Ketoconazole and Liarozole in the Treatment of Advanced Prostatic Cancer

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Background. **Ketoconazole, an imidazole derivative, is an orally active antifungal agent. In high doses (400 mg three times a day), it inhibits the biosynthesis of testicular and adrenal androgens and may therefore be useful for the treatment of hormone dependent diseases such as advanced prostatic cancer. Similarly, a new imidazole derivative, liarozole, was recently found to interfere with testicular and adrenal steroid biosynthesis in animals and healthy volunteers.**

Methods. **The therapeutic and endocrine effects of ketoconazole and liarozole in patients with disseminated prostatic cancer are discussed, including data from the literature and personal experience.**

Results. **Using high-dose ketoconazole, medical castration with the expected clinical response was achieved easily in previously untreated patients in all clinical series (personal data include seven patients). In patients with prostatic cancer who had relapses after castration, few objective remissions were achieved. By contrast, long-lasting subjective remissions, especially pain relief, were seen in more than half of the patients (personal data include 20 patients). Gastrointestinal intolerance, which was the main side effect, severely limits the routine use of the drug. Recently, the authors studied the effect of liarozole on adrenal steroid production in castrated patients whose disease was progressive after first-line treatment. Unlike ketoconazole therapy, adrenal androgen and cortisol levels were not modified. A Phase I–II trial was then done in 44 patients with metastatic prostatic cancer in clinical relapse. In patients with measurable disease, objective responses, including tumoral volume reduction, occurred in approximatively 30%. A prostate specific antigen reduction of 50% or more was noted in approximatively 50% of patients. Pain relief occurred in most patients. Mucocutaneous side effects were observed in most patients—dryness of the skin and onychomalacia. Raised tissue retinoic acid levels suggested a possible pathway by which this drug might exert its cytotoxic effects.**

Conclusions. **Ketoconazole in high doses is effective in first-line and second-line therapy for advanced prostatic cancer, but gastrointestinal side effects limit its routine use. Liarozole is a new imidazole that is also effective in second-line therapy for prostatic cancer and has fewer side effects. Unlike ketoconazole, its effect is not mediated by inhibition of steroid biosynthesis.** *Cancer* **1993; 71:1068–73.**

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Ketoconazole is an imidazole derivative with broad-spectrum antimycotic activity. At a single oral dose of 200 mg/day, ketoconazole inhibits the cytochrome P-450 enzyme-dependent synthesis of ergosterol in fungi, leading to their eventual destruction.[1] The antiandrogenic effects of this drug were detected in 1981 after gynecomastia occurred in two patients treated with 400 mg of ketoconazole three times a day for systemic mycotic disease.[2] Thereafter, in vitro and in vivo studies showed the inhibiting effects of ketoconazole in high doses (400 mg three times a day) on gonadal and adrenal steroids by interfering with the cytochrome P-450-dependent enzymes of steroid biosynthesis.[3–5] The possible therapeutic potential of this drug as a steroid inhibitor in hormone-dependent diseases such as prostatic cancer (PC) soon was recognized. The initial case report showed a clear effect of high-dose ketoconazole (HDK) in a patient with advanced PC.[6] Since then, many groups have studied the effect of HDK in metastatic PC.

In this article, we first will review the mechanisms by which the effects of ketoconazole are mediated, then survey the literature about the published therapeutic results in metastatic PC, and finally report our own experience with HDK. In the second part, we will discuss some data with respect to a recently developed derivative of the imidazole group, liarozole, in the treatment of PC.

