Efficacy of a combination of sodium valproate and baclofen in Meige's disease (idiopathic orofacial dystonia)

Meige's disease is a bizarre, often disabling movement disorder of the elderly characterised by symmetric dystonic contractions of the orofacial muscles; at times other midline muscles such as the tongue and the palatopharyngeal, respiratory, and neck muscles may be affected.^{1,2} Although the spasms are often thought to be psychogenic in origin, there exists no convincing evidence that they represent a manifestation of a psychiatric disorder.¹ Similarly, there is little information on the pathophysiology of the disorder. Neophytides *et al*³ reported decreased cerebrospinal fluid γ -aminobutyrate concentrations in patients with adult-onset dystonia. If this reflects a reduction in central γ -aminobutyric-acid-mediated inhibition, the syndrome might result from a striatal dopaminergic predominance secondary to disinhibition of dopaminergic nigral neurons. Indeed, drugs with dopamine-receptor-blocking properties have been used, with limited success, for the dystonic spasms.⁴ We report a good clinical response in one case of Meige's disease treated with the γ -aminobutyric-acid-mimetic combination of sodium valproate and baclofen.

Case report

A 56-year-old black man presented with a three-year history of a prominent facial dystonia that was not part of a well-known neurological disorder. He had been treated previously with haloperidol, pimozide, and diazepam; neither haloperidol nor pimozide had produced noticeable improvement; diazepam had alleviated the involuntary spasms considerably but produced drowsiness to the extent that he spent most of the day sleeping. At the time of evaluation he had received no medication for three months.

A detailed medical and family history was obtained from the patient, his sister, and his hospital records. Specific inquiries about siblings, children, parents, aunts and uncles, and grandparents did not disclose any familial history of movement disorders. Examination of the sister showed nothing abnormal. There was no history of administration of neuroleptics before the onset of the disorder. Results of general systemic examination were within normal limits. The types of spasm observed in the patient were mild bilateral blepharospasm, mouth retraction, eyebrow raising and frowning, jaw opening, mouth clenching, lip pursing and tightening, platysmal contractions and neck spasms (lateral rotation), and spasms of flexion of the right fingers. He had dysarthria but no appreciable dysphagia. The dystonic movements were aggravated by stress or emotion and often initiated by speaking. Spasms were not observed during sleep. The patient also often complained of deep pain in the region of the left ear; indeed, this symptom was subjectively the most distressing. He had no other neurological abnormality, and mental state examination showed no evidence of dementia or psychiatric disorder. No specific cause for the dystonia was found despite an extensive work-up, which included routine serum biochemical estimations; thyroid function studies; measurement of serum caeruloplasmin, vitamin B₁₂, and folate concentrations; skull radiography; electroencephalography; computed tomography; and examination of cerebrospinal fluid. Based on these findings Meige's syndrome was diagnosed.^{1,2}

Treatment with a combination of sodium valproate (Epilim) and baclofen (Lioresal) was started and the doses increased over 10 days to 2400 mg and 90 mg daily respectively in three divided doses. After 14 days the frequency and severity of the dystonic spasms were greatly reduced, though occasional spasms affecting the buccal and platysmal muscles were still present. The patient reported a pronounced subjective improvement and no longer complained of ear pain. Eight weeks later the condition remained in remission and no side effects or toxic effects of treatment were noted.

Comment

Though its precise mechanism of action is not known, sodium valproate is thought to act by increasing the synaptic concentration of γ -aminobutyric acid in the brain; baclofen has recently been shown to be a selective agonist for γ -aminobutyric acid B receptors which are present on central nerve terminals and through which the release of several transmitters, including dopamine, appears to be inhibited.⁵ Thus a combination of the two drugs could be expected to act synergistically, reducing activity in the nigrostriatal dopaminergic pathway and inhibiting release of dopamine from dopaminergic terminals in the striatum. Such a combination of actions might represent a more physiological means of reducing striatal dopaminergic preponderance than simple blockade of dopamine receptors. Although this hypothesis must be tested, our report of substantial improvement in a case of Meige's disease treated with

sodium valproate and baclofen suggests that a more extensive and prolonged trial of these agents is warranted in this distressing and often intractable disorder.

Requests for reprints should be sent to MJWB.

- ¹ Marsden CD. Blepharospasm-omandibular dystonia syndrome (Brueghel's syndrome). *J Neurol Neurosurg Psychiatry* 1976;**39**:1204-9.
- ² Tolosa ES. Clinical features of Meige's disease (idiopathic orofacial dystonia). *Arch Neurol* 1981;**38**:147-51.
- ³ Neophytides A, Suria A, Chase TN. Cerebrospinal fluid GABA in neurological disease. *Neurology* 1978;**28**:359.
- ⁴ Tolosa ES, Lai C. Meige's disease: striatal dopaminergic predominance. *Neurology* 1979;**29**:1126-30.
- ⁵ Hill DR, Bowery NG. ³H-baclofen and ³H-GABA bind to bicuculline-insensitive GABA_B sites in rat brain. *Nature* 1981;**290**:149-52.

