Acute cerebral oedema induced by methotrexate

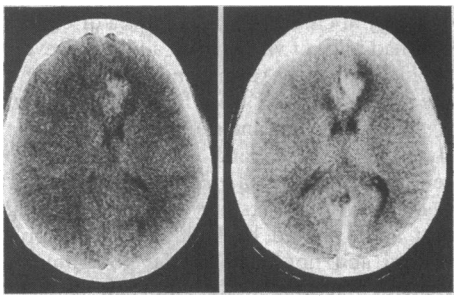
Drs P J HUGHES and R J M LANE (Regional Neurosciences Unit, Charing Cross Hospital, London W6 8RF) write: Many reports document a variety of neurological complications resulting from both intravenous and intrathecal administration of methotrexate, but acute cerebral oedema is not among them. We describe a patient with acute myeloid leukaemia who developed cerebral oedema after treatment with intrathecal methotrexate.

A 23 year old Jamaican woman was admitted with a diagnosis of acute myeloid leukaemia (M3). cytarabine 100 mg, hydrocortisone 100 mg, and methotrexate 12·5 mg were administered intrathecally. Systemic chemotherapy consisted of daunorubicin 85 mg intravenously for three days, cytarabine 170 mg intravenously for seven days, and lomustine 340 mg orally for one day. After 36 hours the patient became unwell, complaining of increasing headache and neck stiffness. A computed tomogram of the head showed an irregular 2·5 cm deep right frontal haematoma and considerable cerebral swelling. She was given mannitol and dexamethasone and within 12 hours showed a dramatic improvement. She remained neurologically well, and a repeat computed tomogram seven days later showed an even larger haemorrhagic area in the right frontal lobe but with no cerebral oedema. A third head scan, five weeks after the initial event, was normal.

Acute reactions to intrathecal methotrexate occur within hours to days, and the most common is arachnoiditis.[1] Intravenous methotrexate may cause acute neurotoxicity, and in patients predisposed to increased intracranial pressure by the presence of brain metastases or advanced leukaemia of the central nervous system high dose methotrexate intravenously may precipitate an acute episode of cerebral oedema.[2] As this toxicity has not been reported in patients with normal brains (and neither the Committee on Safety of Medicines nor the manufacturers know of any cases) the pathogenesis of the oedema is presumed to be mediated in part by lysis of tumour cells within the central nervous system.[2]

Our patient had acute myeloid leukaemia without cerebral disease but developed acute cerebral oedema after intrathecal methotrexate treatment. The haemorrhage identified in the first head scan was almost certainly incidental and unlikely to have been responsible for the clinical picture, since even though it subsequently increased in size the patient improved symptomatically after reduction of cerebral oedema with mannitol and steroids.

The pathogenesis of the cerebral oedema may be related to axonal swelling, as this is an early finding in methotrexate encephalopathy,[3] suggesting that the drug has a direct toxic effect on neurones. Intrathecal methotrexate should therefore be used cautiously in the absence of cerebral disease in acute myeloid leukaemia.



Left: haematoma and cerebral swelling after administration of intrathecal methotrexate. Right (seven days later): enlarged haemorrhagic area but disappearance of cerebral oedema

We thank Professor Barrett for permission to report this case.

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2 Bleyer WA. Neurologic sequelae of methotrexate and ionizing radiation: a new classification. *Cancer Treat Rep* 1981;65:89-98.
3 Rubinstein LJ, Herman MM, Long TF, Wilbur JR. Disseminated necrotizing leukoencephalopathy; a complication of treated central nervous system leukemia and lymphoma. *Cancer* 1975;35:291-305.

Retroperitoneal fibrosis in a patient with macroprolactinoma treated with bromocriptine

Drs A HERZOG, H MINNE, and R ZIEGLER (Department of Internal Medicine I, Ruprecht-Karls-Universität, Heidelberg, West Germany) write: A 46 year old man suffering from a prolactin secreting macroadenoma complicated by severe loss of vision was treated with bromocriptine 40-100 mg/day for two and a half years. During the past 10 months the highest dose was administered. These high doses were necessary to suppress further growth of the prolactinoma. The only other drugs our patient received were nicotinic acid 300 mg/day in combination with pentifylline 600 mg/day and testosterone 250 mg intramuscularly every third week. The erythrocyte sedimentation rate was found to be raised after 28 months of treatment with bromocriptine. Two months later we found raised creatinine and urea concentrations, and ultrasonography of the kidneys showed bilateral hydronephrosis. An abdominal computed tomogram suggested retroperitoneal fibrosis, which was subsequently confirmed at laparotomy. The fibrotic masses were removed; histological examination showed fibrosis with predominant lymphocytic inflammatory infiltration. Long term treatment with prednisolone was started. Bromocriptine was discontinued and lisuride substituted. Twelve months after surgery the erythrocyte sedimentation rate, kidney function, and abdominal ultrasonography showed no recurrence of retroperitoneal fibrosis.

