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The Treatment of Advanced Prostate Cancer with Ketoconazole

Safety Issues

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Contents

Abstract

The definition of hormone refractory prostate cancer is changing. It has become clear that patients with advanced prostate cancer whose disease has progressed following treatment with luteinising hormone releasing hormone agonists and antiandrogens can respond to additional hormonal manoeuvres. Ketoconazole is an imidazole antifungal and the antiandrogen effects of this agent have been known about for over 15 years. Initial concerns about the excessive adverse effects associated with this agent appear to have been overstated. Recent studies have demonstrated that treatment with ketoconazole can produce a significant response in a majority of patients with advanced prostate cancer and that the agent has a reasonable toxicity profile. The most common adverse effect is gastrointestinal intolerance, followed by fatigue, liver function abnormalities and skin changes; the agent is also associated with a variety of rarer adverse effects. The most serious potential adverse effects of the drug can be ameliorated by simple measures.

Ketoconazole is a synthetic broad-spectrum antifungal agent that was first used clinically in 1977. Chemically, it is classified as a synthetic imidazole-dioxolane,[1] but is more simply referred to as an imidazole antifungal agent. Its main mechanism of action is through inhibition of the synthesis of a key fungal membrane lipid. As it became widely used as an antifungal agent, various adverse effects of ketoconazole became evident. It was through observation of a fairly uncommon adverse effect of

ketoconazole that its potential endocrinological effects were discovered. A small number of male patients who were receiving higher dose ketoconazole therapy for systemic infections were noted serendipitously to develop painful gynaecomastia. This led to endocrinological studies which confirmed the inhibitory effect of ketoconazole on both gonadal and adrenal steroidogenesis. This then rapidly led to its selective use as an antiandrogen in patients with advanced prostate cancer who were unable to undergo orchiectomy or tolerate the standard diethylstilbestrol therapy available at that time.[1] Initial reports of response were very encouraging, with response rates of 80% being noted and rapid resolution of bony pain from metastases.[2,3] Subsequent studies indicated a more modest efficacy, which response rates or stabilisation of disease ranging from 15 to 50%.[4]

However, interest in ketoconazole waned in the late 1980s and early 1990s, largely because of the introduction of luteinising hormone releasing hormone (LHRH) agonists and the newer antiandrogens, as well as some early (probably exaggerated) concerns over excessive toxicity associated with ketoconazole. Recently, ketoconazole has regained attention as a valuable second-line hormonal agent, with a better defined and understood toxicity profile. In combination with hydrocortisone, we have demonstrated its utility in inducing significant and prolonged responses in prostate cancer patients whose disease has not responded to more traditional hormonal manoeuvres, with a favourable toxicity profile.[5,6] In our centre, a serological [prostate-specific antigen (PSA)] response rate of over 60% has consistently been seen with ketoconazole in patients with advanced prostate cancer whose disease has not responded to therapy with conservative androgen deprivation. The median response duration is 5 to 6 months, and long term responses (>2 years) have clearly been seen. Adverse effects do occur, but at a level substantially less than that indicated in some of the earlier reports with the drug. Given the potential benefit many patients with advanced prostate cancer may derive from ketoconazole, an evaluation of its safety profile is warranted.

1. Biochemistry of Ketoconazole and Rationale for its Use in Prostate Cancer

The formal nomenclature for ketoconazole is: (cis-1-acetyl-4[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxyl]-phenyl])piperazine. A derivative of miconazole, it is a second generation antimycotic in the same class as fluconazole and itraconazole.[7] Its mechanism of action against fungi is through inhibition of 14α-demethylase, which prevents the synthesis of an essential fungal membrane sterol.[8,9] The understanding of the mechanism by which ketoconazole exhibits anticancer activity in patients with advanced prostate cancer is incomplete. Humans are unique in having adrenal glands that secrete large quantities of precursor steroids which are converted into potent androgens, accounting for up to 10% of all androgens. This contribution to the total androgen pool is obviously unaffected by orchiectomy or estrogen therapy. Tissue dihydrotestosterone levels remain as high as 30%[10] of normal in patients treated with orchiectomy or estrogens. An understanding of the adrenal contribution to the androgen pool led to the development of nonsteroidal antiandrogens, agents which reduce the binding of dihydrotestosterone to its intracellular receptor, regardless of the source of androgens (testicular or adrenal).

