LETTERS

Use of prostacyclin (iloprost) in digital vasculitis secondary to meningococcaemia

Extrameningeal complications of meningococcal septicaemia occur in about 11–19% of cases, and include myocarditis, acute renal failure, arthritis, pneumonia, skin gangrene, conjunctivitis, endocarditis, pericarditis, endophthalmitis, urethritis, Waterhouse-Friderichsen syndrome, vasculitis, and digital ischaemia.[1]

We describe the use of a prostacyclin analogue in the treatment of cutaneous digital ischaemia in a patient with meningococcal meningoencephalitis and meningococcaemia.

Case report

A 16 year old female developed progressive headache, photophobia and increasing neck stiffness over 3 days, with nausea and vomiting, and development of non-blanching purpuric rash over her trunk and right thigh. She became increasingly obtunded with depressed level of consciousness, resulting in cardiorespiratory embarrassment.

She was intubated, mechanically ventilated, and treated with volume expanders. Her initial investigations revealed leucocytosis, thrombocytopenia, anaemia, and coagulopathy. Computed tomography (CT) of the brain showed diffuse swelling of both cerebral hemispheres consistent with cerebral oedema. Meningococcal DNA polymerase chain reaction (PCR) was positive for group C serotype. She was treated with high doses of cefotaxime, benzylpenicillin, and steroids from the day of admission. Her condition improved after 48 hours of intensive care, and she was extubated. After 5 days, she developed pain and swelling in the thumb and middle finger of her left hand; within 24 hours these symptoms had worsened with marked swelling and pregangrenous changes of the acral regions of the involved thumb and finger, and there was severe pain and tenderness (fig 1A, B).

A diagnosis of imminent digital gangrene due to digital vasculitis and/or septic embolisation secondary to endarteritis was made. In an empirical effort to improve digital perfusion high dose steroids were recommenced and treatment with intravenous heparin, aspirin and clopidogrel was initiated; little improvement in the digital ischaemia occurred. In an attempt to save the digit she was then started on a prostacyclin (iloprost) infusion at a titrating dose of 0.5 ng/kg body weight/min with marked improvement in pain and coloration after 5 days of treatment. Four weeks following her discharge from hospital her fingers were nearly back to normal and she was pain free (fig 1C, D).

Comment

The pathophysiology of digital ischaemia in meningococcaemia is complex, and involves injury to the endothelium triggering the coagulation cascade, inhibition of the thrombomodulin protein C system, and lodgement of small emboli in digital capillaries. In this report we describe the use of a prostacyclin analogue, iloprost, in digital pregangrene due to digital ischaemia occurring as a complication of meningococcal septicaemia. Prostacyclin is a potent endogenous vasodilator that affects both the systemic and pulmonary circulations; it also inhibits platelet adhesion and aggregation and prevents smooth muscle proliferation. Iloprost, a stable synthetic prostacyclin analogue, has been used with varying success in the treatment of pulmonary hypertension, peripheral arterial occlusive disease,[2 3 5] thromboangiitis obliterans,[6] and digital vasculitis secondary to progressive systemic sclerosis,[2] Sjögren's syndrome and systemic lupus erythematosus.[3 5 6] In these situations, iloprost has been shown to improve perfusion, healing digital ulceration and reducing pain secondary to ischaemia in digital vasculitis, when given in a dose of 0.5–2.0 ng/kg body weight/min (according to individual tolerability) with incremental increases in dose every 30 min. Side effects include headache, nausea, vomiting, and hypotension. Blood pressure and heart rate must be measured at the start of infusion and with each increase in dose.

The use of iloprost in digital ischaemia due to meningococcal septicaemia has not been reported previously. This report suggests that iloprost may be useful in preserving tissue integrity in the cutaneous manifestations of meningococcal septicaemia, and perhaps obviate the need for amputation in some patients. Although our report of a single case does not prove efficacy beyond doubt, the biological and pharmacological rationale behind the use of a prostacyclin analogue in this situation, and the apparent response to therapy in our patient, strongly support a direct therapeutic benefit. We believe that this is of sufficient importance to warrant therapeutic trials in patients with this potentially devastating condition.

