concentration was 0.62 µg/l on one occasion and undetectable (<0.2 µg/l) on another (normal concentration <1 µg/l). Serum inorganic phosphate concentration and alkaline phosphatase activity were within normal ranges. Flurbiprofen 50 mg three times a day was given, and after seven days of treatment the serum calcium concentration had fallen to 2.55 mmol/l (10.2 mg/100 ml) and after 21 days was 2.33 mmol/l (9.3 mg/100 ml). Treatment with flurbiprofen was continued for a further four weeks, and serum calcium concentration remained within the normal range during this period and for a further six months after treatment was stopped. His symptoms had resolved within 48 hours of the start of treatment.

Six months after flurbiprofen was stopped symptoms recurred, and the serum calcium concentration was again found to be raised (2.76 mmol/l (11.1 mg/100 ml)) with a serum albumin concentration of 42 g/l. On this occasion he was admitted to hospital for more extensive study. He consumed a normal ward diet containing a daily intake of at least 800 mg calcium. After an overnight fast blood and two hour fasting urine samples were collected, and biochemical and hormonal variables were measured by methods previously reported.¹

After initial study treatment with flurbiprofen in the same dose as during the first hypercalcaemic episode was started, and fasting blood and urine samples were taken after 10 days. The two sets of results are shown in the table.

Biochemical variables before and after successful treatment of hypercalcaemia with flurbiprofen 50 mg three times a day

	Before treatment	After treatment	Normal range
Serum calcium (mmol/l)	2.81	2.38	2.26-2.60
Serum phosphate (mmol/l)	1.11	1.29	0.80-1.45
Serum creatinine (µmol/l)	140	130	60-120
Serum alkaline phosphatase (IU/l)	83	104	30-95
Serum parathyroid hormone (µg/l)	0.70	0.66	<1
Serum 1,25-dihydroxy vitamin D (pmol/l)	16.0	17.4	5-15
Urine calcium (µmol/l glomerular filtrate)	198.8	109.5	<40
Urine phosphate (µmol/l glomerular filtrate)	405.5	306.4	<218
Urine calcium:creatinine	1.42	0.84	<0.425
Urine hydroxyproline:creatinine	0.033	0.006	<0.022
Tubular reabsorption of calcium (mmol/l glomerular filtrate)	1.64	1.52	1.80-2.20
Tubular reabsorption of phosphate (mmol/l glomerular filtrate)	0.78	1.14	0.7-1.4

Conversion: SI to traditional units—Serum calcium: 1 mmol/l ≈ 4 mg/100 ml. Serum phosphate: 1 mmol/l ≈ 3.1 mg/100 ml. Serum creatinine: 1 mmol/l ≈ 11.3 mg/100 ml. 1,25-dihydroxy vitamin D: 1 pmol/l ≈ 4 pg/ml. Urine calcium: 1 µmol/l glomerular filtrate ≈ 40 ng/ml. Urine phosphate: 1 µmol/l glomerular filtrate ≈ 31 ng/ml. Tubular reabsorption of calcium: 1 mmol/l glomerular filtrate ≈ 4 mg/100 ml. Tubular reabsorption of phosphate: 1 mmol/l glomerular filtrate ≈ 3.1 mg/100 ml.

Comment

The data indicated that the hypercalcaemia was mainly resorptive in origin and that, after treatment with flurbiprofen, serum calcium concentration fell to within the normal range largely because of a reduction in bone resorption. Raised serum concentrations of 1,25-dihydroxy vitamin D are generally associated with increased absorption of calcium from the gastrointestinal tract,² and 1,25-dihydroxy vitamin D is also a potent bone resorbing agent. Raised concentrations of 1,25-dihydroxy vitamin D have been reported in patients with sarcoidosis and hypercalcaemia, and it has been suggested that corticosteroids relieve hypercalcaemia by lowering these concentrations and hence reducing calcium absorption.³ Steroids may also directly reduce synthesis of prostaglandin.⁴

Plasma concentrations of 1,25-dihydroxy vitamin D in our patient were raised before and after treatment, and we therefore do not believe that increased production of 1,25-dihydroxy vitamin D was causing increased bone resorption. Prostaglandins, particularly of the E series, are potent bone resorbing agents and have been thought to be responsible for hypercalcaemia associated with some soft tissue malignancies.⁵ Although we were unable to measure production of prostaglandin directly, our data are best explained by increased absorption of bone induced by prostaglandin and occurring independently of changes in calcium absorption. The latter were caused by raised concentrations of 1,25-dihydroxy vitamin D and were rapidly corrected by flurbiprofen.

Prostaglandin synthetase inhibitors may be useful in patients with sarcoidosis and hypercalcaemia, particularly when the catabolic effects of corticosteroids are to be avoided.