Animal and human studies indicate that ketoconazole inhibits both 17,20-lyase and 17-hydroxylase activity in the adrenal glands, but that it is a more prominent inhibitor of lyase activity.[11] Endocrine studies eventually demonstrated that ketoconazole is capable of inhibiting a number of enzymes within the steroid biosynthesis pathways (fig. 1). These include the hydroxylases, 17-α hydroxylase and 11-ß-hydroxylase, and 17,20-lyase. The most significant inhibitory activity appears to be against 17,20-lyase, which blocks synthesis of the intermediates dehydroepiandrosterone and androstenedione, immediate precursors to testosterone. However, inhibition of the hydroxylases

also inhibits production of glucocorticoids.[12] The cholesterol side-chain cleavage, mediated by 20,22-desmolase, can also be partially inhibited by ketoconazole. This could potentially lead to complete inhibition of adrenal steroid synthesis,[4] resulting in clinically significant adrenal insufficiency. All of these inhibitory effects are the result of inhibition of cytochrome P450 (CYP)-dependent enzymes. Details of the impact of ketoconazole on human adrenal hormone levels are lacking, but some of these parameters are under investigation in an ongoing cooperative trial.

Ketoconazole also has clear effects on retinoic acid metabolism. Van Wauwe et al.[13] demonstrated the ability of ketoconazole to inhibit the metabolism of 4-OH and 4-keto-retinoic acid by CYP-dependent microsomal enzymes *in vitro*. In addition, ketoconazole suppressed conversion to polar retinoic acid metabolites *in vivo*. The role of this inhibitory effect on retinoic acid metabolism in the antitumour effect of ketoconazole is not entirely clear. However, such effects could easily explain some of the cutaneous and mucosal effects of the drug.

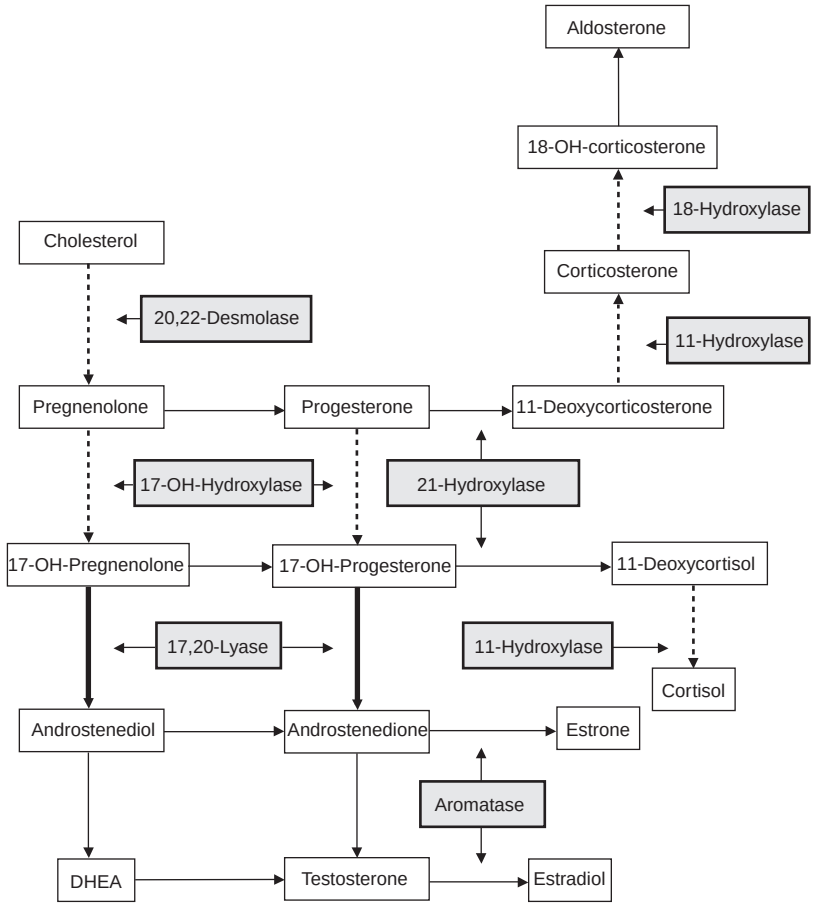

Fig. 1. Steroid biosynthesis pathway (only the cytochrome P450–dependent enzymes are shown).[11] The heavy arrows indicate the major sites of ketoconazole inhibition; the dotted arrows indicate sites of partial inhibition by ketoconazole. **DHEA** = dehydroepiandrosterone.