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Rising female predominance in incidence of gastric ulcer

Over the past five decades there has been a remarkable change in the pattern of frequency of gastric and duodenal ulcers. For example, it has been suggested that the overall incidence of peptic ulcers has been steadily decreasing. Many analyses have used "peptic ulcer" as one disease and not recognised gastric and duodenal ulcers as separate entities. Most of the available data have been based on morbidity—for example, perforated peptic ulcer—or mortality figures¹ and tend to give a biased sampling when compared with a survey using radiographic or endoscopic techniques, or both.

Patients, methods, and results

We analysed retrospectively all the patients who had undergone upper gastrointestinal endoscopy in the department of gastroenterology at Auckland Hospital from January 1974 to December 1981. Patients (outpatients and inpatients) with gastric ulcers were selected and classified into type I (ulcers in the body), type II (gastric and duodenal ulcers in combination), and type III (ulcers in the antrum). Ulcers in the pyloric channel, malignant gastric ulcers, and gastric ulcers in association with previous gastric surgery were excluded. The table gives the distribution of patients with benign gastric ulcers. The overall male to female ratio was 0.7:1. When further divided into subgroups, the overall female predominance could be exclusively accounted for by the striking male to female ratio of 0.2:1 in the group with type I gastric ulcer. Patients with type I gastric ulcers also tended to be older, but the difference was not statistically significant ($p > 0.4$; χ^2 test).

There were 787 patients with duodenal ulcers (male to female ratio 3.7:1; mean age $47.2 \pm \text{SD } 9.3$ years). The duodenal to gastric ulcer ratio was 3.1:1. Forty-two patients had histologically or cytologically confirmed carcinomas, and 10 of these were associated with an ulcer.

Clinical data and grouping of patients with benign gastric ulcers

	Gastric ulcers (n = 242)		
	Type I	Type II	Type III
No (%) of patients	82 (34)	37 (15)	123 (51)
Mean age $\pm$ SD (years)	63 ± 11.0	59 ± 9.7	52 ± 1.2
Male to female ratio	0.2:1	1.3:1	1.1:1

Comment

These results show a dramatic reversal of the male predominance in gastric ulcers over the past several decades. It is extremely difficult to compare various epidemiological data on gastric ulcer, but a slow

and steady trend of reversal of sex ratio is apparent.²⁻⁵ Miller *et al*⁴ investigated the subsites of gastric ulcers and also found a higher proportion of women with type I ulcers. Type I gastric ulcer is thought to be pathophysiologically different from types II and III. Hypo-secretion and bile reflux have been associated with type I ulcers, and hypersecretion with types II and III. Our study shows that the increase of gastric ulcer in women is due solely to the conspicuous increase in type I ulcers.

The reason(s) for the reversal of sex ratio is not clear. It is unlikely to be explained by genetic factors. The steady rise in incidence of bronchial carcinoma and cirrhosis of the liver in past decades has been correlated to the increase in cigarette smoking and alcohol consumption by women. Theoretically alcohol damages the "gastric mucosal barrier" either by itself or synergistically with other ulcerogenic substances; and smoking is associated with delayed ulcer healing as well as a greater risk of ulcer relapse after healing. Drugs like aspirin, steroids, and other non-steroidal anti-inflammatory drugs have been implicated in gastric ulceration. In a retrospective study such as ours the list and quantities of all drugs used by patients are notoriously inaccurate. A prospective study on effect of drugs at the time of diagnosis of the ulcer may yield more meaningful results. These factors, however, should be considered to explain the large number of women with type I gastric ulcers.

¹ Langman MJS. Changing patterns in the epidemiology of peptic ulcer. *Clin Gastroenterol* 1973;2:219-26.

² Madanagopalan N, Subramaniam R, Kirshanan MN. Comparative study of operated cases of peptic ulcer in Madras in the 1940s and 1960s. *Gut* 1968;9:69-74.

³ Comfort MW, Priestley JT, Dockerty MD, *et al*. The small benign and malignant gastric lesions. *Surg Gynecol Obstet* 1957;105:435-48.

⁴ Miller LJ, Resseguie LJ, Taylor WF, Malagelada JR. Cholecystectomy and gastric ulcer—an etiologic relationship? *Mayo Clin Proc* 1980;55:255-7.

⁵ Billington BP. Observations from New South Wales on the changing incidence of gastric ulcer in Australia. *Gut* 1965;6:121-33.

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Endocarditis due to viridans-type streptococci tolerant to beta-lactam antibiotics: therapeutic problems

A patient with subacute bacterial endocarditis caused by a viridans-type streptococcus failed to respond to a β -lactam antibiotic despite apparent sensitivity of the organism to the drug used. Investigation showed that the organism was tolerant to the antimicrobial agent. This phenomenon in which the ratio between the concentration of antibiotic which kills an organism (minimum bactericidal concentration) and the concentration that inhibits its growth (minimum inhibitory concentration) is 10 or greater is recognised among viridans streptococci *in vitro*,¹ but therapeutic problems due to such streptococci have not hitherto arisen.

