ophthalmoplegia, and ptosis developed in 20% of cases of cavernous sinus thrombosis,[6] but prompt treatment has eradicated these complications. Occasionally, traumatic carotid cavernous fistulas produce bilateral acute signs, including orbital bruits and visual loss. The history usually makes the diagnosis obvious.[7] Inflammatory causes include pseudotumour and Wegener's granulomatosis, which are less acute than cellulitis and respond dramatically to steroids. Blodi and Gass[8] emphasised that pseudotumour is rarely bilateral and that this finding may indicate underlying systemic disease.[9] Metastatic disease, usually from breast, lung, or kidney, may present with orbital signs, but in a series of 227 patients only 2 were bilateral.[10]

The cardinal features of dysthyroid eye disease are orbital congestion, proptosis, lid lag and retraction, and ophthalmoplegia. The condition is usually chronic and bilateral and accompanied by ocular discomfort. Optic neuropathy occurs in only 5% of patients with Graves' disease.[11] Visual loss is usually insidious, the symptoms and signs suggesting compression of the optic nerve. Symptoms include visual loss, flashing lights, and constricted fields. Poor colour vision and an afferent pupillary defect confirm optic nerve dysfunction. The visual fields may show central scotomas (94%) or arcuate defects, usually inferior (61%), but occasionally superior as well, to produce constricted fields.[12] Optic disc swelling is an important sign. Most patients with dysthyroid eye disease have general clinical evidence of thyroid dysfunction.[13–19] However, in one series 5% of patients with an ophthalmopathy were clinically euthyroid, though investigation of these patients showed evidence of disordered thyroid regulation.[17,20,21]

The orbital CT[22] scan is a vital investigation in the diagnosis of these patients. Although patients with pseudotumour may have orbital myositis the affected muscles are diffusely thickened near their insertions. In dysthyroid eye disease generalised extraocular muscle enlargement is common, and Moseley and Sanders[18] have emphasised that this occurs mainly towards the orbital apex, accounting for optic nerve involvement. The orbital CT scan appearances of grossly enlarged extraocular muscles prompted revision of the diagnosis to dysthyroid eye disease in the two cases reported here, even though the patients were clinically euthyroid. The scan also distinguished dysthyroid disease from invasive or other inflammatory conditions of the orbit and confirmed that the paranasal sinuses were clear.

The immunology of dysthyroid eye disease is complex. Kodarma et al[23] have reported a circulating autoantibody against soluble ocular muscle antigen in patients with ophthalmic Graves' disease but not in those with thyrotoxicosis or goitre.

Both patients had high titres of thyroglobulin and microsomal antibodies, and one had the haplotype B35, previously reported with severe dysthyroid ophthalmopathy.[24] A dramatic response to steroids occurred in both patients, consistent with their known effect on immunoglobulin production and release of lysosomal enzymes. Although autoantibodies are usually not thought to cause tissue damage in dysthyroid eye disease it is tempting to postulate such a role in these patients with acute ophthalmopathy and to speculate about a viral infection as a precipitating factor.

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References at foot of next column

Preliminary Communication

KETOCONAZOLE THERAPY FOR ADVANCED PROSTATE CANCER

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Summary Fifteen patients with biopsy-proven prostate cancer were treated with ketoconazole 400 mg every 8 h. Two patients withdrew from therapy, one for personal reasons and one because a paraspinal mass developed. The other thirteen patients completed at least 6 months of therapy. Ketoconazole greatly reduced the need for analgesics; serum prostatic acid phosphatase levels fell to normal, and testosterone levels were reduced. After 6 months thirteen of fourteen evaluable patients were in remission. The side-effects of ketoconazole therapy were limited.

INTRODUCTION

PROSTATE cancer accounts for 18% of all clinically detected cancers and for 10% of all cancer-related deaths in

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TABLE I—ADMISSION STATUS OF PATIENTS

Patient	Age (yr)	Prostatic acid phosphatase*
1	64	55
2	62	2
3	84	43
4	68	327
5	64	2680
6	82	10
7	64	6
8	62	1
9	67	9
10	77	9
11	66	20
12	83	26
13	67	4
14	68	9
15	67	4

*Measured by radioimmunoassay and expressed in ng/ml in patients 1–5 (normal <3·4 ng/ml); measured by enzymic assay and expressed in IU/l in patients 6–15 (normal <1·1 IU/l).

males.[1] In 1941, Huggins and Hodges reported that hormonal manipulation could benefit patients with prostate cancer.[2] It is now established that in 70–80% of patients with metastatic prostate cancer the disease regresses or stabilises when serum testosterone levels are lowered.[3,4] In clinical practice, testosterone levels are reduced by orchidectomy or by diethystilboestrol treatment.[5] Bilateral orchidectomy may be psychologically unacceptable; and diethylstilboestrol can have side-effects such as gynaecomastia, fluid retention, thromboembolism, and myocardial ischaemia.[6] Thus, other methods of lowering testosterone levels are being sought.

