

Objective Responses to Ketoconazole Therapy in Patients with Relapsed Progressive Prostatic Cancer

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Summary—The contribution of adrenal androgens to the maintenance and progression of so-called hormone-unresponsive prostatic carcinoma was studied in 20 patients with advanced relapsed disease. The role played by testicular androgens had been negated by prior orchiectomy or concurrent LHRH analogue therapy. Ketoconazole, an antifungal agent which inhibits adrenal and testicular androgenesis, administered in a dose of 400 mg 8-hourly, resulted in optimal suppression of adrenal androgens. The mean serum androstenedione concentration fell from 8.01 ± 0.84 nMol/l to 1.55 ± 0.25 nMol/l, $P < 0.001$, and serum testosterone from 1.25 ± 0.14 nMol/l to 0.36 ± 0.06 nMol/l, $P < 0.01$, after 6 months treatment. There was, however, no significant difference between patients receiving 400 and those receiving 200 mg. Androgen suppression resulted in six objective and ten subjective clinical responses. Ablation of both testicular and adrenal androgens can now be achieved using ketoconazole in combination with orchiectomy or LHRH analogues, but the high incidence of side effects may preclude its use in all patients with prostatic cancer. The results of this study support the concept of "total androgen ablation" as primary therapy in advanced prostatic cancer as a possible means of improving survival in this common malignancy.

Endocrine treatment of advanced prostatic cancer has been aimed at suppressing the major source of circulating testosterone from the testes and is achieved by either oestrogen administration, which inhibits pituitary secretion of gonadotrophins, or orchiectomy. Initial clinical response rates of 70 to 80% following either form of therapy have been reported (Resnick and Grayhack, 1975; Whitehead, 1981). However, most of these patients will relapse in 2 to 3 years of commencing endocrine therapy, and once relapse occurs 50% will die within 6 months. These therapies do not suppress adrenal androgens, which may increase after orchiectomy and encourage continued tumour growth (Sciarra *et al.*, 1973). Attempts to inhibit adrenal androgen production using pituitary ablation, adrenalectomy (Murphy *et al.*, 1971) or aminoglutethimide (Sanford *et al.*, 1976; Worgul *et al.*,

1983) have been made in patients who have failed conventional endocrine treatment. These latter therapies all have considerable disadvantages and when instituted for end-stage relapsed disease, objective response rates are poor and of short duration (Sanford *et al.*, 1976; Fitzpatrick *et al.*, 1980; Worgul *et al.*, 1983). The use of these forms of therapy as a component of primary endocrine treatment has not been attempted because of the high incidence of serious side effects. Steroid supplements, which are obligatory following pituitary ablation or aminoglutethimide therapy, may be responsible in part for the adrenal suppression achieved.

Ketoconazole, an imidazole antifungal agent, has been shown to inhibit both testicular and adrenal androgenesis (Pont *et al.*, 1982a and b). Objective responses following ketoconazole administration in patients with newly diagnosed pro-

Pont, 1984), but serum testosterone did not reach castrate levels in all patients and its short duration of action necessitates a strict 8-hourly dose regime. We have previously reported two patients with relapsed progressive disease treated with ketoconazole who have shown an improvement in objective response measurements (Allen *et al.*, 1983). We now present our experience of ketoconazole administration in a further 20 patients.

Patients and Methods

Informed consent was obtained prior to treatment from 20 patients aged 55 to 77 years (mean 68.5) with histologically confirmed prostatic carcinoma who had relapsed following single or multiple sequential endocrine therapy (Table 1). Each patient

Table 1 Previous Hormonal Therapies

Previous hormonal treatment	No. of patients	Time from initial diagnosis to introduction of ketoconazole (months)
LHRH	4	8.5
Oestrogen + orchiectomy	2	24
Oestrogen + LHRH	5	23
Orchiectomy + LHRH	6	29
Orchiectomy + oestrogen + LHRH	2	43
Orchiectomy + cyproterone acetate + LHRH	1	60

underwent the following staging procedures: digital rectal examination, tartrate labile acid phosphatase, alkaline phosphatase, intravenous urography, technetium labelled bone scanning with appropriate radiographs, and in one patient a sagittal section nuclear magnetic resonance scan before and 6 months after treatment. All objective response measurements were documented at regular intervals throughout the study, using the British Prostate Group Criteria.

