symmetrical periventricular hypodense areas, which did not enhance with contrast. The encephalopathy was considered to be treatment-related and therapy was withdrawn. There was continued deterioration and the patient died without disease recurrence 6 months later.

Immediate postmortem examination of the neuraxis confirmed appropriate placement of the catheter tip and showed a swollen brain, with diencephalic compression and bilateral tentorial herniation. Coronal sections of the cerebral hemispheres revealed extensive symmetrical areas of yellow and chalky-white discolouration, occupying the periventricular regions and most of the centrum semi-ovale. Similar foci of necrosis were evident in the corpus callosum, the white matter of the temporal lobes, cerebellum and spinal cord funiculi. The cortical ribbon was essentially unremarkable, but the basal ganglia were pale and poorly defined. Atrophy of the head of the right caudate nucleus was noted.

Histopathology (Fig. 1) showed widespread coagulative necrosis and a variety of changes in the microvasculature of the brain, including thickening of vessel walls, with hyalinisation and/or perivascular fibrosis and cuffing by lymphocytic cells.

The course and pathology exemplify methotrexate neurotoxicity, with the pathogenesis remaining uncertain [6, 7]. It is postulated that radiation damages vessels, leading to oligaemia, with potentiation in the toxic effects of the methotrexate or, by disrupting the blood–brain barrier, allowing large amounts of drugs to reach the white matter [6]. However, the present case is unusual in that the intrathecal instillations preceded cranial irradiation. A second remarkable feature is the extent and severity of the necrosis, occurring maximally in tissues bathed in CSF, which include the spinal cord, in contrast to previous reports [6]. This neuro-anatomical distribution suggests that methotrexate concentration in the spinal fluid is an important factor in determining the severity of the necrosis.

In seeking to identify factors which may have caused extraordinarily high concentrations of the drug in CSF pathways, we considered the role of direct intraventricular instillation, but remain unaware of kinetic studies that would incriminate such a mechanism as opposed to the more conventional translumbar intrathecal administration; catheter misplacement could not be invoked in this instance. It is also possible that active meningeal disease, which may have impaired clearance of methotrexate from the spinal fluid, may have led to an extraordinarily high concentration of the drug along these pathways.

Finally, the contributing role of radiation also remains controversial. However, it has previously been noted that encephalopathy can develop at the time of irradiation in patients with active meningeal disease treated with a sequence of intrathecal methotrexate followed by cranial irradiation [8]. It is noteworthy that prior cranial irradiation is not an absolute prerequisite for the development of methotrexate-induced encephalopathy [9], although such cases are rare. These studies lead us to conclude that CSF concentrations of methotrexate play a role in the development of this form of encephalopathy in certain instances and that intraventricular administration of methotrexate may be particularly hazardous if given in the presence of active meningeal leukaemia.

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Influence of Dexamethasone Dose on the Control of Chemotherapy-induced Nausea and Vomiting

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DURING THE PAST 10 years there have been significant advances in the management of chemotherapy-induced emesis. Combination antiemetic therapy is now well established, even though the contribution of individual drugs is often poorly defined. Dexamethasone has antiemetic properties [1], and enhances the efficacy of metoclopramide [2], ondansetron [3] and other agents [4]. However, the optimum dose of corticosteroid which needs

to be given at the time of chemotherapy is not known. Some evidence exists for a dose-response relationship [5] but this has not been confirmed.

Most antiemetic studies concentrate on the control of cisplatin-induced emesis, but chemotherapy-induced vomiting is still a major problem for some non-cisplatin treatments, particularly when treatment is given as an outpatient. Our aim was to identify a simple outpatient regimen for control of chemotherapy-induced emesis and to compare the contribution of dexamethasone at low or high dose.

57 consecutive patients receiving emetogenic non-cisplatin-based chemotherapy for a variety of malignancies were studied in a double-blind, randomised parallel study. Patients received the antiemetic combination haloperidol 3 mg orally, lorazepam 2 mg orally and dexamethasone 5 mg or 20 mg intravenously over 10 min (SAD regimen) immediately before the administration of chemotherapy. Patients who were receiving chemotherapy as outpatients delayed taking the lorazepam until arriving home. The doses of haloperidol and lorazepam were reduced by 50% in patients over 70 years of age or less than 50 kg in weight. On days 2–5, patients were prescribed metoclopramide 20 mg orally to be taken 4-hourly as required. All patients received highly emetogenic chemotherapy including doxorubicin (n = 37), intravenous cyclophosphamide 1000 mg or more (n = 7), ifosfamide (n = 2) or carboplatin (n = 11). Assessment of efficacy was by a patient-completed diary recording nausea, vomiting, appetite, drowsiness and overall acceptability of treatment.

