug has been confirmed in vitro in tissue slices of the excised tumors or hyperplastic adrenals.[30,85,86] Beneficial endocrine effects of ketoconazole at doses ranging from 200 to 1000 mg per day have been observed in patients with Cushing's disease and in patients with either adrenal adenomas or carcinomas.[87] Increasing doses (from 400 to 1200 mg per day) have been used to reduce excess steroid effects in a patient with Cushing's syndrome secondary to a functioning adrenal-rest tumor of the liver,[25] in a patient with primary adrenocortical micronodular adenomatosis,[88] and in one with Cushing's syndrome due to ectopic production of adrenocorticotropin by a small-cell lung cancer,[89] with improvement in clinical symptoms.

Since ketoconazole interferes with C_{17-20} lyase and is a more potent inhibitor of cholesterol side-chain cleavage activity, it can be expected that patients treated with the agent will be free of side effects such as mineralocorticoid excess or worsening of hirsutism, which may occur during treatment with metyrapone, which acts predominantly on 18- and 11β-hydroxylases (Fig. 2). On the other hand, the antiandrogenic effects of ketoconazole may be disturbing in male patients. We used prolonged ketoconazole therapy (two to six months) in five patients with pituitary-dependent Cushing's disease and recurrent hypercortisolism after transsphenoidal surgery.[81] A sixth patient was treated for two weeks before undergoing bilateral adrenalectomy. A dose of 400 mg every 12 hours was given during the first month and lowered thereafter, depending on individual responses. Urinary cortisol levels decreased to normal in all patients, and rapid clinical improvements were observed.[81] No patient had signs of drug toxicity. Female patients had regression of hirsutism, whereas in the only male patient, who was treated for four months, gynecomastia developed. We are now treating additional patients with Cushing's disease with ketoconazole (600 mg per day). Drug doses necessary to maintain cortisol levels

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