Subjective criteria were recorded before treatment and at each subsequent visit using a scoring system for activity, pain and analgesia (Oken *et al.*, 1982). Blood for measurement of serum testosterone and dihydrotestosterone (Ghanadian *et al.*, 1975), androstenedione (Ghanadian and Puah, 1983), cortisol by "Gamma Coat" kit (Clinical Assays, Cambridge, USA), ACTH (Rees *et al.*, 1971) and LH (Marshall *et al.*, 1973) were taken before treatment, at 5 days, 2 weeks, 1 month and monthly thereafter. All samples for endocrine as-

the first treatment day 4- and 8-h samples were taken to measure the acute response of androstenedione to a single dose of ketoconazole. The diurnal rhythm of serum cortisol and ACTH was studied in all patients after 6 months of ketoconazole therapy.

Those patients who had not received a prior orchiectomy and were taking the LHRH analogue ICI 118630, 250 µg daily, were continued on this therapy.

Ketoconazole was administered to 15 patients at a dose of 400 mg 8-hourly (high dose) but was reduced to 200 mg 8-hourly (low dose) in 6 patients because of anorexia and nausea, after a mean interval of 30 days (range 5-70). The remaining five patients started on 200 mg tds. A satisfactory clinical response has been reported at this lower dose (Trachtenburg *et al.*, 1983). Endocrine data were analysed in accordance with the dose of ketoconazole being administered at the time of each follow-up visit and were expressed as mean \pm SEM. Significance was determined using paired and unpaired Students *t* tests.

Results

Clinical

Eight patients died of progressive metastatic disease within 14 weeks of commencing treatment (mean 7.5 weeks, range 4-14) (Fig. 1). Six of these

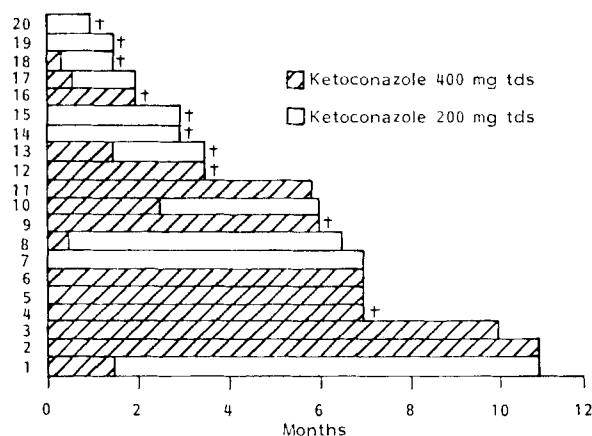


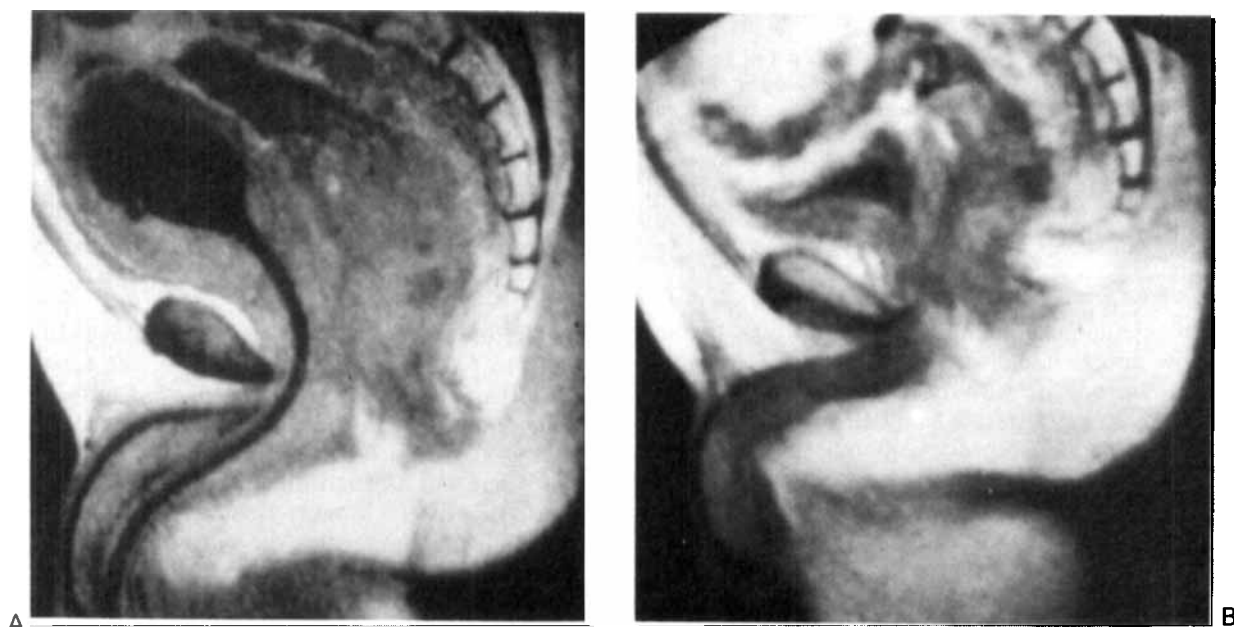
Fig. 1 Clinical outcome in 20 patients with advanced relapsed prostatic cancer following two dose regimens of ketoconazole.

