Hypoglycaemia and hypothermia due to nimesulide overdose

Editor—Although toxicity due to chronic administration of nimesulide has been reported, 1 to the best of our knowledge there is no report about poisoning due to a single ingestion. We report a 20 month old boy who accidentally took a high dose of nimesulide; 40 mg/kg, 8 times the recommended daily dose.

Physical examination was unremarkable. Laboratory findings, including hepatic and renal function, were normal, except for low to normal glucose concentration (4.3 mmol/l) and mild acidosis (pH 7.35, bicarbonate 16.9 mmol/l). Gastric lavage with activated charcoal was performed. One hour later, serum glucose concentration was 3.14 mmol/l, venous pH 7.26 and bicarbonate 18.1 mmol/l. His systolic blood pressure and body temperature fell to 60 mm Hg and 35.1°C (axillary), respectively. The patient was rewarmed and the intravenous infusion rate increased to 2000 ml/m 2/day. Six hours later, his serum glucose concentration was 4.44 mmol/l, venous pH 7.33, and bicarbonate 16.5 mmol/l. Body temperature and blood pressure rose and 20 hours after admission all vital signs became normal, mild acidosis resolving within 24 hours. He was discharged after 48 hours. Physical examination and laboratory findings were normal six days after discharge.

The most striking events in our patient were the development of hypotension and hypothermia. Hypothermia has been reported due to non-steroidal anti-inflammatory drugs overdose, but hypothermia due to the antipyretic action of nimesulide has not been reported. Nimesulide produces a dose dependent antipyretic action in rats by inhibiting COX-2, 2 but its effect under normothermic conditions is not known. Although it has been reported that nimesulide might be given to children with hypoglycaemia, it may cause hypoglycaemia in high dosage.

Port-A-Cath use in refractory seizure disorders

Editor,—The use of a totally implantable venous access system (Port-A-Cath) in children has become widespread in the last 15 years. We report a series of three children for whom the Port-A-Cath improved management of their refractory seizures.

Two patients both females with a diagnosis of severe myoclonic epilepsy of infancy and recurrent status epilepticus presented in the first year of life. Both had seizures, which were intractable to multiple anticonvulsants and became refractory to benzodiazepines. Intravenous benzodiazepine infusion was sought, and to ease management of status epilepticus a Port-A-Cath was inserted at the age of 16 months in the first child and 13 months in the second. The third patient presented at 4 years with Lennox-Gastaut syndrome. Hospitalisation every 2–3 weeks became necessary for management of clusters of generalised tonic clonic seizures with intravenous medications. As seizure control was resistant to multiple anticonvulsant therapies, intravenous immuno-globulin therapy once every 2 weeks was started with some success. Again venous access was difficult and a Port-A-Cath was implanted at 4½ years.

The first patient developed a candida albicans infection 9 months after insertion. Amphotericin B was given for 14 days and the Port-A-Cath removed. A second device was inserted after the infection was treated and remains in place 6 years later with no further complications. The second patient had her Port-A-Cath removed after 6 years and 5 months when the catheter blocked. A second device has just been inserted. The third patient has had no complications nine months after insertion.

Port-A-Cath devices are widely used in the management of children requiring venous access for longer than 3 months, where peripheral access is difficult and for administration of medications or blood products. 14 Children who typically benefit have haemophilia, cystic fibrosis, or, malignancies. To our knowledge, there are only two previous references to Port-A-Cath usage in neurological disease. 2 In this study of 81 children, one child had the device inserted for home administration of medication. This was removed after a portal infection 3 months after insertion. 2

The benefits to a Port-A-Cath include rapid reliable venous access, low maintenance, fewer restrictions on lifestyle, low incidence of infection and malfunction, when compared with externalised systems. 2 These benefits are attractive for children with a refractory seizure disorder and their families. Rapid venous access is invaluable to the physician when managing status epilepticus.


Pica in sickle cell disease: “She ate the headboard”

Editor,—Within our sickle cell population, there are a small number of school aged children who eat sponge. Knowing that pica—the compulsive ingestion of non-nutritive substances—is more common in tropical countries where cultural and dietary factors play a role, it may not be a surprising finding. However geophagia (soil), pagophagia (ice), and trichophagia (hair) are the commonest non-nutritive substances eaten. We cannot explain the prevalence of sponge amongst our patients. Infants place everything in their mouth, and pica occurs in a variety of syndromes associated with brain damage and developmental delay. It is also more common in deprived and neglected children. Neuropsychological complications are not uncommon in sickle cell disease (SCD) but none of our children had cognitive impairments.