2. Adverse Effects

The common adverse effects of ketoconazole discussed in section 2 are summarised in table I.

2.1 Gastrointestinal

By far the most common adverse effects of ketoconazole are gastrointestinal, although estimates of the frequency of these events vary widely in the literature. Williams et al.[14] evaluated the effects of ketoconazole in 20 patients with prostate cancer and found that 11 of the patients noted nausea or anorexia but only 1 patient required withdrawal of drug. Shaw et al.[15] noted little toxicity 'with minor adverse effects such as nausea occurring only infrequently'. Other reports have noted nausea/vomiting in 25% of patients, if milder, transient forms of distress were counted.[2]

Gastrointestinal adverse effects appear to be reduced in incidence and intensity by taking ketoconazole with milk or food. However, before recommending such manoeuvres or the use of histamine H_2 receptor blockers routinely it must be kept in mind that the absorption of ketoconazole is enhanced by an acidic environment.[16] Trump et al.[17] evaluated 38 patients with advanced prostate cancer who were treated with high dose ketoconazole and observed a 37% incidence of mild to moderate nausea and vomiting. However, only 3 individuals (8%) required discontinuation of therapy. In contrast, Jubelirer and Hogan[18] thought the toxicity of ketoconazole would limit its usefulness – citing a 42% incidence of nausea or vomiting in a review of the literature. Similar concerns about the adverse effects of ketoconazole were raised by De Coster et al.[11] who estimated that about one-third of patients developed gastric discomfort. More recently, we reported on 48 patients treated with ketoconazole, noting only mild adverse gastrointestinal effects (grade 1 or 2 nausea) occurring in just 10% of patients.[5,6] In patients with pre-existing gastrointestinal disturbance, it is sometimes helpful to initiate therapy with a lower ketoconazole dosage (200mg 3 times daily) and then gradually increase the dosage to the full therapeutic dosage after several days (400mg 3 times daily).

Table I. Summary of the common adverse effects observed with ketoconazole

Adverse effect	Symptom/sign	Incidence (%)
Gastrointestinal	Nausea/vomiting	10
	Abdominal pain	NA
	Anorexia	2
Hepatic	LFT abnormality	4-20
	Fulminant hepatitis	0.01-0.1
Cutaneous	Nail dystrophy	NA
	Dry skin	NA
	Sticky skin	NA
	Rash	NA
	Pruritus	NA
	Hyperpigmentation	NA
Mucosal	Dry mouth	NA
Cardiovascular	Hypertension	NA
	Oedema	6
	Lowered LDL	NA
Endocrine	Impotence	NA
	Gynaecomastia	10-15
	Adrenal insufficiency (asthenia)	NA
	Hypocalcaemia	NA

LDL = low density lipoprotein; **LFT** = liver function tests; **NA** = estimates of incidence not available.

2.2 Hepatic

The frequency of reported hepatic adverse effects also varies widely. On close scrutiny, however, the frequency of clinically significant hepatic injury appears to be low. Within 3 years of its introduction as an antifungal agent in the UK (in 1981), 82 cases of hepatotoxicity had been reported, including 3 deaths which could be directly linked to ketoconazole use. Subsequently, use of this drug was restricted in the UK.[19] By late 1982, 77 cases of symptomatic hepatotoxicity had been reported worldwide among about 930 000 prescribed courses of the drug – an incidence of 1 in 12 000 courses of treatment.

Over 50% of patients experiencing hepatic adverse effects were found to have a prior history of hepatitis or idiosyncratic drug reaction. Hay[20] noted an incidence of 'liver disease' in 1 out of

15 000 patients exposed to ketoconazole, which was not dose related. In the 2 patients who developed fatal hepatic toxicity reported by Janssen and Symoens,[21] delayed recognition and inadequate follow-up were believed to have contributed to both outcomes. Most patients in whom symptomatic hepatic adverse effects occurred, recovered uneventfully after discontinuation of ketoconazole. However, the hepatotoxicity associated with ketoconazole was the subject of a warning by the UK Committee on Safety of Medicines.[14] Transient and asymptomatic elevations the levels of liver enzymes are much more common. Williams et al.[14] reported transient liver function test abnormalities in about 50% of their patients receiving ketoconazole; all of the abnormalities resolved despite continuation of therapy. In the evaluation by Williams et al.[14] of ketoconazole use in 20 patients with advanced prostate cancer, 6 patients experienced a transient increase in AST levels, with 3 of these patients also having a mild increase in bilirubin levels. In 2 of those 3, the liver function test abnormalities resolved despite the fact that ketoconazole therapy was not stopped.