Effect of HDK on Steroid Synthesis (Fig 1)

Testosterone

In the testes, cholesterol is converted to pregnenolone by the side chain cleavage enzyme 20,22-desmolase. Pregnenolone and progesterone, the precursors of testicular androgens, then are transformed by a series of enzyme-controlled steps to dehydroepiandrosterone,

androstenediol, androstenedione, and testosterone. Two cytochrome P-450-dependent enzymes, first 17-α-hydroxylase and then 17,20-lyase, catalyze this conversion. Ketoconazole inhibits the 17,20-lyase, although the 17-α-hydroxylase also is affected.[7] As a result of this inhibition, the androgen precursors (17-OH-progesterone and progesterone) accumulate and increase twofold to fivefold.[5] Within 48 hours, testosterone values reach castration levels in men.[3,8] As long as serum ketoconazole levels more than 5 ng/ml are maintained, this inhibition persists; eventually, there is a compensatory rise in luteinizing hormone.[3,9,10]

Adrenal Androgens

Although not identical, the biosynthetic pathways of androgens in the adrenal glands are similar to those in the testes. Pregnenolone is converted partially to dehydroepiandrosterone, its sulfate, and androstenedione. Clinical studies confirmed the diminished synthesis of androgens through blockade of the 17,20-lyase and 17-α-hydroxylase.[9-11]

Mineralocorticoids and Glucocorticoids

In high doses, ketoconazole has been found to be a potent inhibitor of 11-β-hydroxylase, the adrenal enzyme that converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone, the immediate precursor of aldosterone.[12] As a consequence of this inhibition of cortisol synthesis, there is a compensatory increase in corticotropin levels, resulting in maintaining nearly normal basal cortisol values.[10] However, by challenging the adrenal glands of patients undergoing chronic HDK therapy with intravenous corticotropin, we showed that the cortisol response to corticotropin is blunted completely (Fig. 1).[13,14] Therefore, and in view of the fact that a subclinical adrenocortical insufficiency would not be detected before treatment was started, it is recommended that HDK therapy be combined with supplemental doses of a glucocorticoid. Basal mineralocorticoid levels change little during HDK therapy,[13] but accumulation of 11-deoxycorticosterone and corticosterone may cause arterial hypertension.[15]

There is in vitro evidence that the cholesterol side chain cleavage enzyme, 20,22-desmolase, also can be inhibited partially by HDK.[16] Because this enzyme catalyzes the transformation from cholesterol to pregnenolone, blocking this reaction could lead to a complete inhibition of adrenal steroid synthesis.[6] All these blockades are reversible completely after discontinuation of HDK, are dose dependent, and correlate with the plasma concentration of the drug.[11]

Therapeutic Effects of HDK in Prostatic Cancer

First-Line Therapy

In the initial report,[17] successful HDK results (400 mg every 8 hours) were found in 15 patients with advanced prostatic cancer. HDK was considered to be effective and well-tolerated first-line treatment, which could be regarded as an alternative to orchiectomy or other methods of lowering or blocking androgens.[9,17] Castration levels of testosterone could be achieved within 48 hours[3] and maintained for more than 1 year despite a small increment after a compensatory increase in luteinizing hormone.[10] The swift onset of action of HDK and its additional blockade of adrenal androgens (to promote a state of total androgen deprivation) were considered by some more advantageous than other treatments. Therefore, HDK has been used by many other groups as the "sole" therapy of advanced PC. A review of the literature in 1986 evaluated a total of 68 previously untreated patients with PC who were treated with HDK.[18-20] In 38 treated patients followed for at least 1 year, 4 patients had complete remissions, 14 had partial remissions, and 7 had disease progression. These findings later were confirmed in 7 patients who were able to tolerate the treatment (1 partial remission and 2 subjective remissions),[21] in 11 patients (2 complete responses, 4 partial responses, and 2 subjective remissions),[22] and in 17 patients (15 subjective remissions).[23] Recently, others reported similar effects (1 complete and 1 partial remission and 4 stable disease) in a group of 16 patients who received HDK for more than 1 year.[12] Subjective improvement (mainly pain relief) was noticed in 92% of their patients, greatly reducing the need for analgesics. In our experience treating seven previously untreated patients with advanced PC, we found one partial remission and three subjective remissions, especially pain relief, lasting up to 6 months.[25] Unfortunately, during long-term therapy, the use of HDK has several disadvantages. First, patient compliance is critical because, as a result of its short half-life, the drug must be taken strictly every 8 hours. If this regimen is not followed, testosterone values can rise above castration levels.[26] Moreover, long-term therapy is associated with various unpleasant side effects. Gastrointestinal disturbances with nausea and vomiting affects approximately 33% of patients, leading to discontinuation of therapy in a considerable number of them.[24] Impotence is another, although expected, side effect. Probably as a result of androgen deprivation, dry skin sometimes accompanied by pruritus, nail dystrophy, and desiccation of the mucosa occurred in some patients. Gynecomastia was observed in 10–15% of patients especially when 17-beta-estradiol levels were