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(Accepted 18 August 1983)

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Testicular pain caused by mazindol

Testicular pain is an unusual adverse effect of a drug. We provide details of eight voluntary reports sent to the Australian and Netherlands national centres for monitoring drug safety attributing this symptom to the anorectic drug mazindol. This drug is marketed in Australia as Sanorex and in the Netherlands as Teronac.

Case reports

AUSTRALIA

Case 1—In 1975 a 37 year old diabetic man weighing 93.7 kg took mazindol 1 mg daily. Within 48 hours he developed pain in the testes, which retracted and became round and hard. He also experienced dysuria with a poor erratic stream. He recovered when he stopped taking the drug. He took mazindol again on four occasions and each time the symptoms recurred within 24 hours.

Case 2—In 1976 a 57 year old man weighing about 95 kg was taking alprenolol hydrochloride for angina and prochlorperazine maleate for Menière's syndrome. His prostate was moderately enlarged. He then also took mazindol 1 mg daily and after about one month developed painful testes, which were sore to touch, and dysuria. The symptoms resolved within 24 hours of stopping the drug and recurred within 12 hours on each of three occasions when he took it again.

Case 3—In 1978 a healthy 38 year old man weighing about 73 kg took one mazindol tablet daily for more than a month. Four hours after taking the first tablet he experienced testicular pain. He complained of minor swelling in his testes when voiding and of a seminal discharge each time he had a bowel action. The problem was treated as prostatitis but resolved completely when mazindol was stopped. Rechallenge led to recurrence. Details of this patient have been published.¹

Case 4—In 1982 a 34 year old man weighing 96 kg and not taking other drugs took mazindol 2 mg daily. After taking the first tablet he experienced very severe pain in his testes and groin. Symptoms began about two hours after taking the drug and resolved within eight hours. They recurred when he took it on each of the next two days. About 14 days later he again took the drug with the same result. He also complained of "penile shrinkage" and possibly had erectile impotence each time he took mazindol.

Case 5—In 1983 a 29 year old man weighing 115 kg was taking allopurinol for hyperuricaemia. He then also took mazindol 0.5 mg daily for one week and then 1.0 mg daily for about two months. After about eight weeks of treatment with mazindol he developed impotence, sore testes, and non-organic spontaneous ejaculation that resolved promptly when he stopped taking the drug. He had no history of sexual dysfunction.

NETHERLANDS

Case 6—In 1977 a 36 year old man was reported to have developed a "prostatitis like" condition with painful micturition, painful testes, and lower abdominal pain after taking mazindol for obesity. Details of dosage were not provided. The condition occurred on each of three occasions when he took the drug. Investigation of his urine showed no sediment, and culture gave a negative result.

Case 7—In 1977 a 40 year old man took mazindol 1 mg twice daily for about 10 days. About one hour after taking each dose he developed tender testes, which remained so on each occasion for about two hours.

Case 8—In 1977 a 49 year old man took mazindol 1 mg daily for four days. Within one hour of taking each tablet he experienced an urge to urinate and pain in the perineal region "as in prostatitis." The pain lasted for about 12 hours. He also developed nervousness and a sensation of heavy legs. When he again took mazindol 1 mg four days later the symptoms recurred. Urine testing showed no abnormalities.

Comment

Voluntary reports to national centres for monitoring drug safety are sometimes deficient in relevant details. We believe, none the less, that these case reports show adequately that mazindol may occasionally cause testicular pain. Sexual impotence, dysuria, and difficulty in initiating micturition have been attributed to mazindol, and a solitary episode of testicular pain was recorded in a clinical trial of the drug.²

The importance of the case reports presented here is that an association with drug use was apparently not always obvious. Repeated rechallenge occurred in four cases and rechallenge in two cases. The urine of two patients was investigated, and one other patient was treated for prostatitis. We believe that this adverse effect deserves to be better known.

Mazindol is said to block the reuptake of noradrenaline by central nervous system neurones.³ There is little published information about the drug's effect on peripheral neurones and muscles. We have not speculated on a possible mechanism by which the drug might cause testicular pain.

We acknowledge the contributions of the doctors in Australia and the Netherlands who reported these cases. John McEwen thanks Mr L J Willett, Director General of Health, Commonwealth of Australia, for permission to publish this paper and the members of the Adverse Drug Reaction Advisory Committee for assistance in its preparation.

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(Accepted 26 August 1983)

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Fulminant human T cell leukaemia lymphoma masquerading as acute viral infection of the nervous system

Human T cell leukaemia lymphoma virus has been associated with acute T cell lymphomas in black American,¹ Japanese,² and West Indian patients.^{3,4} We report on a Jamaican patient with lymphoma associated with human T cell leukaemia lymphoma virus, who presented with features strongly suggestive of an overwhelming acute viral infection of the central nervous system.