The overall incidence of hepatitis therefore appears to be low and has been estimated in the 0.01 to 0.1% range, although this may be a low estimate due to under-reporting of cases of patients with symptomatic hepatitis and many cases being subclinical. Indeed, others have reported an overall incidence of hepatic injury of 0.1 to 1%.[22] In our group of 48 patients, only a 4.2% incidence of hepatotoxicity was observed.[5,6] This toxicity consisted of asymptomatic rises in transaminase or alkaline phosphatase levels, which resolved spontaneously upon discontinuation of ketoconazole.

Many previous reports indicate that the hepatic injury is type 3 necrosis.[19,23-25] At the cellular level, Rodriguez and Acosta[7] describe histopathology showing massive centrilobular necrosis, which does not appear to be mediated by immunoallergic mechanisms. Thus, although the mechanism of hepatic damage is not entirely clear, it is probably idiosyncratic and thus dose independent. Recently, more data on the biochemical basis of the hepatic injury has become available. *N*-deacetyl ketoconazole is the major metabolite of ketoconazole and undergoes further metabolism to a potentially toxic dialdehyde.[26]

2.3 Cutaneous

Another documented adverse effect of ketoconazole therapy is dermatological, sometimes referred to as acquired cutaneous adherence or sticky-skin syndrome. The first formal report linking this adverse effect with ketoconazole was by Polsen et al.[27] in 1995, which occurred in the setting of combination ketoconazole plus doxorubicin therapy. The incidence of this adverse effect is not known. In our experience at the University of California, San Francisco/Mt Zion Cancer Center, approximately 10% of patients have noted this symptom, but no formal data collection on its frequency has been undertaken. It is essentially a 'subjective sensation of stickiness to the skin'[27] and is usually noticed in the axillary area. The sticky skin can be demonstrated by the adherence of paper to the elbows, legs and skin folds, especially in the axillae.[28] Importantly, this symptom has never been sufficiently discomforting to warrant discontinuation of therapy.

Rashes have been infrequently reported in association with ketoconazole therapy. We noted an incidence of around 4%.[5] Nail dystrophy is also commonly noted but statistics on the frequency of this effect are not available. The cutaneous effects are most probably related to the inhibitory effect of ketoconazole on retinoic acid metabolism. Hyperpigmentation has been described, but may be mostly secondary to the endocrinological adverse effect of the drug, i.e. its potential to induce adrenal insufficiency and an Addisonian-like state (see section 2.6).

2.4 Mucosal

Desiccated mucosa has been observed and reported by De Coster et al.[11] in a review. This symptom may largely be due to inhibitory effects of ketoconazole on retinoic acid metabolism. The incidence of this adverse effect is not known, ei-

ther, but in our experience has never been severe enough to influence the course of therapy.

2.5 Cardiovascular

A variety of adverse cardiovascular effects has been described with ketoconazole, although the frequency of these effects appears to be low. Accumulation of 11-deoxycorticosterone and corticosterone may occur secondary to inhibition of 11- and 18-hydroxylases by ketoconazole and contribute to arterial hypertension.[29] Oedema is most likely secondary to some mineralocorticoid excess produced by both the blockade by ketoconazole and hydrocortisone supplements. In our series, 6% of patients experienced oedema.[5,6] A 30% decrease in serum low density lipoprotein levels is usually observed within the first week of therapy; no change in high density lipoprotein levels has been noted.[30] Cholesterol synthesis in general is inhibited by ketoconazole and appears to be a dose-dependent phenomenon.[3,31]

2.6 Endocrine

The endocrinological effects of ketoconazole are multiple and are a consequence of its intended inhibitory action within the steroid biosynthesis pathways. The theoretical risk of adrenal suppression with ketoconazole therapy has been appreciated for some time.[32] Serum cortisol levels were checked in early studies of prostate cancer patients treated with ketoconazole.[33] While these levels were normal, some indirect evidence of adrenocortical hypofunction was detected, i.e. a 25% reduction in urinary cortisol level. White and Kendall-Taylor[34] found that 5 out of 6 patients had blunted response to corticotropin (adrenocorticotrophic hormone) stimulation while taking ketoconazole; 2 of the 6 patients had decreased urinary cortisol levels.