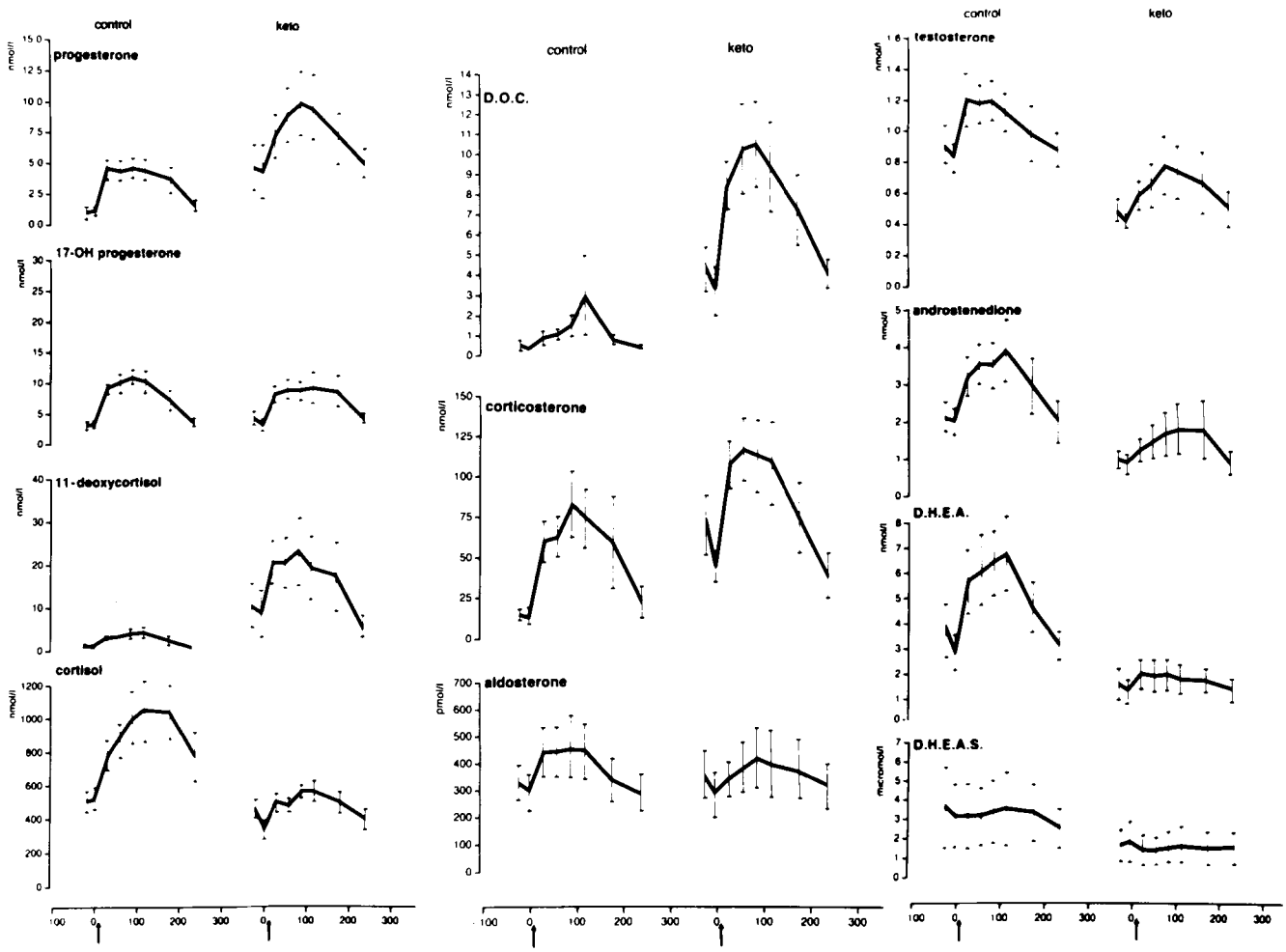

Figure 1. Effects of a 1-hour infusion of synthetic corticotropin on plasma adrenal steroid levels before (control) and after HDK (keto) in seven patients with metastatic PC who previously had undergone orchiectomies. The first two samples of each challenge dose were administered before start of the infusion (↑) and represent the basal hormonal values. The results are expressed as the mean ± the standard error of the mean.