K Siddiqui, A R R Razak
Department of Neurology, Beaumont Hospital and Royal College of Surgeons in Ireland, Beaumont Road, Dublin 9, Ireland

B Kneafsey
Department of Plastic Surgery, Beaumont Hospital, Ireland

N Delanty
Department of Neurology, Beaumont Hospital and Royal College of Surgeons in Ireland, Beaumont Road, Dublin 9, Ireland

Correspondence to: Dr Norman Delanty; normandelanty@eircom.net

References

1 **Kirsch EA**, Barton RP, Kitchen L, *et al*. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J* 1996;**15**:967–78.
2 **Poggesi L**, Comeglio M. The role of Iloprost in treatment of critical ischemia of the limbs. *Ann Ital Med Int* 1993;**8**:71S–77S.
3 **Veale DJ**, Muir AH, Morley KD, *et al*. Treatment of vasculitic leg ulcers in connective tissue disease with iloprost. *Clin Rheumatol* 1995;**14**:187–90.
4 **Trifeletti A**, Scamardi R, Pizzoleo MA, *et al*. Haemostatic effects of iloprost in patients with lower limb ischemia. *Panminerva Med* 1997;**39**:202–4.
5 **Banyai S**, Jenelten R, Wagner S, *et al*. Outpatient treatment of severe peripheral ischemia with intravenous intermittent low-dose Iloprost. An open-pilot study. *Int Angiol* 2002;**21**:36–43.
6 **Duthios S**, Cailleux N, Levesque H. Tolerance and therapeutic results of iloprost in obliterative arteriopathy in lower limbs at the severe chronic ischemia stage. A retrospective study of 29 consecutive cases. *J Mal Vasc* 2000;**25**:17–26.

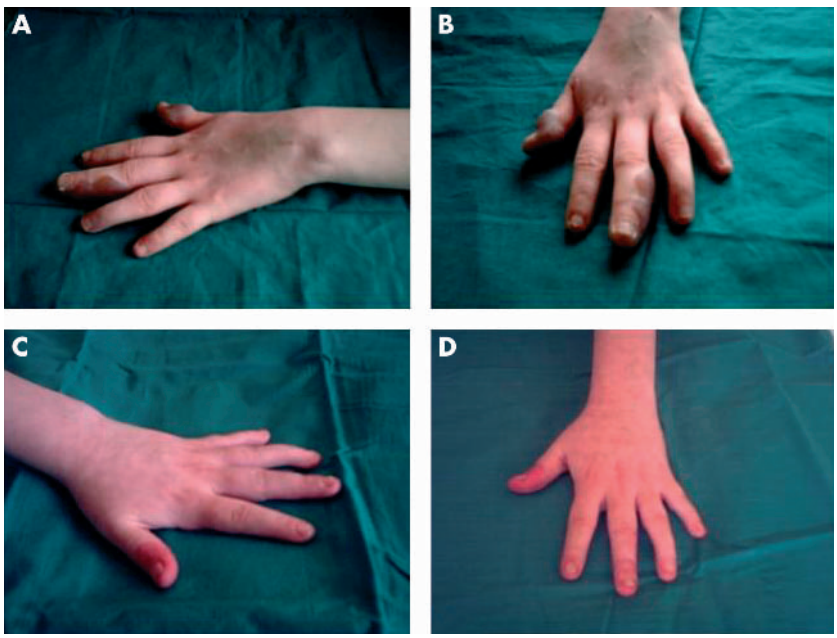

Figure 1 Pregangrenous changes (A, B) of thumb and middle digit of left hand, which resolved (C, D) following treatment with prostacyclin.