patients were on low dose and two on high dose regimens.

Eleven patients have survived for more than 14 weeks. Four maintained on low dose therapy are alive for a mean period of 8 months. Partial objec-

Table 2 Changes in Objective Response Measurements and Resulting Clinical Response (British Prostate Group) in 11 Patients Following 6 Months of Ketoconazole Therapy

Patient	Dose	T stage	Acid phos. (iu/l)	Bone scans	Clinical response
2	1200 mg/day	T0→T0	28→25	Stable	Stable
3	" "	T4→T4	20→6	Stable	Partial
4	" "	T1→T0	125→322	Improved	Partial
5	" "	T0→T0	2.9→N	Stable	Partial
6	" "	T4→T4	6→N	Improved	Partial
9	" "	T3→T4	6→N	Worse	Progression
11	" "	T0→T0	9→N	Complete resolution	Complete
1	600 mg/day	T3→T0	68→69	Stable	Stable
7	" "	T0→T0	5.4→N	Worse	Progression
8	" "	T4→T4	1.8→2.1	Worse	Progression
10	" "	T4→T4	241→6.5	Resolution some lesions	Partial

**Fig. 2** Sagittal section nuclear magnetic resonance (NMR) scans (A) before and (B) after 6 months ketoconazole 400 mg tds. Prostatic tumour volume has halved and the previously stenosed bowel lumen is clearly visible.

another has stable disease, but the other two have shown evidence of disease progression manifest by worsening bone scans. Seven patients have been on high dose therapy throughout and have shown evidence of response (Table 2). The likelihood of a response to ketoconazole did not appear to relate to any previous combination of therapies.

Objective Response

1. Local disease

The volume of prostatic tumour halved and uni-

resonance scanning (Figs. 2A and B) and serial ultrasonography. Digital assessment in the remaining patients showed a prostate tumour volume reduction of at least 50% in two patients (4 and 6). Downstaging of the prostatic tumour occurred in one of these. No change in the state of local disease was detected in the remaining four patients.

2. Prostatic Acid Phosphatase

The tartrate labile acid phosphatase was elevated in 11 of 12 patients who commenced and continued on high dose therapy for at least 1 month. Values fell by more than 50% in seven of these within this

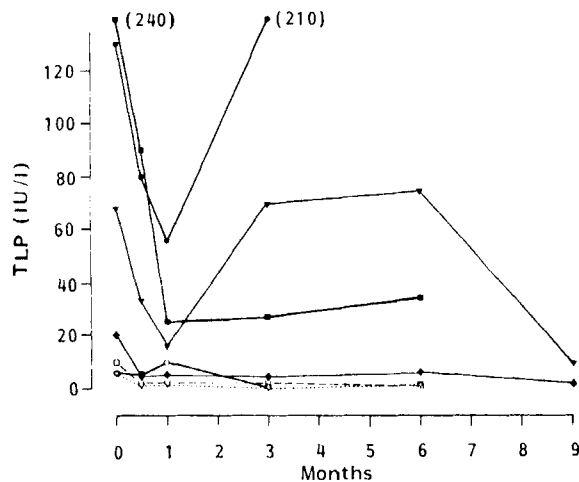


Fig. 3 The tartrate labile acid phosphatase fell by more than 50% in seven patients following ketoconazole 400 mg tds. This initial fall is maintained in six patients and three have normal values after 6 months' treatment.

mal range in three of eight patients treated with high dose therapy for 3 months (Fig. 3).