high.[10] Addisonian crises can occur if HDK therapy is not combined with dexamethasone administration.[25] Hepatitis with mostly mild elevations of transaminases have been reported in all series, but fatal hepatitis was exceptional. Because of all these problems, HDK currently is only considered for a limited number of indications: (1) prompt therapeutic use, such as in disseminated intravascular coagulation or acute paraparesis associated with advanced PC; (2) when orchiectomy, surgical or medical, or other forms of therapy, such as estrogens, are contraindicated; or (3) as initial empiric therapy to obtain prompt clinical relief during the diagnostic workup when PC is suspected.[27]

Second-Line Therapy

Soon after the discovery of the androgen-inhibiting effects of ketoconazole, HDK was administered in combination with luteinizing hormone-releasing hormone analogues in a patient with a PC relapse.[8] Thereafter, HDK was assessed extensively in the management of relapses after earlier hormonal treatment failure. The rationale behind this therapy is based on the hypothesis that, after testicular castration, adrenal androgens play a significant role in prostatic tumor cell stimulation. These androgen levels can be reduced effectively by HDK therapy.[27] In support of this concept, a small but substantial advantage was reported in patients who underwent "total androgen ablation" compared with only testicular castration.[29] It is well known that approximately 20% of patients who have disease progression after orchidectomy may benefit from removal of adrenal androgens by adrenalectomy,[30] hypophysectomy,[31] or aminoglutethimide administration.[32] Apart from decreasing adrenal androgen levels, a direct cytotoxic effect of ketoconazole on prostatic cells also was postulated.[33,34] Table 1 depicts the clinical effects reported by different groups of investigators using HDK to treat pa-

Table 1. Therapeutic Effect of Ketoconazole in Relapsing Prostatic Cancer

Author	Year	No. of patients	Objective remission	Subjective remission	Stable disease	Duration of response (mo)
Debruyne et al.	1986	39	0	21	23	—
Williams et al.	1986	20	1	11	2	—
Bredt et al.	1986	15	8	3	—	1–12
Van Cangh et al.	1986	14	0	4	4	3–9
Pont	1987	11	0	5	4	—
Havlin et al.	1987	15	0	3	6	3–4
MacKintosch et al.	1987	12	0	0	10	—
Johnson et al.	1988	22	2	13	7	3–8
Jubelirer et al.	1989	16	0	2	6	3–12
Eichenberger et al.	1989	44	6	33	25	Mean, 7
Trump et al.	1989	36	5	++	18	0.3–12
Witjes et al.	1989	19	0	++	4	After 1 yr

tients with progressive disease after first-line or second-line therapy failure.[23,24,35–44] As expected, the responses were less impressive than after first-line treatment in these seriously ill patients. In general, objective remissions occur in approximately 15%[42] of patients and temporary stable disease can be accomplished in approximately 50% (range, 10–83%). Although a temporary decrease in prostate-specific antigen levels was detected in 80% of patients,[45] this was not always associated with clinical recovery.[44] By contrast to the lack of objective effects, subjective responses often were impressive, especially in pain control. Our experience in treating 20 patients was comparable. We did not encounter any objective responses, but eight patients had subjective improvement for a mean period of 5 months (range, 3–16 months). Similar to first-line treatment, a high incidence of side effects was found in all series, including ours. This severely limits the extensive use of HDK in this condition, and alternatives, such as antiandrogens or aminoglutethimide, often are preferable.

Liarozole

Recently, a new imidazole derivative liarozole was shown to possess an inhibitory effect on steroid synthesis in the testes and adrenal glands.[46] Its potential usefulness in advanced PC prompted us to assess its endocrine and antitumor effects.