We believe that in our patient the ergot derivative bromocriptine induced retroperitoneal fibrosis. Our observation agrees with recent reports of retroperitoneal fibrosis in three patients after long term treatment with bromocriptine for Parkinson's disease with doses of 30-140 mg/day.[1-3] Since high dose treatment with bromocriptine appears to bear the risk of severe fibrotic reactions a regular screening programme, including measurement of erythrocyte sedimentation rate and ultrasonography, has to be considered in patients treated with doses higher than 30 mg/day.

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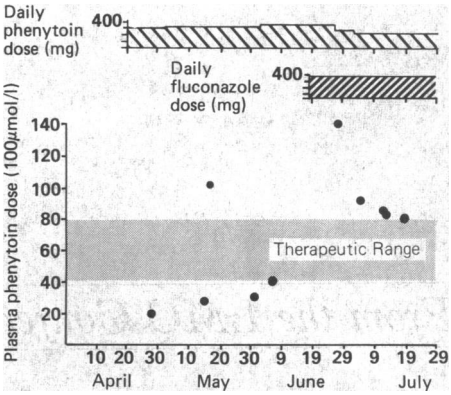
2 Bowler JV, Ormerod IE, Legg NJ. Retroperitoneal fibrosis and bromocriptine. *Lancet* 1986;ii:466.
3 Ward CD, Thompson J, Humb MD. Pleuropulmonary and retroperitoneal fibrosis: case report. *J Neurol Neurosurg Psychiatry* 1987;50:1706-7.

Fluconazole and phenytoin: a predictable interaction

Mr ANDREW S MITCHELL (Department of Clinical Pharmacology) and Dr J T HOLLAND (Department of Neurology, Royal Newcastle Hospital, Newcastle, New South Wales, Australia 2300) write: A 60 year old man with cryptococcal meningitis was started on oral phenytoin 300 mg/day as prophylaxis against fits; the dose was adjusted to produce a therapeutic steady state serum concentration (see figure). After the failure of intravenous amphotericin B and oral flucytosine oral fluconazole 400 mg/day was substituted. Within two days the patient complained of dizziness and developed nystagmus and profound ataxia. Phenytoin toxicity was confirmed (serum concentration 140 μmol/l) and the dose was reduced, with rapid resolution of the clinical signs of toxicity and return of the serum phenytoin concentration to therapeutic values, allowing continuing combination therapy.



Effect of fluconazole 400 mg on plasma phenytoin concentration and daily dosage adjustments

Fluconazole, a new oral triazole drug structurally and pharmacologically related to the imidazole antifungal agents, was recently approved for marketing in the United Kingdom. Although fluconazole itself has not been reported to inhibit phenytoin metabolism, strong circumstantial evidence suggests that this patient's phenytoin toxicity was the result of such an interaction.

The imidazole antifungal agents act by inhibiting the fungal demethylation of lanasterol to ergosterol, which is essential for fungal cell wall integrity.[1] The similarity of this system to the human liver's cytochrome P450 enzyme system (responsible for metabolising drugs such as cyclosporin, phenytoin, phenobarbitone, warfarin, and antipyrine) probably explains the increased serum concentrations of these drugs when given with ketoconazole or miconazole. Fluconazole is more selective for fungal cytochrome P450.[2] At 50 mg/day for seven days it did not affect antipyrine metabolism[3] (a recognised non-invasive marker of human cytochrome P450 activity and an accepted predictor of hepatic metabolism drug interactions, particularly phenytoin and warfarin) and at 100 mg/day for 14 days it did not affect serum concentrations of cyclosporin.[4]

We suggest, however, that this selectivity is lost when higher doses are used. At 200 mg/day for five days fluconazole has interacted with warfarin.[5] Therefore at 400 mg/day we suggest that fluconazole inhibited the hepatic metabolism of phenytoin in our patient, resulting in raised serum phenytoin concentrations and clinical signs of phenytoin toxicity. Fluconazole appears to show a dose related inhibition of the human cytochrome P450 enzyme system.

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2 Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. *Antimicrob Agents Chemother* 1988;32:1-8.
3 Purba HS, Back DJ. Effect of fluconazole (UK-49,858) on antipyrine metabolism. *Br J Clin Pharmacol* 1986;21:603P.
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5 Isalska BJ, Standbridge TN. Fluconazole in the treatment of candidal prosthetic valve endocarditis. *Br Med J* 1988; 297:178-9.

Correction

Prevalence of reflex anal dilatation

A printer's error occurred in the letter by Dr Margaret A Lynch (29 April, p 1179). In true reflex anal dilatation there is also dilatation of the internal sphincter usually up to 2-3 cm, not 2·3 cm as published.