Drug Points

Acute cerebral oedema induced by methotrexate

Dr 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 frontotemporal haematoma and considerable cerebral swelling. She was given mannitol and dexamethasone and at 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 frontotemporal 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. 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. 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 by factors present in the central nervous system.

Our patient had acute myeloid leukaemia without central 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, 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.

Retroperitoneal fibrosis in a patient with macroprolactinoma treated with bromocriptine

Dr A HERZOG, H MINNE, and R ZIEGGLER (Department of Internal Medicine I, Ruprecht-Karls-Universität, Heidelberg, West Germany) write: A 46 year old man suffering from a polyoid macroprolactinoma 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 pentifyline 600 mg/day and a multivitamin preparation 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, but histological examination showed fibrosis with predominant lymphocytic inflammatory infiltration. Long term treatment with prednisolone was started. Bromocriptine was discontinued and lurasidone 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.

We conclude that 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 20 mg/day.

References