Effect of Liarozole on Steroid Synthesis

In vitro and in vivo experiments in male rats, dogs, and healthy volunteers showed that liarozole is at least twice as potent as ketoconazole in blocking testosterone secretion by inhibiting the cytochrome P-450-dependent enzymes, 17,20-lyase and the 11-β-hydroxylase.[46] This causes an accumulation of the precursors progesterone and 11-deoxycorticosterone. The inhibition lasts more than 8 hours, twice as long as the one induced by ketoconazole.

Therapeutic Effects of Liarozole in PC

Preliminary Studies

We first evaluated liarozole in eight patients (mean age, 77.3 years; range, 62–86 years) who had disease progression after failure of second-line treatments and a poor prognosis.[47] All had been castrated for at least 2 years before onset of this trial. Liarozole was given for 28 days (dose, 300 mg twice a day). After the first 14 days, dexamethasone 0.75 mg twice a day was added to the regimen.

A corticotropin challenge was done on days 0, 14, and 28. Endocrine evaluation showed only minimal interference with cortisol biosynthesis, suggesting that corticoid supplementation would not be required with this drug. To our surprise, adrenal androgen suppression was minimal compared with the effects of ketoconazole or those of liarozole in healthy volunteers.

No significant changes in hematologic, biochemical, and urinary parameters were detected, except for a low potassium level after 10 days of treatment in one patient. After dexamethasone administration, there was progressive normalization.

All patients had increased levels of prostate-specific antigen. In two patients, there was normalization of the prostate-specific antigen values. In another four, there was a more than 50% decrease, and in the last two patients, no change occurred. We did not expect, within a 4-week period of treatment, to see significant changes in the tumor burden. Nevertheless, one patient with a big soft tissue tumor mass in the pelvic region, enlarged lymph nodes, and unilateral edema of the right leg im-

proved dramatically within the first 2 weeks of therapy. Leg swelling disappeared, and computed tomographic scanning showed a marked volume regression of the tumor and the lymph nodes. Pain, when present, disappeared within days. In five patients, performance status improved.

The drug was well tolerated. There were no gastrointestinal intolerance problems. One patient had occasional pruritus during the second week of therapy, and dry skin occurred in four patients. Compliance was good, and no patient had to interrupt the treatment regimen. There were intermittent weight increases in two patients during combined therapy that were attributed to the dexamethasone, and these decreased again after reducing the dexamethasone dose.

Phase I and II Study

Because of these promising initial clinical results, a Phase I–II study was conducted in 42 patients with metastatic PC in clinical relapse.[48,49] The first 31 patients were given 300 mg of liarozole twice a day; 11 others received 150 mg twice a day. Confirming our primary observations, adrenal steroidogenesis interference was limited, and only slight changes in adrenal androgen levels were recorded.

In patients with measurable disease, objective responses, including tumor volume reductions, occurred in 30%. Prostate-specific antigen levels were reduced by at least 50% in 50% of patients. In most patients, pain relief was noticed, reducing the need for analgesics.

The side effects were acceptable. A few patients had gastrointestinal disturbances, and some had muscle fatigue. Many patients had dry skin, dry mucosa, and nail dystrophy, signs mimicking symptoms of hypervitaminosis A. Tissue retinoic acid levels were elevated and might explain these side effects on the skin and mucous membranes.

Because androgen production was not influenced by liarozole, one hypothesis of the mechanism of action of this drug is a cytotoxic effect through the raised plasma and tissue retinoic acid levels, which might influence malignant cell differentiation and behavior.

Conclusions

Although ketoconazole can be administered as first-line or second-line treatment of advanced PC, its side effects severely restrict its routine use in this disease. Nevertheless, in a small subgroup of patients, HDK may be a valuable substitute when other treatment regimens cannot be used or have failed.

The first results of liarozole therapy suggest that this drug might be an important alternative in the therapy of PC relapses. However, much more extensive investigations are required to understand its mechanisms of action and evaluate its effect on survival and quality of life in this disease.

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