Etizolam and benzodiazepine induced blepharospasm

Drug induced blepharospasm is an independent clinical entity, but it has not been established whether blepharospasms can be induced by benzodiazepine or by thienodiazepine derivatives, which are the most frequently used antipsychotic agents in Japan. To determine whether benzodiazepine or thienodiazepine derivatives can induce blepharospasm, the medication history of 254 consecutive patients (67 men, 157 women) with blepharospasm were examined retrospectively. There were 35 patients (13.8%) who had used etizolam before onset of blepharospasm, and this incidence was significantly higher than the two cases (3.3%) in the control group of 61 patients

that had used etizolam ($p<0.05$) before onset of hemifacial spasms. Other psychotropics were used in 53 patients (20.9%) prior to development of blepharospasm, and this was significantly higher than those who had used other psychotropics (6.5%) in the control patients ($p<0.01$). The patients felt asymptomatic following termination of etizolam or benzodiazepines in five patients who had noted increased blinking and difficulty keeping eyes opened after a relatively short duration of the drug use. Significantly more women were seen in both groups pretreated with etizolam ($p<0.05$) or other psychotropics ($p<0.001$) when compared with the group with no drug history. We conclude that prolonged administration of etizolam or benzodiazepines can induce blepahrospasms, especially in women.

Blepharospasms and Meige syndrome are loca1 dystonias that can result in functional blindness and can develop in patients taking various neuroleptic agents.[1–3] In Japan, benzodiazepines, which are prescribed most frequently for patients with insomnia, psychosis, and depression have not been included in these neuroleptic agents. Ethizolam, a thienodiazepine derivative, is a popular anxiolytic with a high affinity for benzodiazepine receptors.

We have had several patients who used benzodiazepine derivatives before the onset of blepharospasms, and we have thus hypothesised that benzodiazepine usage will induce blepharospasms. To test this hypothesis of a causal relationship between the drug and disease, we conducted a detailed drug history for patients with blepharospasm.

We retrospectively examined the medication history of 254 consecutive patients (187 women and 67 men) before and after the onset of blepharospasm. These patients had two or more of the following characteristics; (1) could not generate rapid voluntary blinks but blinked frequently with spasmodic eyelid movements, (2) had high frequency or irregular, involuntary blinking, (3) had difficulty in maintaining their eyes open while walking or watching television, and (4) complained of photophobia or dry eyes. Exclusion criteria were; (1) exact medication history not available from the chart, (2) had irritated or painful ocular surface disease, and (3) dropped out before the six month follow up examination.

For control, the medication history of 61 age matched patients (17 men/44 women) with hemifacial spasm was examined. The spasm resulted from vascular compression and was not related to any central nervous system disorder.

Etizolam was taken by 35 of the 254 patients (13.8%; 7 men, 28 women) before the blepharospasm developed, and only two of the 61 control patients (3.3%) before the hemifacial spasms. This difference in the incidence was statistically significant ($p<0.05$, Yates' correction of χ^2 test).

Other psychotropic drugs had been used in 53 patients (20.9%; 6 men, 47 women) before development of blepharospasm. This incidence was significantly higher than that of the control group where three of 61 patients (5.1%) had taken other psychotropic drugs before the development of hemifacial spasm ($p<0.01$, Yates' correction of χ^2 test).

The mean age of the group with a history of using etizolam was 51.6 (SD 14.0) years with a range of 27 to 75 years. These patients were slightly younger than the patients who had not used etiozolam (55.2 (SD 11.2) years) but the difference was not statistically significant ($p = 0.10$, unpaired t test).

Thirteen patients had used only etizolam (table 1), and another 21 patients had also received other drugs; 11 received a benzodiazepine derivative, three had major tranquilizers, and seven had received both tranquilizers and etizolam.

The duration of etizolam use before the onset of blepharospasm was more than one year in 28 patients, and over five years in 13 of these 28 patients. The average dose of etizolam could be determined in 20 patients; 10 patients received 0.5 mg/day or less, five received 1.0–1.5 mg/day, and five received >2.0 mg/day.

Three patients noted an increase in the frequency of blinking and difficulty keeping eyes open within 6 months of etizolam use, and they stopped using the drug. Two of them felt a gradual improvement and became asymptomatic. In total, the drug was either stopped or the dosage was decreased in 16 patients including the two patients. Seven of the 16 patients reported that the symptoms of blepharospasm improved.

In the group that received psychotropics other than etizolam, the mean age was 56.3 (SD 15.8) years with a range of 23 to 79 years. This was not significantly different from the group with no drug history ($p = 0.58$, unpaired t test).

