patients with frontal, temporal, parietal, thalamic or mesencephalic brain tumours. Extraaxial masses with compression of the basal ganglia appeared to be more common than infiltrating lesions, whereby basal tumours may create Parkinsonism by impairment of the tissue perfusion in the striatopallidal region by the tumour oedema. The signs caused by the various tumour locations are not significantly different; bradykinesia and rigidity are the most common, rarely also rest tremor. Compression or infiltration of the midbrain or the corpus striatum as a possible reason of the syndrome were revealed in our patient by CT and MRI; compression of the callosal connection can not be excluded in our case but CT and MRI did not support this explanation. The incidence of a Parkinsonian syndrome in the population is 0.1–0.5% and the incidence of low grade glioma is 0.5–0.2%, therefore the changes of both diseases occurring at the same time is smaller than 0.005–0.1%. The response to medication does not contradict this and has been reported by other studies. We therefore favour another explanation.

In 1955 Travis demonstrated that a unilateral lesion of the SMA caused by a transient contralateral grasp reflex and a moderate bilateral hypertonia in the monkey. Schell et al. showed the connections of the basal ganglia to the SMA. Investigations of the “Bereitschaftspotential” in patients with unilateral lesions of the SMA supported the idea that the SMA is involved in the initiation of voluntary movements and in the temporal organisation of sequential tasks. Recently Benecke et al. and Dick et al. suggested that some motor disturbances in patients with Parkinsonian’s disease are possibly caused by an impairment of this basal ganglia output to the SMA. Furthermore Dick described a patient with infarction of the right SMA showing a deficit in programming simultaneous and sequential movements in both arms with a preponderance of the contralateral extremities. These findings are similar to those in patients with “idiopathic” Parkinson’s disease and could be found also in our patient at the beginning of the illness. Therefore we believe that in rare instances lesions of one SMA may lead to a Parkinsonian syndrome which may itself be due to an impairment of the basal ganglia output to the SMA.

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Extrapyramidal reactions to anti-inflammatory drugs

Sir: The association between the recognised dopamine receptor blocking agents such as the phenothiazines and acute dystonic reactions is well known and these reactions are readily recognised and treated by most physicians. A review of the published literature shows that non-steroidal anti-inflammatory drugs (NSAIDs) have only rarely been implicated in causing extrapyramidal reactions. We present evidence suggesting that such reactions occur more commonly than is generally appreciated.

A 51 year old man who took indomethacin 200 mg/day for intermittent acute gout was also prescribed azapropazone 1-2 g/day when an attack failed to respond to the indomethacin alone. He did not take any other medication. Two days after starting the azapropazone he suffered an oculogyric crisis, complaining of retrocollis with upward deviation of his eyes. This lasted about an hour and was witnessed and described by his general practitioner. The following day he suffered another oculogyric crisis after taking another dose of his medication. Both drugs were discontinued and there was no recurrence of the neurological symptoms although the gout worsened temporarily. Currently, neurological examination is normal. Investigations including measurement of serum caeruloplasmin and copper concentrations are normal.

NSAIDs frequently cause adverse effects on the central nervous system. These include, for instance, “confusion” and ataxia with indomethacin. However, extrapyramidal reactions are only reported infrequently. Mefenamic acid has been implicated in causing an acute dystonic reaction and a generalised dyskinesia with dystonic features. A schizophrenic patient was reported to develop bilateral ballistic movements after starting ibuprofen; these resolved on withdrawal of the drug. Sulindac has been claimed to exacerbate the extrapyramidal features of Parkinson’s disease in a patient who was receiving a levodopa/carbidopa preparation but another NSAID, diflunisal, was said to improve Parkinsonian disability in six patients. We have been unable to find any published reports of indomethacin- or azapropazone-related extrapyramidal reactions. However, a review of reports of indomethacin-related adverse reactions to the Committee on Safety of Medicines (CSM) shows nine listings under various headings encompassing extrapyramidal disorders quite separately from nine more than were listed under the heading, “tremor” (personal communication—CSM). Adverse extrapyramidal reactions to azapropazone have not previously been reported to the CSM.

The close temporal association between starting the azapropazone and the onset of the dystonic reaction suggests that this drug was responsible for precipitating the reaction. In view of the reports to the CSM linking indomethacin with extrapyramidal reactions, it seems possible that the azapropazone interfered with the protein-binding of indomethacin, allowing more of it to cross the blood-brain barrier. Prostaglandin synthetase inhibitors, such as NSAIDs have been shown to alter catecholamine turnover within nervous tissue. The mechanism by which NSAIDs effect their extrapyramidal side-effects is not known but, by analogy with the phenothiazines and butyrophenones, an action on dopaminergic function may be important.