Reports of adrenal suppression in patients treated with ketoconazole for fungal infections surfaced by 1985.[35,36] The first case report of adrenal insufficiency associated with ketoconazole therapy for prostate cancer was only recently published.[12] The authors thought that the frequent, 4-times daily administration used by their patient predisposed him to adrenal insufficiency. The authors hypothesised that this frequent administration prevented recovery of vital steroid synthesis during nadirs of ketoconazole that usually occur with 3-times daily administration.

Asthenia, a term used to describe a constellation of weakness, fatigue, apathy, and anorexia, has been noted as a adverse effect in patients taking ketoconazole and may be largely related to the adrenal suppressive effects of the agent. Consequently, it has been our practice to routinely provide hydrocortisone replacement therapy to patients receiving ketoconazole therapy for prostate cancer. We treat our patients with hydrocortisone 20mg each morning and 10mg each evening; others give 30mg in the morning and 20mg at night.[16]

Impotence is an anticipated adverse effect of the androgen-suppressive effect of ketoconazole therapy. However, since the clinical use of ketoconazole for prostate cancer is largely restricted to patients who are already impotent as a consequence of primary hormonal therapy with an LHRH analogue or orchiectomy, it is rarely of clinical importance. At low dosages of ketoconazole (200 to 400 mg/day), gynaecomastia is rare.[32,37] At the higher dosages used to block androgen production, the incidence is around 10 to 15%. The breast pain associated with gynaecomastia appears to resolve after several weeks, even though therapy is continued. The breast enlargement will persist, however.[37]

2.7 Other

A variety of miscellaneous adverse events have been noted with ketoconazole therapy, for which no precise statistics or even crude estimates are available. These include headache, dizziness, drowsiness and even papilloedema.[38] Interestingly, hypocalcaemia developed in 2 out of 20 patients treated by Williams et al.[14] and serum calcium levels remained low during the 4-month period of their therapy. Occasionally, psychiatric disturbances have been noted in patients. Significantly depressed mood has been observed anecdotally during ketoconazole therapy and we recom-

mend discontinuation of the drug in this situation. The steroid replacement therapy typically given with ketoconazole may also play some role in these cases.

3. Drug Interactions

Because of its inhibitory effect on hepatic oxidative enzymes, ketoconazole is contraindicated with several common medications. These include triazolam, alprazolam, terfenadine, astemizole and cisapride. Ketoconazole significantly inhibits the CYP3A4 isozyme, the hepatic enzyme responsible for metabolism of these medications, resulting in elevated plasma concentrations of the drugs or early metabolites. Elevated concentrations of terfenadine, astemizole or cisapride can all cause cardiotoxicity via the prolongation of the QT interval and precipitation of torsade de pointes, a potentially life-threatening ventricular arrhythmia. Ketoconazole can enhance the anticoagulant effect of coumarin and concomitant use of these drugs warrants close monitoring of coagulation tests. Ketoconazole can also have significant interactions with the new protease inhibitors employed in HIV therapy. Saquinavir, indinavir and nelfinavir concentrations are all elevated when given concomitantly with ketoconazole, and require appropriate dose reduction.

4. Conclusion

Ketoconazole is generally well tolerated and a valuable adjunct to the hormonal armamentarium currently available to patients with advanced prostate cancer. As with many therapeutic agents, clinically significant adverse effects can and do occur. The most common adverse effect, gastrointestinal intolerance, occurs in about 15% of patients, can usually be managed, and generally is not severe enough to warrant discontinuation of therapy. The most dangerous potential adverse effects of this agent are severe hepatic injury and adrenal suppression, both of which can be life-threatening, but both of which occur in a small minority of patients. Fortunately, these adverse effects can easily be managed by careful monitoring and by replacement of essential adrenocortical steroids.

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