3. Bone Scans

Seven patients who had been on high dose therapy for 6 months had a further bone scan. Three scans have improved, with resolution of lesions confirmed radiographically, and three remain stable. Patient 4 had an improvement in both local tumour and bone scan but also a steady rise in acid phosphatase; the bone scan showed no new lesions, improvement of existing lesions and resolution of some. These changes in objective response parameters are summarised in Table 2.

Subjective Response

The changes in the subjective scores are shown in Table 3. The maximum benefit was seen in the first month's treatment.

Endocrine Response

A prompt fall in the mean serum androstenedione concentration was seen within 8 h of commencing therapy and was most marked in patients on high dose (Fig. 4A). The continuing fall in both groups is shown in Figure 4B. All patients had castrate levels of serum testosterone before treatment. Further falls in the mean serum concentrations of testosterone are shown in Figure 5.

The mean serum concentration of dihydrotestos-

Table 3 Changes in the Subjective Scores After Ketoconazole. Significant Responses are Indicated by an Improvement of Two or More Points (Rees *et al.*, 1971)

Time	Dose	Subjective score: points improvement			
		<2	2	3	4 or more
One month	High	5			6
	Low	6	1	1	
Three months	High	6	2		
	Low	7			
Six months	High	7			
	Low	2	1		

0.12 nMol/l ($n=6$, $P>0.1$) after 6 months' high dose treatment and to 0.64 ± 0.06 nMol/l ($n=6$, $P>0.3$) after 3 months of low dose therapy.

Serum cortisol remained within the normal range (200-700 nMol/l) during the course of study in all patients. The mean serum concentration changed from 747 ± 77 nMol/l ($n=17$) to 548 ± 80 nMol/l ($n=6$, $P>0.05$) after 6 months of high dose ketoconazole treatment. Low dose resulted in a fall to 544.5 nMol/l in two patients after 6 months.

The serum ACTH was in the normal range (10-80 ng/l) in 12 of 14 patients studied prior to treatment. Six of these patients (five high dose and one low dose) showed elevation of serum ACTH (range 88-311 ng/l) within 3 days of commencing treatment. There was a progressive rise in four of these patients alive after 3 months' treatment. Of the two patients alive at 6 months, the serum ACTH has returned to normal in one. The six patients with no rise in ACTH at the beginning of treatment remained normal throughout the period of study. Five further patients had ACTH estimations for the first time after 6 months' treatment and four (two high and two low dose) were elevated (range 89-260 ng/l).

The diurnal variation of serum cortisol and ACTH was studied in seven patients (four high and three low dose) between 6 and 12 months of ketoconazole therapy. The 8 a.m. serum cortisol was normal in all patients but at midnight four patients (two high and two low dose) had elevated levels (range 260-450 nmol/l; normal range <250 nmol/l).

Correspondingly, four patients (three high and one low dose) had elevated serum ACTH concentrations at 8 a.m. (range 154-260 ng/l) and three were normal. At midnight all ACTH values were

