Miconazole and clobazam; a useful interaction in Dravet's syndrome?

Chiron and the STICLO study group report a dramatic improvement in seizure control in children with severe myoclonic epilepsy in infancy or Dravet's syndrome (DS) when treated with valproate and clobazam, and stiripentol.1 Stiripentol inhibits the metabolism of clobazam and its metabolite norclobazam by P450 cytochromes.

SM, 9 year old girl with DS and severe developmental delay had poor seizure control and frequent status epilepticus despite various combinations of antiepileptic medicines, most recently lamotrigine 35 mg/kg/day and nitrazepam 0.8 mg/kg/day. Careful seizure diaries were kept by her mother CM while lamotrigine and nitrazepam were slowly withdrawn and valproate and clobazam were introduced. Several 14 day courses of miconazole 2% oral gel were given SM for oral thrush. During each course CM observed that SM’s seizure control improved remarkably, and she progressed from being wheelchair bound to standing and displaying more interest in her environment. No unwanted side effects of this treatment were observed. Miconazole is partly absorbed orally, and inhibits P450 cytochromes including isoenzymes 3A4 and 2C9, causing interactions with antiepileptic medicines including benzodiazepines.1 We hypothesised that miconazole may have a similar action to stiripentol when given with valproate and clobazam in DS.

With CM’s informed consent, we analysed steady state trough plasma levels of valproate, nitrazepam, clobazam and the metabolites aminonitrazepam and norclobazam while SM was taking these medicines (baseline) and then while taking added miconazole (day 22) or stiripentol (day 50) (see table 1). The analyses were performed by MH, SD, and RB using liquid chromatography–tandem mass spectrometry, except for valproate, where gas chromatography–mass spectrometry was used. The results show markedly increased levels of norclobazam during miconazole or stiripentol treatment compared with baseline, similar to Chiron’s results for stiripentol, which supports our hypothesis.

The safety of long term miconazole use is unknown. Literature searches and correspondence with the distributor of miconazole in New Zealand (Janssen-Cilag Pty Ltd, 4 March 2002) have identified no studies of long term miconazole use in children, nor has this interaction between clobazam and miconazole been reported.1 Miconazole may be a useful medication in DS for trialling the possible benefits of stiripentol when the latter is not readily available, when stiripentol cannot be tolerated,3 or during episodes of fever when children with DS are more likely to develop status epilepticus. Miconazole and stiripentol are also likely to interact with other medicines used in children with DS. This interesting and potentially useful interaction warrants further cautious study.

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References
Such negative outcomes, even if rare, are of particular concern because there is no need to combine paracetamol and ibuprofen in this way. If antipyresis or analgesia is required, there are existing safe treatments in the form of the two drugs separately, and so the combined use of paracetamol and ibuprofen is simply unnecessary. The HTA should therefore reconsider this call, and redirect the resources to the many other urgent projects that require funding.

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References

Juvenile myasthenia gravis mimicking recurrent VI nerve palsy of childhood
A 5 year old Asian boy presented to the paediatrician with diplopia following ear ache. Isolated VI nerve palsy was suspected. Full blood count, ESR, magnetic resonance imaging (MRI), and ENT examination were normal. He recovered within a week, but subsequently suffered six episodes of transient convergent squint with abduction deficit. He was referred to our neurologist for further opinion.

His developmental milestones, family history, and ocular and general examination as well as investigations were normal apart from respiratory and ocular myasthenia. His orbicularis oculi muscle was normal, but single fibre EMG could not be done as the child became very distressed. Saccadic studies showed longer and slower saccades which strongly suggested myasthenia (fig 1).

The clinical features, saccadic studies, positive antibody titres, and the association of vitiligo confirmed the diagnosis of ocular myasthenia. During the follow up, his AchR Ab levels, interestingly, were negative. Benign idiopathic VI nerve palsy, sometimes recurrent, is a diagnosis of exclusion. Variable strabismus is a known feature of myasthenia gravis. Elevated AchR Ab is the hallmark of myasthenia gravis. Periocular single fibre EMG is often difficult and stressful to perform in younger children. The tensilon test needs a frank clinical sign to demonstrate the improvement in his orbicularis strength. Strabismus is known to be resistant to cold stimulation by ice pack compared with ptosis. The saccadic velocity pattern of myasthenia differs from paralysis or restrictive problems. The myasthenic eye can reach a normal peak saccadic velocity, but cannot sustain it. This report highlights the difficulty in diagnosing some ocular myasthenia and the value of saccadic studies, which are simple, non-invasive, and repeatable.

