Letters

Neuroleptic malignant syndrome associated with metoclopramide

Sir: The neuroleptic malignant syndrome is a rare idiosyncratic drug reaction comprising muscular rigidity, altered consciousness and autonomic dysfunction, which has been described following the administration of major tranquillisers such as butyrophenones, thioxanthenes and phenothiazines.1 2 It is thought to be due to dopamine receptor blockade in the basal ganglia and hypothalamus.2 We describe a patient who developed the neuroleptic malignant syndrome after metoclopramide therapy.

A 53-year-old Jamaican man was given 20 mg of metoclopramide by intramuscular injection for nausea during an acute illness characterised by pyrexia and productive cough. Three days later he noticed stiffness and weakness of his legs; over the next week he became increasingly immobile and tremulous, with difficulties in swallowing, speaking and breathing, and frequent bouts of sweating. On examination on admission to hospital he was agitated and sweaty but apyrexial. He had a sinus tachycardia of 120 beats/min and his blood pressure was 190/110 mm Hg. He was dysarthric and could not protrude his tongue. There was moderate bradykinesia and marked axial and limb rigidity, with a tendency to maintain a catatonic posture, and a coarse resting tremor at 6 Hz. A full blood count was normal; serum bilirubin and creatine kinase were elevated at 44 μmol/l and 440 μmol/l (normal <200) respectively. Hepatic enzymes, cerebrospinal fluid examination and computed tomography of the brain were normal. No phenothiazine metabolites or other drugs were detected in blood or urine.

Treatment with anticholinergic drugs and levodopa in doses of up to 2 g/day was ineffective. The patient's pulse and blood pressure fell to normal within 10 days of admission, and his neurological signs slowly resolved between two and six weeks after admission.

Metoclopramide is known to produce a number of extrapyramidal syndromes, such as acute, or more rarely chronic, dystonic reactions and mild drug induced parkinsonism.3 4 The autonomic and other neurological features of our patient's illness suggest a diagnosis of the neuroleptic malignant syndrome, as does the lack of response to dopaminergic and anticholinergic drugs.5 Abnormal liver function tests and elevation of serum creatine kinase concentrations often occur in the neuroleptic malignant syndrome.1 Pyrexia, leucocytosis, and stupor have been described in a number of previously reported cases, and there is an overall mortality of 20%, often due to respiratory failure.1 Although the neuroleptic malignant syndrome has not been reported before in association with metoclopramide administration, its occurrence could be expected in view of the dopaminergic activity possessed by this drug.6

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Catamenial exacerbation of action myoclonus: successful treatment with acetazolamide

Sir: Lance and Adams first described action (intention) myoclonus in 1963 as a syndrome following severe hypoxia. This consists of incapacitating lightning-like jerks induced by voluntary movements,1 and was later shown to be associated with consistently low cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.2 Successful treatment has been reported using l-5-hydroxytryptophan (5-HTP), valproic acid and clonazepam.2–4 Each of these drugs raises CSF 5-HIAA levels.

Methysgide, a serotonin receptor blocker, tends to increase the myoclonus.4 Hence it is believed that action myoclonus is an effect of serotonin insufficiency, presumably from damage to or dysfunction of the raphe nuclei.

I report a case of postanoxic action myoclonus that was effectively treated with 5-HTP, clonazepam and valproic acid. Premenstrually she suffered severe exacerbations. Acetazolamide produced prompt and marked improvement.

The patient is a 35-year-old woman who suffered prolonged hypoxia when aged 27 years during the excision of a polypoidal cyst. This resulted in a mild cognitive impairment, tonic-clonic and tonic seizures, and severe action myoclonus. While being treated with valproic acid, clonazepam, phenytoin and quinine her seizures were well controlled but her myoclonus was only modestly improved. She was confined to bed or her wheelchair and was unable to transfer herself or perform most self care. Her speech was often unintelligible because of myoclonus. Premenstrually her symptoms regularly worsened. At age 22 years 5-HTP and carbidopa were added to her regimen as phenytoin and quinine were discontinued. This resulted in marked improvement of her myoclonus and thus her functional ability. She was able to dress and feed herself, speak with much clearer, performed transfers, and to walk with assistance. Her seizures continued to be well controlled.