Case report

A 32 year old black man, born in Jamaica but resident in London, presented on 18 August 1982 with a history of fever, nausea, headaches, dizziness, photophobia, unsteadiness, and double vision for about one week. His previous general health had been excellent. A blood sample showed haemoglobin concentration 15.5 g/dl and white cell count $8.2 \times 10^9/l$, with 55% neutrophils, 4% monocytes, and 41% lymphocytes including many "atypical lymphocytes." A blood film was reported as "suggestive of viral infection," and a Paul-Bunnell test yielded a negative result. There were no abnormal signs, and he was sent home.

On 21 August he was admitted to St Stephen's Hospital, London, with a temperature of 38°C; he was drowsy and disorientated. The only other ab-

normal physical signs were neck stiffness and one enlarged inguinal lymph gland. Investigations showed white cell count $24.7 \times 10^9/l$, with 75% "atypical lymphocytes"; cerebrospinal fluid clear with protein concentration 0.9 g/l, white cells $0.07 \times 10^9/l$ with 70% "atypical lymphocytes," red cells $0.24 \times 10^9/l$, and no organisms seen or cultured; and serum calcium concentration 3.8 mmol/l (15 mg/100 ml) (normal 2.2-2.6 mmol/l (8.8-10.4 mg/100 ml)). Blood cultures and numerous other microbiological investigations yielded negative results. He became comatose, developed terminal pneumonia, and died on 25 August.

A bone marrow aspirate on 24 August had shown pronounced lymphocytic infiltration. The lymphocytes comprised 66% of the nucleated marrow cells and were of atypical morphology with irregular convoluted or clefted nuclei, many of which contained prominent nucleoli. The cells had plentiful basophilic cytoplasm, which showed acid phosphatase activity. These features were consistent with a T cell infiltration, considered at the time to be a reaction to a viral infection.

Postmortem examination showed abdominal lymphadenopathy, which was especially severe in the para-aortic and ilioacaecal regions. The meninges were intensely congested, and confluent bronchopneumonia was present. Cultures of tissues were negative for cytopathic viruses. Histological examination of the abdominal lymph nodes, spleen, lungs, liver, stomach, heart, and kidneys showed infiltration by pleomorphic lymphoid cells; the nuclei were convoluted, sometimes bizarre, with several nucleoli and many mitoses. The brain showed infiltration of the leptomeninges and, along the brain, perivascular spaces.

Serum collected on 22 August 1982 was strongly positive for antibodies to human T cell leukaemia lymphoma core and membrane antigens.⁵ Serum collected in June 1983 from a West Indian girl who had had sexual intercourse with the patient was negative for antibodies to human T cell leukaemia lymphoma virus (table).

Results of serological tests for antibodies to human T cell leukaemia lymphoma virus (HTLV)

	Immunofluorescence* (%)	Syncytium inhibition†	Neutralisation‡
Patient	89	100	1250
Female contact	0	<10	<10
Positive controls	87	30	250
Negative controls	0	<10	<10

*Percentage of cells fluorescing for HTLV internal antigens (p19 and p24) using a one in 10 serum dilution in an indirect immunofluorescence test on acetone fixed C91/PL HTLV infected T cells.⁶

†Reciprocal titres of syncytium inhibition⁷ specific for viral membrane antigen of HTLV type I, the serotype prevalent in Japan and the West Indies.

‡Reciprocal titres for plaque neutralisation of vesicular stomatitis virus pseudotypes bearing HTLV-I envelope antigens.

§A West Indian immigrant patient with typical manifestation of adult T cell leukaemia lymphoma.

Comment

The predominant clinical and laboratory findings in our patient suggested a severe acute viral meningoencephalitis; the course of the disease was remarkable, with death occurring within three weeks of the onset of his first symptom. A previous British report of lymphoma associated with human T cell leukaemia lymphoma virus in black West Indian patients described distinct clinical and pathological features including an aggressive malignant disease in young adulthood, rising peripheral lymphocyte counts with abnormal forms, hypercalcaemia, and the presence in serum of antibodies to the virus.³ These features were all ultimately observed in our patient. The diagnosis, however, was considered only after he had died, when unfixed tissues were no longer available for full T cell marker studies.

Acute T cell leukaemia lymphoma should be considered in any black West Indian patient who presents with an unusual febrile illness and has atypical lymphocytes in the peripheral blood and hypercalcaemia. Serum should be tested for antibodies to human T cell leukaemia lymphoma virus and T cell marker studies should be promptly carried out. Our patient was a promiscuous heterosexual, and it is perhaps reassuring that the one girl friend who could be traced showed no serological evidence of infection with human T cell leukaemia lymphoma virus.

We thank Dr J Collins for permission to report his case; Dr A Lawrence for providing serum from the female contact; Dr P Morgan-Capner at King's College Hospital, London, for carrying out virological screening studies; Dr M R Crompton at St George's Hospital, London, for examining the brain; and Dr R Cheingsong-Popov and Mr P Clapham at the Institute of Cancer Research for help with the assays of human T cell leukaemia lymphoma virus.

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