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Use of mefloquine in epileptic patients

Sir: I consider the following observation to be of particular interest.

A 38 year old man began to have complex partial seizures when aged 15 years. No cause was found to explain this epilepsy. Treatment with carbamazepine (1.2 g/day) and sodium valproate (1 g/day), reduced the frequency of his seizures to about three per month. Plasma levels of anti-epileptic drugs confirmed compliance (carbamazepine: 6-2 g/l and sodium valproate: 82 g/l, on the 22 June 1987.

Having planned to spend his holidays in Kenya, he was advised to take mefloquine to prevent malaria (250 mg tablet per week).

The day after he took the first dose (26 June), he had three partial seizures. Twenty-four to 72 hours after he took the other regular doses of mefloquine, several partial seizures and three generalised seizures occurred. He was hospitalised before taking the last dose (on 20 August). We observed then three partial seizures on the same morning, needing IV injection of clonazepam.

Epileptic seizures, or the aggravation of known epilepsy, have never been reported with this dose by the manufacturers as a side effect of treatment of mefloquine; only one case has been reported (1 000 mg/dose) with an acute brain syndrome.

During hospitalisation, we studied the kinetics of anti-epileptic drugs after the patient took his last dose of mefloquine. We observed a reduction of biological half-life of sodium valproate (5-65, normal: 8-20 hours), though that of carbamazepine was unchanged. Consequently, it is possible mefloquine accelerated sodium valproate metabolism, both having the same hepatic metabolism. This observation should lead to a careful administration of mefloquine to epileptic patients, especially when they are treated by sodium valproate.

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Midazolam in the treatment of epileptic seizures

Sir: Midazolam (Dormicum) is a benzodiazepine used for the premedication and induction of anaesthesia. Its diazepine nucleus is fused with a nucleus of the imidazol group having a basic azo in position 2, which allows the formation of water soluble salts. Its antiepileptic properties have been most recently studied on interictal spikes and on status epilepticus.

Fourteen patients, nine females and five males, from 19 to 72 years old, suffering from subsequent repeated epileptic seizures were treated with 0-2 mg/kg intramuscular midazolam. We performed 18 interventions: three for complex partial seizures, nine for tonic-clonic seizures, two for myoclonic, one for tonic, one for atonic seizures, and two for partial motor prolonged seizures. The clinical status (heart and respiratory rate, blood pressure, waking state and clinical evolution of seizures) was followed during one hour after the injection. In nine cases, classical EEG was recorded for the whole of this period.

A slight decrease of blood pressure (15%) was noted in only three cases with a slower heart rate (10%) in one of them. The disappearance of the epileptic seizures was observed in all cases, 5 to 10 minutes after the injection. This response was complete in 15 interventions and partial in three.

On the nine recorded EEGs, the epileptiform activities had disappeared in 10 min in five cases, but reappeared at the end of the recording in one of them. They diminished significantly in one cases and remained unchanged in one case. The EEG changes were concomitant with the clinical improvement. The response to this treatment was stable in all but four cases, when presented with a relapse within the first 24 hours after the injection (two after 3 hours, one after 4 hours and one after 18 hours), two of which were then treated by a second injection of midazolam and responded very well.

Our results are comparable with those of Egli and Albani and Jawad et al., reporting respectively 12 complete clinical responses on 15 cases of tonic-clonic and complex partial seizures, and 21 complete responses on 26 cases. In our study, the mean of complete clinical responses reached 82%.

Compared with other benzodiazepines, midazolam is used in emergency for iterative epileptic seizures, midazolam offers two advantages. First, its action is rapid and effective by the intramuscular route. Jawad et al. have compared intramuscular midazolam with intramuscular and intravenous diazepam on the ability to reduce interictal spikes. It appears that 10 or 15 mg intramuscular midazolam is as effective as 20 mg intravenous diazepam, while 10 or 15 mg intramuscular midazolam is more effective than 10 mg diazepam administered, intramuscularly or intravenously. The second advantage of midazolam is its short half life (1 to 2 hours), as compared with diazepam, lorazepam and clonazepam which have values from 15 to 21 hours. This short half life allows us to exclude from the number of relapses the patient who presented with a seizure after 18 hours, as we consider this seizure as a new event.

In conclusion, these results indicate that midazolam is an effective treatment for repeated epileptic seizures. In addition, this drug may be easily and safely administrated by the intramuscular route.

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