Ketoconazole ('Nizoral', Janssen Pharmaceutica, Beerse, Belgium) is an imidazole derivative which is active after oral administration against various pathogenic fungi in man.[7] It is a potent inhibitor of testicular and adrenal steroid synthesis.[8,9] In patients taking ketoconazole for serious fungal disease high doses and frequent administration of the drug suppressed testosterone levels throughout the day.[10] Therefore, ketoconazole seemed to have a potential use in the management of prostate cancer. It has the advantage over currently used treatments of also lowering adrenal androgens.[11] Our initial case-report showed that ketoconazole was objectively and subjectively beneficial in a patient with advanced disease.[12]

This study was designed to define the efficacy of high-dose ketoconazole in patients with stage D-2 previously untreated prostate carcinoma.

PATIENTS AND METHODS

Patients were eligible for study if they had biopsy-proven prostate cancer; pain; extrapelvic metastases as shown by bone scan or radiographs, high prostatic acid phosphatase level, or both; and no previous endocrine manipulations, chemotherapy, steroid therapy, or radiotherapy. All patients gave written informed consent. The study was approved by local and federal human research committees.

Ten patients were studied in Toronto and five in San Francisco (table I). All fifteen had bony metastases and patients 4, 12, and 13 had urinary-tract obstructions. All patients took 400 mg ketoconazole every 8 h by mouth. They were assessed clinically and biochemically every week for 4 weeks and once a month for 6 months. Clinical evaluation included assessment of pain, activity, urological symptoms, and side-effects. Blood was drawn for determination of prostatic acid phosphatase, blood count, electrolytes, serum cholesterol, triglycerides, calcium, phosphorus, liver and kidney function tests, and serum testosterone and ketoconazole concentrations. Serum androstenedione, dehydroepiandrosterone, luteinising hormone (LH), corticotropin, and 24 h urine cortisol results have been reported elsewhere.[13]

Serum prostatic acid phosphatase was determined by enzymic assay[14] in the Toronto patients and by radioimmunoassay (Roche Biochemical, Columbus, Ohio) in the San Francisco patients. Serum biochemistry tests were done with the multichannel analyser in the clinical laboratory. Serum testosterone was measured by radioimmunoassay. Results in San Francisco were originally expressed in ng/dl and have been converted to nmol/l by multiplying by 0·03467. Normal testosterone levels for this population are 10–35 nmol/l. Bone scans and electrocardiograms were repeated after 6 months of therapy.

RESULTS

Thirteen of the fifteen patients completed at least 6 months of therapy. One patient who experienced pain relief and a drop in prostatic acid phosphatase withdrew after 1 month for personal reasons. The other patient who withdrew initially had a normal prostatic acid phosphatase level and a histologically undifferentiated tumour; he had excellent pain relief for 3 months. A paraspinal mass, presumably from prostate cancer, then developed and the patient was assigned to conventional therapy.

After 2 weeks of therapy, pain which had previously required narcotic analgesics had greatly diminished in all fifteen patients. Most patients had no further pain after 3 days. Eight patients have completely stopped taking analgesics; three take acetominophen occasionally, and three require acetominophen-codeine preparations intermittently. After 1 month, three patients who had needed help with ambulation could walk unaided. Severe urinary-tract obstruction was relieved in the three patients with obstructions. Digital rectal examinations showed softening of prostatic tissue in all patients and disappearance of evidence of primary tumour in six patients.

Prostatic acid phosphatase fell rapidly in the thirteen patients with initially raised levels (table II). After 6 weeks of therapy, the level was normal in nine of the thirteen. The level varied greatly in patient 1, who had difficulty in complying with therapy.

After 1 week of ketoconazole therapy testosterone levels had declined to <3·5 nmol/l in thirteen patients in multiple samples measured throughout the day. At 1 month, the levels

TABLE II—EFFECT OF KETOCONAZOLE

—	Days after starting therapy (mean±SEM)							
	0	3	7	14	30	60	90	180
Testosterone (nmol/l)	15±1	3·2±0·6	2·6±0·4	2·3±0·7	3·9±0·8	3·8±0·5	3·8±0·6	5·1±1·0
Prostatic acid phosphatase								
RIA (ng/ml)*	622±517	371±284	261±227	87±70	68±56	27±17	18±8	23±12
EA (IU/l)	10±2	6±1	2±1	2±1	1±1	1±1	1±1	1±1
LH (mIU/l)†	9±3	13±3	17±4	22±5	31±6	31±5	31±5	36±4

n = 15 to day 30, 14 for days 60 and 90, 13 for day 180.
*Normal values for prostatic acid phosphatase by radioimmunoassay <3·4 ng/ml, by enzymic assay <1·1 IU/l.
†In five San Francisco patients; normal = 4–18 mIU/ml.

had generally risen slightly but remained below 3·5 nmol/l in seven of twelve patients in whom they were measured. Adrenal androgens were suppressed or undetectable in thirteen patients. LH levels rose with therapy in all patients (table II).