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RCPCH guideline appraisal on EEG after first seizure
A recent RCPCH guideline appraisal asserted: “There is no need for an EEG following a first simple afebrile seizure.” This is puzzling. A “simple afebrile seizure” is not an entity recognised in the ILAE diagnostic scheme. More importantly, we disagree both with the recommendation and the contention that it is based on grade B evidence.

The recommendation is principally based on a meta-analysis by Gilbert and Buncher, which found the sensitivity and specificity of EEG in helping to predict recurrence after a first seizure to be too low to justify its routine use. However, they concluded: “EEG should be ordered selectively, not routinely, after first unprovoked seizure in childhood”, which is different from, “There is no need for …”. Moreover, the principle purpose of performing an EEG after a first seizure is not to predict recurrence.

There are many different disorders in which a seizure may be the first symptom. While it may be useful for statistical purposes to lump these together, clinically this is indefensible. There are many common scenarios when, following an initial generalised tonic-clonic seizure (GTCS), an EEG may be helpful for diagnostic, therapeutic, and/or prognostic purposes. This may be the case if one suspects a benign focal seizure disorder, a phlyctically induced seizure, or an idiopathic generalised epilepsy in which the first GTCS may have been preceded by hundreds of unrecognised minor seizures. The guideline might be better worded: “An EEG following a first definite seizure may not yield useful information regarding recurrence risk, but may provide useful information regarding syndrome diagnosis, the role of precipitating factors, and management. The need for an EEG should be determined following clinical evaluation by a clinician with expertise in seizure disorders”. In this the guideline would reflect other evidence based guidelines that EEG should be “… part of the neurodiagnostic evaluation of the child with an apparent first unprovoked seizure.”

References
Severe vitamin D deficient rickets in black Afro-Caribbean children

Concern has been raised over the past few years, at the prevalence of rickets in British Asian children and recent immigrants to the UK. Here we describe five cases of severe rickets in children of second generation Black-African or Caribbean parents who presented to paediatric outpatients in a socially deprived area of inner London. Weaning had been unsuccessful in all of the cases. The affected children all had biochemical (table 1) and radiological evidence of severe rickets.

Case 1
This child was referred to clinic by his GP due to delay in walking. His mother was still breast feeding as he refused to drink cows’ milk. Solids had been introduced at 6 months of age but he was a “fussy” eater. His mother did not drink milk. She had tried to introduce solids into the child’s diet from birth. This child was referred by his GP with recurrent fevers. Patients following several visits to the casualty department with recurrent fevers. She had been successfully treated with antibiotics and her knees had improved. Of note, her mother had low levels of vitamin D shown in the present cases. Four of the five cases were exclusively breast fed. As there is relatively little vitamin D in breast milk, it has been recommended that lactating women should supplement their diets with vitamin D (10 μg daily). Weaning can be associated with a lowering in vitamin D levels. Although some commercially available weaning foods have added vitamin D, it is recommended that children under 2 years of age receive additional supplementary vitamin D of 7 μg per day. None of the children or mothers in this series were receiving vitamin supplementation prior to

Table 1 Biochemical bone profiles and characteristics of infants at presentation

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Ethnic group</th>
<th>Birth weight (kg)</th>
<th>Sex</th>
<th>Gestation (wk)</th>
<th>Birth order</th>
<th>Age at weaning (mth)</th>
<th>Age at presentation (mth)</th>
<th>Calcium (mmol/l) (2.2–2.6)</th>
<th>Phosphate (mmol/l) (1.3–2.5)</th>
<th>Alkaline phosphatase (IU/l) (30–130)</th>
<th>25(OH)D (ng/l) (10–42)</th>
<th>Hb (g/l) (99–141)</th>
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<tr>
<td>1</td>
<td>Black-Caribbean</td>
<td>3.1</td>
<td>Male</td>
<td>40</td>
<td>2/2</td>
<td>6</td>
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<td>Female</td>
<td>38</td>
<td>2/3</td>
<td>6</td>
<td>21</td>
<td>2.3</td>
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<td>3180</td>
<td>4.4</td>
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<tr>
<td>3</td>
<td>Black-Caribbean</td>
<td>2.8</td>
<td>Female</td>
<td>40</td>
<td>2/2</td>
<td>4</td>
<td>16</td>
<td>2.5</td>
<td>0.85</td>
<td>2828</td>
<td>6.6</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>Black-Caribbean</td>
<td>3.1</td>
<td>Male</td>
<td>40</td>
<td>3/3</td>
<td>5</td>
<td>13</td>
<td>2.2</td>
<td>0.87</td>
<td>2484</td>
<td>7.4</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>Black-African</td>
<td>3.3</td>
<td>Female</td>
<td>39</td>
<td>1/1</td>
<td>4</td>
<td>10</td>
<td>2.4</td>
<td>0.75</td>
<td>2465</td>
<td>8.5</td>
<td>88</td>
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</table>
referral. Four of the children have responded to treatment with vitamin D, 6000 units/day. In one case, there have been problems with paraplegic compliance. In all the cases, the index of suspicion for rickets had been low, thus delaying referral and treatment. Awareness of rickets in the Black-African and Caribbean population needs to be raised in health visitors, GPs, and parents.