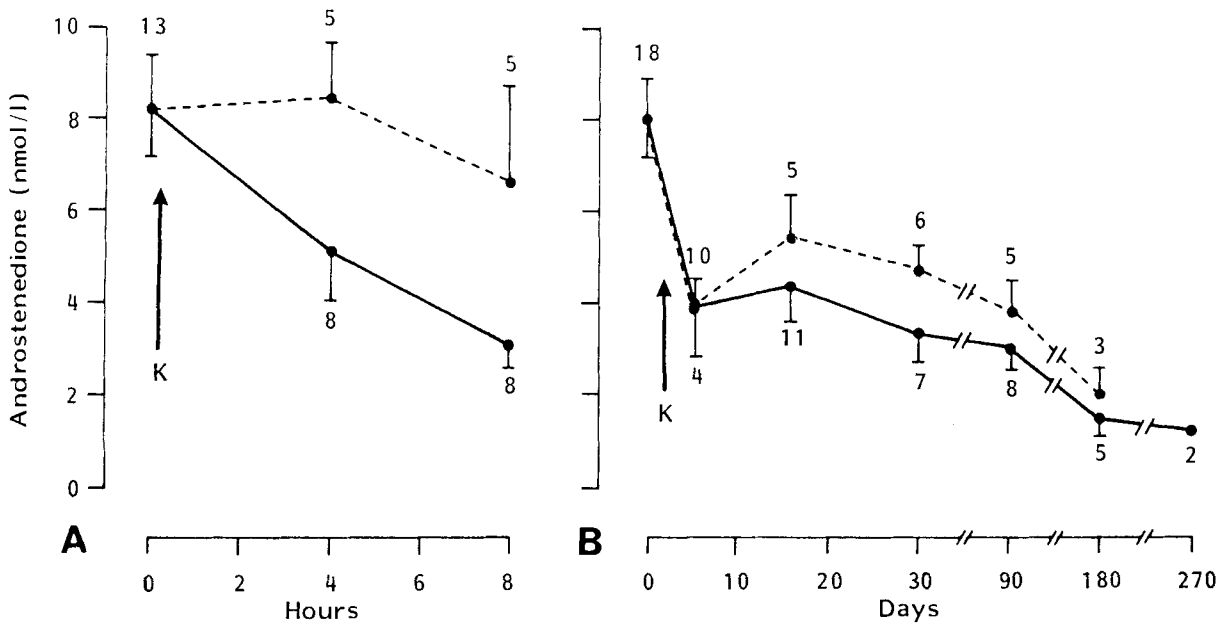


Fig. 4 Mean serum androstenedione concentrations following institution of ketoconazole therapy (K) 400 mg tds — and 200 mg tds - - -. (A) Suppression is seen after 8 h of single dose of 200 mg ($P=0.04$) and 400 mg of ketoconazole ($P=0.005$). (B) A significant difference between the two dose regimes after 8 h ($P<0.001$) is not maintained during long-term follow-up.

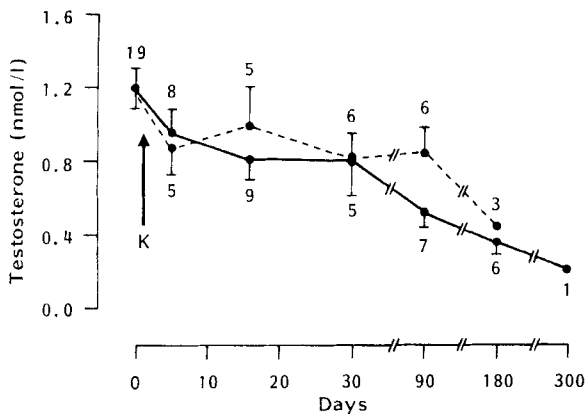


Fig. 5 Mean serum testosterone concentrations following institution of ketoconazole therapy (K) 400 mg tds — and 200 mg tds - - -. A significant fall below castrate concentrations is seen following 180 days of high dose therapy ($P<0.01$).

Side Effects

Eleven of the 20 patients complained of nausea and anorexia immediately after institution of ketoconazole therapy (8 high dose and 3 low dose). Dosage was reduced to 200 mg 8-hourly in six of the eight high dose patients but nausea persisted in four, requiring withdrawal of the drug in one. A persistent but acceptable level of nausea was tolerated by

the serum aspartate transaminase (range 51-77 iu/l; normal range 21-40) which occurred between 5 days and 2 months following the start of ketoconazole. In only one patient was this associated with elevation of serum bilirubin to 22 $\mu\text{mol/l}$ (normal range 4-17) after 1 month of therapy. The serum bilirubin rose transiently in two further patients, one high dose and one low dose, to 18 $\mu\text{mol/l}$ after 2 months and 21 $\mu\text{mol/l}$ after 3 months' treatment respectively but returned to normal without drug withdrawal. None of the patients who have been on therapy for more than six months has any abnormality of liver function.

Hypocalcaemia developed in two patients, one high dose and one low dose. The serum calcium fell to 1.87 nmol/l after 5 days' treatment in the high dose patient (normal range 2.15-2.65) and remained low during 4 months of ketoconazole treatment. The low dose patient was hypocalcaemic prior to ketoconazole treatment but fell further to 1.65 nmol/l after introduction of the drug.

Discussion

Between 60 and 80% of patients with prostatic cancer respond to endocrine therapy aimed at lowering serum testosterone. Because of this success in the palliation of symptoms there has been little de-

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