Bone scans done after 6 months' therapy showed that no patient had any new lesions. Nine of the thirteen patients had regression of some but not all lesions. In the one patient who had apparent progression of disease (paraspinal mass), no new lesions were visible on the bone scan at 3 months. No cardiac or thromboembolic events occurred during therapy and electrocardiograms did not change. Electrolytes, serum calcium and phosphorus, and blood count remained normal or improved. Transient rises in aspartate aminotransferase were seen in six patients, but all patients had normal liver function at 2 months despite continuing therapy. Serum cholesterol fell significantly in all patients (mean before treatment 176±8 mg/dl, 139±6 mg/dl at 6 months).

Mild transient nausea occurred in two patients and all patients experienced diminished libido or impotence, but the side-effects did not require that therapy be stopped in any patient. Slight non-tender gynaecomastia developed in three patients. After 3 months of ketoconazole therapy, two patients had symptoms suggesting mild Addison's disease (darkening of skin and weakness). Urinary cortisol was borderline low and corticotropin raised in both patients. Prednisone (5 mg daily) resulted in amelioration of symptoms.

DISCUSSION

Responses to androgen-ablative therapy, the primary treatment for advanced prostate cancer, average 18 months, and 25% of patients live 3 years.[15] Several aspects of endocrine therapy remain controversial. Should only patients with symptoms be treated? Is reduction of adrenal androgens important? How can testosterone levels best be lowered?

Both orchidectomy and diethylstilboestrol effectively lower testosterone levels. However, neither affects adrenal androgen production. Diethylstilboestrol therapy can be associated with serious cardiac toxic effects,[6,16] and orchidectomy is psychologically unacceptable to many patients. Thus, other means of lowering or blocking androgens have been explored—gonadotropin-releasing hormone agonists,[17] aminoglutethimide,[18] and flutamide.[19]

Ketoconazole inhibits testicular and adrenal steroid synthesis by blocking a variety of P-450 enzyme systems.[20,21] At doses currently licensed for the treatment of fungal disease (200–400 mg daily), the antisteroid effects are clinically minor.[8,9] However, with high doses and frequent administration, ketoconazole suppresses testosterone levels and induces azoospermia.[10] In our study 400 mg ketoconazole every 8 h persistently lowered testosterone and adrenal androgens[13] in patients with prostate cancer; testosterone fell to anorchid levels (<2 nmol/l) within 72 h. Some patients subsequently experienced a moderate rise in testosterone, but the level generally remained below 3·5 nmol/l. Initial analysis suggests that the slight rise in testosterone is LH-mediated (table II).

The clinical response to ketoconazole has been exciting. After 6 months of therapy, thirteen of fourteen evaluable patients are in remission. The side-effects of therapy have been limited, but supplementary steroid therapy may be necessary for some patients taking this dosage of ketoconazole. Further research will define which patients with prostate cancer will derive greatest benefit from ketoconazole. The drug may be useful as sole therapy for many patients, especially those with cardiac disease. Ketoconazole may also be beneficial in combination with gonadotropin-releasing-hormone agonists.[22] It could help prevent the transient rise in testosterone levels induced by these agents[22] and reduce adrenal androgen production.

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"A physician treating a colleague needs to give time and to deliver his normal standard of good care; he may have to state clearly that normal routine management is being observed. Where several physicians are involved communication between them must be excellent so that the doctor-patient is assured that all are agreed on the plan of management. The doctor-patient knows that there is often a high degree of personal judgement in clinical decisions and he needs to understand the logic behind them. For a full understanding of the disorder, the concept of disease has to be discussed; detailed education about the condition might be necessary, just as for any other patient. Explanations must be honest and full. As for any patient, however, only a few new opinions should be introduced at a time so that self-esteem is not undermined. All doctors ought to know a general practitioner with whom they can have a professional physician-to-patient relationship, so that confidentiality is safeguarded, emotional problems can be aired and better long-term care can be provided. The 'corridor-consultation' should be avoided because the doctor-patient is then denied the physician's full attention, and poor communication could be the result."—I. G. FINLAY. Doctors as patients. *J Roy Coll Gen Pract* 1984; **34:** 416.