Except for two patients treated with major tranquilizers only, benzodiazepines were prescribed for 51 patients who developed blepharospasm, 16 of whom were taking benzodiazepines alone. The duration of use of benzodiazepines before onset of blepharospasm was over one year in 44 patients, including 19 patients with over five years of usage. Two women given benzodiazepine for 1–2 months and one woman with a two year drug history became asymptomatic after termination of the drugs, without any further drug or botulinum toxin treatment.

The number of women was significantly higher in the group who had received etizolam (seven men, 28 women, $p<0.05$, χ^2 test) than in the group with no prior use of medication (54 men, 82 women). There were significantly more female benzodiazepine positive patients (six men, 47 women, $p<0.001$, χ^2 test).

Blepharospasm is a female dominated disease, and in the two groups, with no prior use of etizolam or usage of other psychotropics, there were significantly more women when compared with the group with no drug history.

Although the pathogenesis of blepharospasm is not known, abnormalities of cortical or subcortical neural pathways have been suggested.[4] A down regulation of GABAA receptors[5] involved in the neural circuits due to prolonged treatment with ethizolam or benzodiazepine may induce impairment of normal blinking. In any case, ophthalmologists and neurologists should remember that prolonged administration of ethizolam or benzodiazepines is a risk factor for blepharospasm especially in women. Thus, a careful medication history should be made before more expensive neurological tests are performed.

Table 1 Patients taking etizolam alone prior to development of blepharospasm

Onset age (years)	Sex	Dose (mg/day)	Duration (years)	Drug use stopped	Outcome*
68	F	0.25/2 days	9	Yes	Improved 1
28	F	0.5/2 days	1 month	Yes	Improved 2
58	F	0.5/2 days	3	Yes	Improved 1
51	F	0.5	2 months	Yes	Improved 2
57	M	0.5	10 months	Yes	Improved 1
63	F	0.5	1	Changed drug	No change
62	F	0.5	17 months	Yes	No change
41	F	0.5	5	Yes	Improved 1
28	F	0.5	6	No	No change
52	F	0.5	7	Yes	No change
67	F	1.0	6	Reduced to 0.5 mg	No change
57	F	1.0	12	No	No change
42	F	1.5	10	Yes	Improved 1

*Follow up period >6 months. Improved 1: patient reported improvement but still required botulinum toxin. Improved 2: patient became asymptomatic without any further treatment.

M Wakakura, T Tsubouchi, J Inouye
Department of Neuro-ophthalmology, Inouye Eye Hospital, Tokyo, Japan

Correspondence to: Dr M Wakakura, Inouye Eye Hospital, 4–3, Kanda-Surugadai, Chiyoda-Ku, Tokyo, 101-0062, Japan; wakakura-m@inouye-eye.or.jp

References

1 **Weiner WJ**, Nausieda PA, Glantz RH. Meige syndrome (Blepharospasm or blepharospasm-oromandibular dystonia) after long-term neuroleptic therapy. *Neurology* 1981;**31**:1555–6.
2 **Jankovic J**, Ford J. Blepharospasm and orofacial-caervical dystonia: clinical and pharmacological findings in 100 patients. *Ann Neurol* 1983;**13**:402–11.
3 **Mauriello JA**, Carbonaro P, Dhillon S, *et al*. Drug-induced facial dyskinesias. A study of 238 patients. *J Neuro-ophthalmology* 1998;**18**:153–7.
4 **Baker RS**, Andersen AH, Morecraft RJ, *et al*. A functional magnetic resonance imaging in patients with benign essential blepharospasm. *J Neuro-ophthalmology* 2003;**23**:11–15.
5 **Klein RL**, Harris RA. Regulation of GABAA receptor structure and function by chronic drug treatments in vivo and with stably transfected cells. *Jpn J Pharmacology* 1996;**70**:1–15.

Pure motor stroke with major involvement of the index finger

A selective weakness of a particular group of fingers due to cortical infarction has been reported by several authors.[1–3] This finding is related to the controversy over the somatotopic organization of the primary motor cortex (M1). Traditionally, a discrete somatotopic arrangement for individual fingers, with the radial fingers represented laterally and the ulnar fingers medially, has been assumed. However, recent theories have suggested functional overlapping of the cortical representation of the fingers. We describe here a case presenting with major weakness of the index finger due to a cortical infarction confirmed by MRI.