Premenstrually her speech was quiet, hypernasal and ataxic. She could speak in whole sentences with each breath and was understandable. Saccades were hypometric and symmetric gaze-evoked horizontal nystagmus was present. All limbs showed mild to moderate ataxia with intention tremor and rebound. Myoclonic jerks occurred infrequently in association with volitional movements. Deep tendon reflexes were normal and the plantar responses were downgoing. Her gait was markedly ataxic.

Beginning 2 days premenstrually and lasting for about 3 days she would return to her previous status. During an untreated exacerbation her speech markedly deteriorated. She could speak no more than two words per breath. Opsoclonus was present. At rest multifocal myoclonus occurred every few seconds. Intentional movements were profoundly contaminated by large amplitude myoclonic jerks. This was noted on seven consecutive cycles. Valproic acid levels were unchanged during these exacerbations. She was then placed on acetazolamide 250 mg, four...
times a day. Within a few hours she noticed improvement. She was able to perform her usual activities and stated that she felt 80% to 90% better. She started a 5 day course of acetzolamide at the onset of each exacerbation.

While taking acetzolamide her speech was no different from the postmenstrual state. Opsoclonus was absent. The myoclonic jerks were infrequent at rest and were markedly reduced in amplitude and incidence during intentional motion. Efficacy continued for five consecutive cycles without side effects. A double-blind placebo trial during the next menstrual period was aborted on the second day as she became bedridden with myoclonus. Several hours after starting acetzolamide she improved. The next menstrual cycle went smoothly with this medication. Valproic acid serum levels were unchanged with the addition of acetzolamide.

Catamenial exacerbation of action myoclonus has been described. The mechanism is not apparent. The patient previously described underwent bilateral ophthalmectomy and worsened. She improved with very high dose conjugated estrogen (Premarin 6-25 mg/day). Progesterone and acetzolamide were not administered. Declining progestrone levels prior to menstruation are known to increase seizure activity in some epileptics. Whether this plays a role in action myoclonus is uncertain.

Acetzolamide has failed to improve myoclonus in patients without catamenial exacerbations. However, it does elevate brain anticonvulsant concentrations, brain carbon dioxide levels and gamma amino butyric acid, all of which have antiepileptic effects. The impact on serotonin is unknown.

The mechanism of acetzolamide in this patient is likely to be by direct effect on the central nervous system or tissue anticonvulsant concentrations. Antagonism of hormones or another systemic physiologic change is also possible.

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Enophthalmos and metastatic carcinoma of the breast

Sir: Enophthalmos is an uncommon finding in neurological practice. It may be seen fol-
lowing orbital trauma, in patients with Horner's syndrome, facial hemiatrophy and in a small proportion of patients with orbital metastases from carcinoma of the breast. The latter association is recognised in ophthalmological practice but has not received much attention in the neurological literature. We describe a 66-year-old woman in whom enophthalmos was the presenting feature of a breast carcinoma.

A 66-year-old woman developed ptosis, enophthalmos, and diplopia 3 years before her present admission. At the same time the symptoms first appeared, computed tomography of the head and orbits revealed abnormal tissue behind the left eye. At another hospital a biopsy was taken from this area (via a left frontal approach) but the tissue obtained only revealed non specific changes and a definite diagnosis was not possible. Two years later she developed progressive weakness of both legs which appeared to respond to a course of methyl prednisolone. Over the months prior to her present admission she had become aware of blurred vision in the right eye. Vision in the left eye remained normal. Her general health was otherwise satisfactory and there was no significant past or family history. Examination revealed a left frontal craniotomy defect, the site of the previous orbital biopsy. Higher mental functions and speech were normal. She was able to stand only with support and to walk with the aid of a frame. The corrected visual acuities were VAR 6/18 and VAL 6/9. Colour vision was impaired in the right eye and there was a right relative afferent pupillary defect. The right optic disc was grossly swollen and there were haemorrhages and exudates. The left disc was normal. The right blind spot was markedly enlarged but the left visual field was full. There was left enophthalmos with narrowing of the palpebral fissure. Abduction and vertical movements of the left eye were restricted but a full range of ocular movement was present on the right. There was a mild facial diplegia. The remainder of the cranial nerves were normal. There was global wasting of the muscles of both legs. Upper limb strength was normal and reflexes were present. There was truncal weakness and moderate to severe global leg weakness particularly distally. Deep tendon reflexes were absent in the legs. The plantar responses were absent. Vibration was not perceived in the legs and the sense of joint position was

Fig Orbital CT scan showing abnormal enhancing tissue throughout left orbit and extending intracranially with retraction of the left globe.