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 meningencephalitis 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 digital vasculitis 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 septicemia. 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 analogue, iloprost, in digital pregangrene due to digital ischaemia occurring as a complication of meningococcal septicemia. 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 analogue, 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 septicemia has not been reported previously. This report suggests that iloprost may be useful in preserving tissue integrity in the cutaneous manifestations of meningococcal septicemia, 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.

References


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.

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

Blepharospasms and Meige syndrome are local dystonias that can result in functional blindness and can develop in patients taking various neuroleptic agents.1 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 tiendiazepine 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 blepharospasms. 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 reported that benzodiazepine usage may induce blepharospasms, and (3) dropped out before the six month follow up examination.

For control, the medication history of 61 patients (20 men, 67 women) before and after the six month follow up examination. The number of women was significantly higher in the group who had received etizolam (seven men, 28 women, p<0.05, \( \chi^2 \) 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, \( \chi^2 \) 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. A down regulation of GABA A receptors involved in the neural circuits due to prolonged treatment with etizolam or benzodiazepine may induce impairment of normal blinking. In any case, ophthalmologists and neurologists should remember that prolonged administration of etizolam 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

<table>
<thead>
<tr>
<th>Onset age (years)</th>
<th>Sex</th>
<th>Dose (mg/day)</th>
<th>Duration (years)</th>
<th>Drug use stopped</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>F</td>
<td>0.25/2 days</td>
<td>9</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0.5/2 days</td>
<td>1</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>0.5/2 days</td>
<td>1</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>0.5/2 months</td>
<td>2 months</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>0.5/2 months</td>
<td>10 months</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>0.5/2 months</td>
<td>1</td>
<td>Changed drug</td>
<td>No change</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>0.5/2 months</td>
<td>17</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>0.5/2 months</td>
<td>1</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0.5/2 months</td>
<td>6</td>
<td>No</td>
<td>No change</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>0.5/2 months</td>
<td>7</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>1/2 months</td>
<td>10</td>
<td>Reduced to 0.5 mg</td>
<td>No change</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>1.5/2 months</td>
<td>10</td>
<td>Yes</td>
<td>Improved 1</td>
</tr>
</tbody>
</table>

*Follow up period >6 months. Improved 1: patient reported improvement but still required botulinum toxin. Improved 2: patient became asymptomatic without any further treatment.
The effect of interferon beta-1a on spasticity in primary progressive multiple sclerosis

It has been suggested that spasticity may be increased in primary progressive multiple sclerosis (PPMS) following treatment with interferon beta-1a. In an open study using the Ashworth Scale and a reflex scale, Bramanti et al measured change in spasticity in 19 subjects treated with interferon beta-1b and in 19 untreated subjects. An increase in spasticity during treatment was seen in 68% of the treated participants compared with 11% of the untreated participants. To investigate this phenomenon further, we conducted a retrospective analysis of the spasticity studied in the recently published randomised controlled trial of interferon beta-1a in PPMS. We randomised 50 subjects to receive weekly for two years an intramuscular injection of either interferon beta-1a 30 µg (15 subjects); or interferon beta-1a 60 µg (15 subjects); or placebo (20 subjects). Following completion of the study, the clinical notes of all cases were reviewed and the occurrence of spasticity documented. Spasticity was not a predetermined outcome, but symptomatic spasticity had been recorded in the notes by the blinded treating physician, including both post-dose spasticity and any independent, sustained increase in the level of spasticity. Any increase in anti-spasticity medication was also documented. Statistical analysis was carried out on an intention to treat basis. Comparisons were made between the placebo and combined interferon group and the individual treatment groups using Fisher’s exact test. Two years of follow up were completed by 49 participants; 43 completed the study. There were no significant

References


Figure 1 T2-weighted (A) and (D), fluid attenuated inversion recovery (B) and (E), and diffusion weighted (D) and (F) MRI images are shown for the two axial slices. Two small high intensity spots were identified in the precentral knob (A–C) and at the subcortical white matter (D–F).
A breathtaking headache

Thunderclap headache was the subject of a recent review in this journal, in which the pathophysiology was linked to segmental vasoconstriction. Specifically, the abrupt onset of headache was associated with vasoconstriction caused by neurogenic rather than biochemical mechanisms. Hyperventilation can probably induce generalized vasoconstriction through alkalosis of the cerebrospinal fluid. 

We recently saw a patient where hyperventilation or exertion caused thunderclap-like headaches.

This previously healthy 15 year old boy was admitted to Leiden University Medical Center because of acute (that is, maximum severity within one minute), severe left sided headache associated with, successively, a numb and tingling sensation in the right arm and leg, weakness of the right arm for 30 minutes, and difficulty in speaking. Four weeks earlier, after running for several minutes to catch a train, he suffered an acute, severe bifrontal, throbbing headache, which subsided within minutes after he stopped running. There were no associated symptoms. Three weeks before admission he experienced a similar headache for 30 minutes which started after 10 minutes of running. That evening he had a thunderclap headache, but this time the headache started spontaneously, lasted for two hours, and was accompanied by nausea and vomiting. In the subsequent three weeks until admission, these headache episodes occurred one or two times a day, occasionally triggered by exertion, but often seemingly spontaneous.

On admission, physical examination was uneventful apart from non-fluent speech and momentary bilateral loss of consciousness. On neurological examination, most likely, was migraine with aura, as subarachnoid haemorrhage, posterior fossa tumour, or Arnold-Chiari malformation, but these were all excluded. Cardiac ischaemia is a rare cause of unilateral exertional headache. Although no ECG during exertion was performed, the normal ECG at the time of complaints and the ability to exercise normally after relaxation therapy makes this an unlikely cause. Cerebral angiography was not performed.

Benign exertional headache typically presents as bilateral throbbing headaches for five minutes to 24 hours following physical exertion. In the present patient, however, the headache was induced by hyperventilation following exercise, rather than by the exercise itself. His “spontaneous” headaches, most likely, were also caused by hyperventilation; this is supported by the complete disappearance of these headaches after initiation of relaxation therapy. Although hyperventilation can cause a dull and non-specific generalised headache in about 20% of patients, such an alarming, explosive type of headache has, to our knowledge, never been described. The attack that prompted admission, most likely, was migraine with aura, as supported by the sequential rather than simultaneous development of neurological symptoms. Migraine seems to occur more frequently in patients with benign exertional headache.

Our case illustrates that hyperventilation, both in rest and following physical exertion, may cause severe, acute, “explosive” headaches, and that adequate relaxation exercises and physical therapy can prevent these alarming headaches. The precise mechanism of the headache in our patient remains elusive. Additionally, although breathing exercises would not prevent physiological exercise induced hyperventilation, they may prevent excessive hyperventilation following exercise. Hyperventilation provocation tests can be diagnostic and should be considered in all patients with exertion induced headaches. In light of the recent review, magnetic resonance angiography could be considered in such cases to evaluate a possible involvement of cerebral vasospasm.

References

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K Siddiqui, A R R Razak, B Kneafsey and N Delanty

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