PostScript

LETTERS

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Table 1 Table of results

	Day 1	Day 22	Day 50
Drug			
Miconazole 2% gel (from day 9 to day 23)		2.5 ml tds	
Stiripentol (mg/kg/day) (from day 36 onwards)			50
Nitrazepam (mg/kg/day)	0.45	0.40	0.40
Clobazam (mg/kg/day)	1.0	1.0	0.5
Valproate (mg/kg/day)	24	24	24
Seizures in preceding week	14	2	2
Toxicology results			
Miconazole (mg/l)		~0.02	
Nitrazepam (μg/l)	120	150	120
Aminonitrazepam (μg/l)	40	42	44
Clobazam (mg/l)	0.54	1.0	1.0
Norclobazam (mg/l)	2.6	17	10
Valproate (mg/l)	49	79	68

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, 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 Careful seizure diaries were kept by her mother CM while lamotrigine and nitrazepam were slowly withdrawn and valproate and clobazam were introduced.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,[2] causing interactions with antiepileptic medicines including benzodiazepines.[3] 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.[4] 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,[5] 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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Fever phobia revisited

The National Coordinating Centre for Health Technology Assessment recently issued a commissioning brief calling for proposals to look at "the clinical effectiveness of paracetamol alone, ibuprofen alone, and paracetamol and ibuprofen in combination in the management of fever in pre-school children".[1] This call raises a number of issues regarding the use of such drug combinations in the treatment of febrile children.

Fever phobia is a term that was coined some years ago to describe exaggerated fears that parents have about fever in children. At the time the original research was done these fears included brain damage, seizures, death, coma, and blindness. Twenty years later many of these fears remain,[2] leading to the possibility of over-aggressive treatment and unnecessary worry.

As there is no evidence that fever, as distinct from hyperthermia, causes any harm, therapy is usually aimed at promoting comfort rather than the aggressive pursuit of normothermia. It is somewhat surprising therefore that the HTA are pursuing a line of enquiry that might reinforce fever phobia through the promotion of combination antipyretic therapy. Furthermore, by using two drugs where one was used previously, the chance of parents making an error in administration increases.

Perhaps most worryingly, there is cause for concern about the safety of the combined use of these two drugs, as renal failure has been reported in a child taking this combination. Although not conclusively demonstrated to be the cause, two mechanisms by which the drugs may have acted synergistically to cause this damage have been proposed. The first is that renal damage may occur as the result of the accumulation of oxidative metabolites of paracetamol in the renal medulla during renal ischaemia caused by ibuprofen, while the second concerns the inhibition of urinary prostaglandin synthesis which may also cause renal damage. It is hypothesised that these may be exacerbated by mild to moderate dehydration.[3]

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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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 vitiligo around the lids. At subsequent consultation, a right convergent squint was noted but with apparent full ocular movements. AchR Ab titres, performed this time, were weakly positive at 25×10^10 M (<5×10^10 M = negative and 5–50×10^10 M = positive).

Ophthalmic evaluation at this stage revealed visual acuities of 6/12 (right), and 6/7.5 (left), intermittent alternating convergent squint, normal ocular movements, motor fusion, and refraction. His orbicularis oculi function was weak, but no lid twitch or ptosis on sustained upgaze was elicited. Cold stimulation by ice pack test[2] showed a transient improvement in orbicularis function, but no change in his strabismus. Repetitive stimulation electromyogram (EMG) of orbicularis oculi was normal, but single fibre EMG could not be done as the child became very distressed. Saccadic studies[3] 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,[1] sometimes recurrent, is a diagnosis of exclusion. Variable strabismus is a known feature of myasthenia gravis. Elevated AchR Ab is the hall mark of myasthenia; however, it may be low to normal in younger age, boys, and in ocular myasthenia. 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. The ice pack test is helpful as shown by improvement in his orbicularis strength. Strabismus is known to be resistant to cold stimulation by ice pack compared with ptosis.[2] The saccadic velocity pattern of myasthenia differs from paralysis or restrictive problems.[3] 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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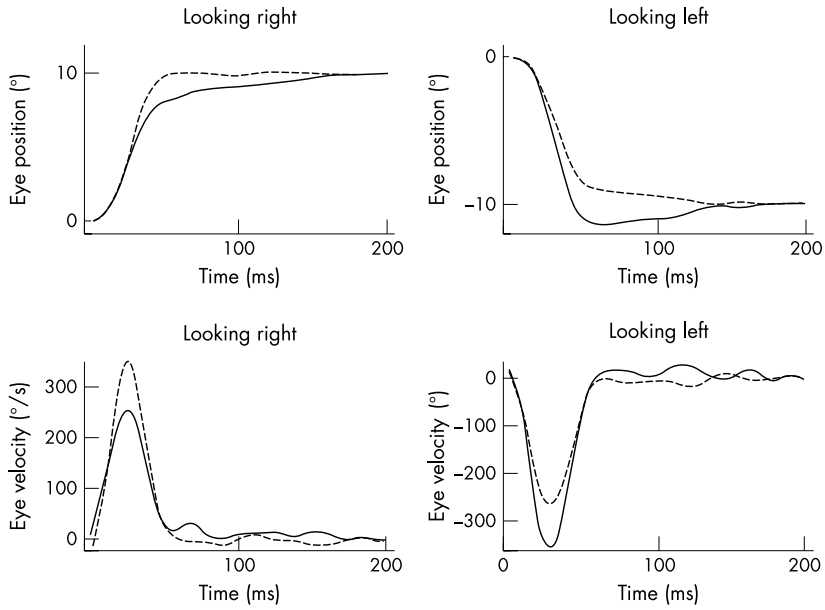

Figure 1 Eye position and velocity during 10° saccades from the midline. The traces show the averages over 10 saccades. The position and velocity of the right eye is shown by a continuous line, while that of the left eye is shown by a dashed line. After an initial rapid movement, saccades into the field of action of the lateral rectus drift slowly towards their target direction. (Courtesy of R Clements)

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''.[1] This is puzzling. A ''simple afebrile seizure'' is not an entity recognised in the ILAE diagnostic scheme.[2] 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.[3] 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 photically 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''.[4]