The SAD regimen was highly effective in controlling nausea and vomiting. Complete control of emesis during the first 24 hours following the first course of chemotherapy was achieved in 46/57 (81%) patients and complete control of nausea reported by 41 (72%) patients. There was no significant difference in efficacy between the two doses of dexamethasone (Fig. 1). Major control of emesis (0–2 vomits) was achieved in 92% and 94% of patients with the 5 mg and 20 mg doses, respectively. Nausea and vomiting beyond the first 24 h was more of a problem. Complete control of emesis throughout the 5-day study period occurred in only 28 (49%) patients and complete control of nausea was achieved in 23 (40%) patients. 6 (11%) patients (4 on 5 mg and 2 on 20 mg dexamethasone) experienced severe (> 4 emetic episodes per day) and/or continuous nausea requiring a change in antiemetic policy for subsequent chemotherapy courses. The main "side-effect" of the antiemetic regimen was drowsiness. 53 patients (93%) reported significant drowsiness but this was rated as "unacceptable" by only 6 patients (11%). Analysis of results in courses 2–6 of treatment showed consistent results with no loss of antiemetic control for the later chemotherapy courses.

The SAD antiemetic regimen gives safe, practical and effective antiemetic cover for the first 24 h after emetogenic non-cisplatin-based chemotherapy. There was no difference in efficacy between the two doses of dexamethasone. Limited experience with the SAD regimen in patients receiving cisplatin indicated that this was inadequate for these patients [6], in whom high-dose metoclopramide or ondansetron are more appropriate and effective. The 5-HT3 antagonists are an undoubted advance in the management of chemotherapy-induced emesis but, in our experience, these expensive drugs are not routinely necessary for non-cisplatin chemotherapy and should be reserved for patients who do not achieve good control with the SAD regimen.

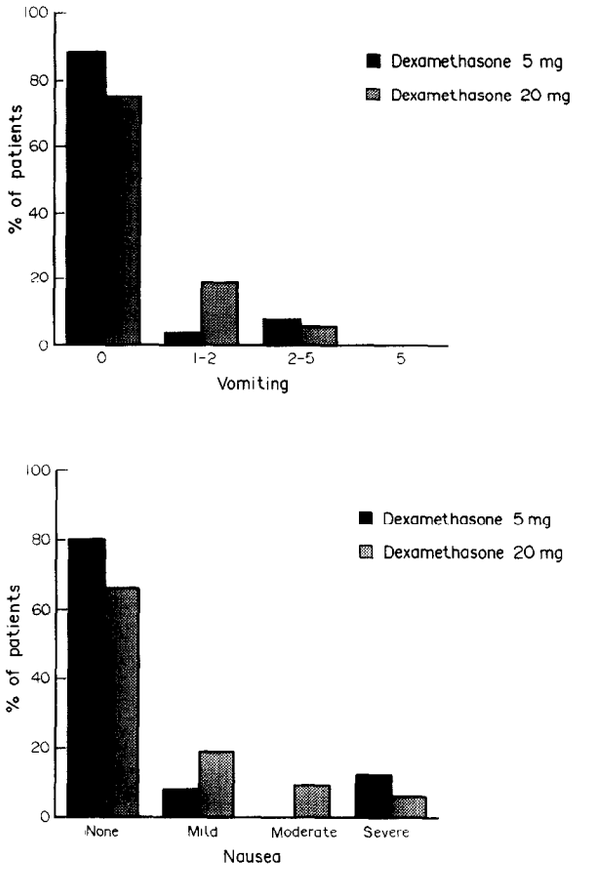

Fig. 1. Comparison of the number of emetic episodes (a) and nausea grade (b) during the first 24 h in patients receiving low-dose (5 mg) and high-dose (20 mg) dexamethasone.

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