High-dose ketoconazole therapy in prostatic cancer

A pilot study

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Summary
There may be contraindications to oestrogen therapy for prostatic carcinoma, and also patient objections to orchidectomy as a form of therapy. Ketoconazole, a systemic antifungal drug, was evaluated in a dosage of 200 mg 8-hourly given orally as an alternative method of lowering serum testosterone levels. Nineteen patients were studied; 1 was withdrawn because of nausea and vomiting. Only 6 patients (33.3%) had serum testosterone levels in the castrate range after 7 days. It seems that higher doses may be needed to keep testosterone levels consistently low.

Since the pioneering work of Huggins and Hodges over 40 years ago, various modes of hormonal therapy have been used for treating cancer of the prostate. These programmes have included oestrogen administration, orchidectomy, a combination of these, adrenalectomy, hypophysectomy, and steroid and anti-androgen administration.

The original basis for the use of hormones was the observation that adult prostatic epithelium atrophies when the normal androgen influence is removed. Adenocarcinoma of the prostate is androgen-dependent in 75 - 80% of patients and this forms the physiological rationale for treating prostatic carcinoma with hormones.

Hormones are palliative and they have been reserved mainly for metastatic disease. The principal goal of hormone treatment is suppression of androgenic stimuli to the prostate, which can be achieved by four mechanisms: (I) suppression of pituitary luteinizing hormone (LH) release - oestrogen effect; (ii) bilateral orchidectomy; (iii) direct inhibition of steroid production with aminoglutethimide (medical adrenalectomy); and (iv) inhibition of androgen action on target tissues by cyproterone acetate or flutamide.

In recent years new drugs have appeared which can suppress testosterone levels: (i) superactive analogues of the hypothalamic gonadotrophin-releasing hormone (luteinizing hormone-releasing hormone (LH-RH) analogues) such as buserelin have been used to inhibit pituitary secretion of luteinizing hormone, and thus gonadal testosterone production; however, adrenal secretion of androgen is independent of this; and (ii) ketoconazole is an oral imidazole drug that is routinely used as a systemic antifungal agent; it has been found that in high doses it blocks both gonadal and adrenal androgen production.

Ketoconazole blocks the conversion of 17α-20α-dihydroxy-progesterone to androstenedione in the manufacture of testosterone from cholesterol (Fig. 1). The blockade is dose-related and reversible. The normal dose required for treatment of fungal infections is 200 mg daily.

![Diagram](https://example.com/ketoconazole-blockade.png)

**Fig. 1. Ketoconazole blockade of testosterone metabolism.**

Previous studies have shown a drop in serum testosterone levels lasting 8 hours when ketoconazole is given in high doses and a compensatory rise in serum LH levels occurs. After a report that 200 mg given 8-hourly led to a good response, we decided on a pilot study to evaluate the effect of this dose.

Patients and methods

Nineteen patients were evaluated. All were thought to have carcinoma of the prostate on clinical evidence. They were given ketoconazole 200 mg 8-hourly by mouth in tablet form pending transrectal needle biopsy for histological diagnosis. The latter confirmed a diagnosis of carcinoma in 16 of the 19 patients. The drug was stopped in the 3 cases with no evidence of carcinoma.

In 14 patients the disease was in clinical stage C and in 2 patients in clinical stage D.

Various parameters were studied: (i) full blood count, platelet count; (ii) serum electrolytes, urea and creatinine; (iii) liver function; (iv) follicle-stimulating hormone (FSH), LH, prolactin and testosterone levels; and (v) serum acid phosphatase.
Serum levels were estimated on presentation, 24 hours after starting ketoconazole, at 48 hours and at 7 days.

**Results**

One patient was withdrawn from the trial because of persistent nausea and vomiting which ceased after stopping the drug.

Serum testosterone levels were found to drop rapidly, but only 7 patients had levels in the castrate range (<5 nmol/l) at 24 hours. At 7 days only 6 patients (33.3%) still had serum testosterone levels in the castrate range. In the remainder the testosterone level had reverted to its previous level.

Most patients showed little appreciable change initially in serum LH levels, but 8 patients showed a rise in LH level at 24 hours. At 7 days only 3 patients still had a significant increase in LH level.

No appreciable variation occurred in serum FSH or prolactin levels; 4 patients had a significant drop in serum acid phosphatase levels at 7 days.

One patient responded dramatically: the acid phosphatase level (radio-immunoassay) dropped from 52 ng/ml to 18.5 ng/ml; the testosterone level dropped from 5.8 nmol/l to 1.2 nmol/l; the alkaline phosphatase level dropped from 565 U to 251 U; and the serum lactate dehydrogenase level dropped from 3134 U/l to 747 U/l.

Serum urea, creatinine, sodium, potassium and chloride values were unaffected by ketoconazole, as were haemoglobin level, white cell count, and platelet count. Liver function, as measured by serum bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and \( \gamma \)-glutamyl transpeptidase levels (GGT) showed no significant change. There were no cases of hepatotoxicity.

**Discussion**

Ketoconazole is used widely as a systemic antifungal agent. Absorption is rapid when taken orally, and peak serum levels occur 1 - 2 hours after intake. Higher and more consistent plasma levels are reached when it is taken with a meal. Oral cimetidine and bicarbonate inhibit absorption. Ketoconazole is rapidly metabolized and about two-thirds is excreted in the faeces and one-third in the urine. Ketoconazole has been found to be a potent inhibitor of testosterone synthesis in humans and in isolated rat Leydig cells.

Side-effects are rare and include mild gastro-intestinal disturbance; 1 patient had to discontinue medication because of severe nausea and vomiting. A new oral suspension has been released which is said to have fewer gastro-intestinal side-effects. Rashes and hepatotoxicity are rare. Transient elevation of ALT, AST and GGT levels can occur but they usually revert to normal. Although some cases of severe hepatotoxicity have been reported, the estimated incidence of symptomatic reactions is ±1/10 000 and none of our patients had any appreciable change in liver function.

The drug can interfere with both adrenal and testicular androgen production, but must be given 8-hourly because escape from blockade occurs as the serum levels drop. This may be a problem, and compliance has to be very good to maintain high levels.

This drug may be of use in patients who refuse orchidectomy or if there is a contraindication to conventional oestrogen therapy, such as previous thrombo-embolic episodes.

Relapse after remission with endocrine therapy is a feature of prostatic carcinoma and has been thought to be due to the tumour cells losing their androgen dependency. However, adenral production of androgens may play a bigger role than previously thought and ketoconazole may have a place in treating the relapsed case.

From our results, however, it seems that ketoconazole given in a dose of 200 mg 8-hourly is insufficient to maintain very low levels of serum testosterone. Only 6 patients (33.3%) still had levels in the castrate range at 7 days. Higher doses, namely 400 mg 8-hourly or even 600 mg 8-hourly, may be needed to suppress testosterone adequately.

It is important to note that ketoconazole can potentiate the anticoagulant effect of warfarin.

**REFERENCES**