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References


Hyperchloroemic acidosis consistent with ammonium chloride administration

We report an infant with recurrent self limiting hyperchloroemic acidosis. This 1 month old girl was admitted with vomiting, decreased feeding, and rapid breathing. On examination she was lethargic and tachypnoeic with normal blood pressure and peripheral perfusion. Investigations revealed uncompensated metabolic acidosis and uraemia (table 1). She was managed with antibiotics and sodium bicarbonate and showed rapid improvement in acidosis and uraemia in 48 hours. Following discharge she was brought to the outpatient department on multiple occasions with vomiting, failure to thrive, and tachypnoea. She was readmitted at the age of 4 months with lethargy, tachypnoea, uncompensated hyperchloroacetic acidosis, and uraemia. She was managed with antibiotics and sodium bicarbonate; the biochemical parameters normalised over 52 hours.

Negative urinary anion gap, normal urinary to blood CO2 difference, and fractional excretion of bicarbonate excluded distal and proximal renal tubular acidosis in this child. Acidic urine in the presence of systemic acidosis and extremely high levels of serum and urinary chloride pointed to a chloride load overwhelming renal excretory capabilities. Negative anion gap of –17.6 mmol/l indicated an excess of unmeasured cation to the level of 30 mmol/l. This, combined with transient increase of urine with normal levels of creatinine and renal ultrasound indicated the possibility of ammonium (NH4+) load, and the clinical-laboratory picture of the child was explained on the basis of ammonium chloride load. Chloride levels of the milk and water given to the child as well as blood gas and serum chloride levels in the parents were normal.

Ammonium chloride is used in the metal-lurgy industry in our city and is readily available. The possibility of Munchausen by proxy syndrome was therefore considered once investigations for environmental over-load were non-contributory; this however could not be proved as the mother repeatedly denied administration of ammonium chloride. The child was discharged on normal feeding without any treatment. At three months follow up the child was growing normally, and did not have tachypnoea, vomiting, or acidosis. The findings of this case are suggestive of exogenous ammonium chloride administration, a possibility that should be considered in unexplained hyperchloroacetic acidosis with negative urinary anion gap and high urinary chloride levels.

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References


Table 1 Laboratory findings in the child

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First admission</th>
<th>Second admission</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Admission</td>
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<tr>
<td>pH</td>
<td>6.95</td>
<td>7.332</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>4.8</td>
<td>15.2</td>
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<tr>
<td>Base excess (mmol/l)</td>
<td>–23.5</td>
<td>–7.2</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>152</td>
<td>145</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td>97</td>
<td>110</td>
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<tr>
<td>Anion gap (mEq/l)</td>
<td>–17.6</td>
<td>–7.2</td>
</tr>
<tr>
<td>Urine chloride (mEq/l)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Urine (mg/dl)</td>
<td>162</td>
<td>60</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Urine net charge*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Urine pH</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

†Urinary pH in the presence of metabolic acidosis: <5.5, proximal RTA/acid load; >5.5, distal RTA.

Voiding dysfunction in Duchenne muscular dystrophy

We read with interest the report by MacLeod et al who described urinary symptoms in 46 (62%) of 74 male children with Duchenne muscular dystrophy (DMD).1

The authors comment that “The neurological basis for this dysfunction is difficult to explain.” Daytime incontinence, urinary frequency, and urgency were reported in 22 (48%), 14 (30%), and 18 (39%) of the 46 boys, respectively. These symptoms suggest the possibility of urge syndrome, a common problem in children that does not have any obvious neurological cause. The pathogenesis of urge syndrome is incompletely understood, but voiding postponement is common in these children and might play an aetiological role.2 Voiding postponement is more common in children with neuromuscular disorders because the physical disability impairs access to a bathroom. There are many reasons why access to a bathroom is impaired or why these children might choose to postpone voiding. Wheelchair patients require specialized bathroom facilities and might require assistance, neither of which might be available. Even for “ambulatory” patients, getting on and off a toilet is often a labour-intensive and time-consuming process for many of these children. Requesting assistance for such a personal task might be difficult or embarrassing for some children.