We describe the case together with another in which a similar tolerant organism was identified.

Case reports

Case 1—A 9-year-old girl with Down's syndrome and congenital heart disease was admitted with signs of subacute bacterial endocarditis. All blood cultures grew *Streptococcus mutans*. Two weeks after beginning treatment with cefuroxime she was still intermittently feverish and her murmur was louder. Studies on the organism (table) showed a gross disparity between the minimum inhibitory and minimum bactericidal concentrations of cefuroxime. Furthermore, even undiluted serum taken from the patient half an hour after a dose failed to kill the organism. With 1 mg gentamicin per l, however, the minimum bactericidal concentration of cefuroxime fell to 0.02 mg/l. Treatment was changed to cefuroxime and gentamicin; she rapidly improved, and remained well.

Case 2—A 15-year-old boy with a ventricular septal defect was admitted with endocarditis after the isolation of *Str mutans* from blood cultures.

Penicillin and gentamicin were started, with the intention of stopping the gentamicin when a satisfactory bactericidal concentration of penicillin had been shown *in vitro*. The organism, however, was tolerant to penicillin. Since the killing titre of his serum was satisfactory, treatment was continued with the combination. After four weeks a rash developed and

Minimum inhibitory and minimum bactericidal concentrations (MIC and MBC) determined by broth dilution. Values expressed in mg/l

Antibiotic	Case 1		Case 2	
	MIC	MBC	MIC	MBC
Penicillin	0.03	≥ 1000	0.04	128
Cefuroxime	0.04	≥ 5	0.1	≥ 12.5
Vancomycin			0.6	≥ 10.0
Gentamicin	2.5	2.5		
Erythromycin	0.06	≥ 1	0.02	1.2

cefuroxime was substituted for the penicillin. As the rash persisted, vancomycin alone was instituted. The organism was also tolerant to that drug, however, and the course was concluded with erythromycin. The table summarises the bacteriological findings. The patient remained well four months later.

Comment

Our case 1 was an example of therapeutic failure due to tolerance, and case 2 an example of the difficulties that may arise in choosing appropriate antibiotics when tolerance is shown *in vitro*. While in many infections bacteriostatic antibiotics are effective, it is accepted that bactericidal drugs are necessary for endocarditis. Tolerance to β -lactam antibiotics has led to treatment failure in endocarditis caused by group C streptococci,² *Str faecalis*,³ and *Staphylococcus epidermidis*.⁴ Most cases of endocarditis, however, are still caused by viridans-type streptococci, for which the choice of β -lactam antibiotics is made with confidence. Cross-tolerance between penicillins, cephalosporins, and vancomycins, all active on cell-wall synthetic pathways, is common but not invariable. It is suggested that while the direct action of β -lactam antibiotics inhibits growth, subsequent cell lysis depends on a lytic enzyme from the organism itself—a murein hydrolase—and that tolerance may be linked with the activity of this enzyme.⁵ In their study on penicillin-tolerant viridans streptococci, Holloway *et al*¹ investigated organisms from children with cardiac disease receiving penicillin prophylaxis to cover dental surgery. This treatment increases the proportion of resistant strains as measured by minimum inhibitory concentrations, and of the 71% of viridans strains with inhibitory concentrations in the sensitive range, 19% were tolerant. It is perhaps surprising that therapeutic problems are so rare. Tolerance must be considered when reviewing patients who fail to respond to β -lactam antibiotics in endocarditis.

Cross-tolerance should be borne in mind when choosing alternative antibiotics. In both of our cases, however, adding an aminoglycoside was successful both therapeutically and *in vitro* in reducing the minimum bactericidal concentration to close to the minimum inhibitory concentration.

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¹ Holloway Y, Dankert J, Hess J. Penicillin tolerance and bacterial endocarditis. *Lancet* 1980;i:589.

² Portnoy D, Wink I, Richards GK, Blanc MZ. Bacterial endocarditis due to a penicillin-tolerant group C streptococcus. *Can Med Assoc J* 1980;122:69-75.

³ McDonald M, Miles H, Hart D, Sonenberg N. Penicillin tolerance in *Streptococcus faecalis*. *Lancet* 1980;ii:321.

⁴ Arthur JD, Bass JW, Keiser JF, Harden LB, Brown SL. Nafcillin-tolerant *Staphylococcus epidermidis* endocarditis. *JAMA* 1982;247:487-8.

⁵ Horne D, Tomasz A. Tolerant response of *Streptococcus sanguis* to beta-lactams and other cell wall inhibitors. *Antimicrob Agents Chemother* 1977;11:888-96.

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