Children with urge syndrome commonly demonstrate squatting behaviour, which is a learned response to minimize incontinence associated with an unwelcome detrusor contraction. Even for DMD children with proximal muscle weakness and might be limited in their ability to squat or otherwise to develop muscular strategies to cope with an unwelcome detrusor contraction.

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References

Prevention of hyponatraemia

At least two children in Northern Ireland have died in recent years as a result of severe hyponatraemia (serum sodium <130 mmol/l). Death or neurological morbidity related to this condition has been reported in more than 50 children. Although risk factors include vomiting, pain, anxiety, disturbances of the central nervous system, and metabolic and endocrine disorders, it has become recognised that any child receiving intravenous fluids or oral rehydration is potentially at risk. The particular risks associated with the postoperative period were highlighted by Arieff in 1998, who pointed out that plasma levels of vasopressin (antidiuretic hormone, ADH) are raised in virtually every child in the postoperative period. If such children are given fluids containing less than 140 mmol/l of sodium there will always be a tendency towards postoperative hyponatraemia.

A solution containing 0.18% sodium chloride in 4% glucose is commonly used in paediatric practice and is generally held to be isotonic. However, in the catabolic child the glucose is metabolised rapidly, causing the fluid to become hypotonic in vivo, with the potential for significant fluid shifts. If the child is in the postoperative period or in any other situation where there is a high level of circulating vasopressin, a situation can arise where excess free water is retained within the circulation. This can be compounded by water effectively administered in the intravenous fluids. This condition has been called “dilutional hyponatraemia” because the “free” water component of the serum has increased, causing dilution of the major cation, sodium. This “free” water will pass rapidly and unhindered across cell membranes with the particular risk of development of cerebral oedema. Children may be at particular risk of brain damage due to increase in intracranial pressure in this situation.2

A working group in Northern Ireland has developed guidelines which have been published by the Department of Health Social Services and Public Safety.4 These guidelines emphasise that every child receiving intravenous fluids requires a thorough baseline assessment, that fluid requirements should be assessed by a doctor competent in determining a child’s fluid requirement, and fluid balance rigorously monitored. The value of accurate measurement of weight, and monitoring of urea and electrolytes, in any child requiring prescribed fluids after 12 hours is emphasised, together with the importance of assessment of fluid balance and prescription at least every 12 hours by an experienced member of clinical staff.

This must take account of all oral and intravenous intake, together with the measurement and recording of all losses (including urine, vomiting, diarrhoea, etc) as accurately as possible.

Replacement fluids must reflect fluid loss, and in most situations this will imply a minimum sodium content of 130 mmol/l. This must be considered and prescribed separately, reflecting the fluid loss in both volume and composition. In some situations laboratory analysis of the electrolyte content of the fluid lost may be helpful. It is important to remember that, while children receiving intravenous fluids are at particular risk, children receiving oral rehydrating fluids may also be at risk, as these are often also hypotonic. Vigilance is therefore required for all children receiving fluids. Medical and nursing staff need to be aware of risks in this situation, and of early signs of developing cerebral oedema such as vomiting, deteriorating level of consciousness, or headache, before more serious symptoms such as seizures occur, as deterioration to this extent is associated with significant morbidity and mortality.

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A 7 year old male child was admitted to our hospital during the summer with staphylococcal scalded skin syndrome (SSSS). After five days of appropriate treatment, he was to be discharged. Unexpectedly, while he was playing in the ward, his skin suddenly erupted with crops of clear, 2–10 mm, waterdrop-like vesicles as we watched. The parents and nursing staff became anxious as the vesicles were extremely fragile and broke with the slightest touch. They also involved previously unblistered skin. This seemed typical of miliaria crystallina except for the size. After reassurance, he was sent home. The rash lasted for 18 hours and resolved spontaneously by peeling.

Miliaria crystallina is a transient occlusive sweat gland disorder resulting in the leakage and retention of sweat into the epidermis. It is characterised by diffuse eruption of extremely fragile, asymptomatic, epidermal, 1–3 mm size, waterdrop-like vesicles which appear in crops on a non-inflammatory base. In children and adults, it can be seen in febrile illnesses due to increased sweating and also following the use of drugs including bethanechol and isotretinoin. Miliaria has been hypothesised to be due to sweat duct disruption and occurs when a potential space develops between the affected epidermal cells and the new proliferating cells beneath them.

In our patient, we postulate that staphylococcal toxins weakened the epidermis, creating a potential space. His increased activity while playing led to pooling of sweat in this space which manifested as miliaria crystallina. We would like to remind paediatricians of the occurrence of this self-limiting, harmless, but sometimes alarming disorder in any fever, although in SSSS there is a particular reason for the spread of the lesions.

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