There is a recognised association between iron deficiency and pica, leading to debate as to which is cause and which effect. Natural sponge contains proteins and minerals, and is often fortified with silica or calcium salts, however, synthetic sponge consists of cellulose alone. We wondered whether a craving of an unidentified salt fuels the eating of sponge, or whether the texture of sponge is simply orally stimulating.

In one study of pregnant women, 33% with pica had a history of childhood pica and 56% had a positive family history. In our children, four had a positive family history. Therefore, pica can be a response to a nutritional deficit,
it can be familial suggesting a learnt behaviour, or developmental and emotional issues may be involved. In America it is classified as an eating disorder, in the UK it is considered a behavioural disorder; it can also be an obsessive-compulsive disorder, or a manifestation of depression.

Our children could shed no light on their compulsion. In six cases the parents found the behaviour so unacceptable that they requested psychological intervention and in four, the behaviour has now stopped. Thus whilst we find this behaviour fascinating, we are no clearer in understanding the aetiology of pica for sponge in this small population of children with SCD.

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Maternal nutrition and pregnancy outcome

EDITOR,—Symonds et al raise interesting issues about the potential use of animal models in examining the impact of nutrition during pregnancy on future risk of adult disease.1 However, their discussion of recent epidemiological research in humans includes several important factual inaccuracies. The authors imply that our analyses and those of Godfrey et al grouped women into categories of energy intake, and suggest that different results might have been obtained had “all the raw data points [been used] to determine potential relations between maternal nutrition and birth weight”. Yet as clearly indicated in both papers,2,3 this is precisely the analysis that was conducted. For information, figure 1 shows the relationship of maternal energy intake to birth weight in our study and that of Godfrey et al, grouped women into categories in both papers.

Yet as clearly indicated in both papers,2,3 this is precisely the analysis that was conducted. For information, figure 1 shows the relationship of maternal energy intake to birth weight in our study and that of Godfrey et al, grouped women into categories in both papers.

Figure 1 Birth weights were individually adjusted to the mean sex and gestational age of the cohort and for maternal smoking and height indicated in both papers,2,3 this is precisely the analysis that was conducted. For information, figure 1 shows the relationship of maternal energy intake to birth weight in our study and that of Godfrey et al, grouped women into categories in both papers.

The outcome of specialist registrars in the southwest region

EDITOR,—The UK national directive is to increase consultant paediatric numbers substantially over the next 5–10 years which requires the delivery of suitably trained doctors. Higher specialist training in paediatrics takes five years and there is no basis for suggesting has any importance to populations in industrialised countries.

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Nitrous oxide and vitamin B12

EDITOR,—The paper by Kanagasundaram et al on the use of nitrous oxide to alleviate pain and anxiety during painful procedures fails to mention the effect of this gas on cobalamin metabolism. Nitrous oxide inactivates cob(III)alamin, the active derivative of vitamin B12, and essential cofactor for the transfer of the methyl group from methyltetrahydrofolate to homocysteine to form methionine. For subjects with good body stores of cobalamin this effect is unimportant, but no-one using this agent should remain unaware of the potentially devastating complications in the nervous system of using nitrous oxide in subjects who are of borderline or deficient vitamin B12 status. Onset of subacute combined degeneration affecting the brain and spinal cord is a well documented event when individuals with low body stores of cobalamin are exposed to nitrous oxide.

There is a long list of situations which put children at substantial risk of cobalamin deficiency—for example, systemic malignancy or chemotherapy. Children with chronic conditions often need painful procedures, and depleted cobalamin stores may not be apparent unless measurements of serum B12 are made routinely. What is more, repeated use of nitrous oxide depletes the body stores of cobalamin even in well people.

Given the scale of use which would result from routine use of nitrous oxide in children undergoing painful procedures, there should be real concern about the potential for an accident in a child with occult cobalamin deficiency. The message must be: never forget vitamin B12 when thinking of using nitrous oxide.

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Adrenaline syringes: community perspective

Editor—We read with interest the paper by Unsworth regarding the over-prescribing of adrenaline syringes. We are sure we are not the only community paediatric team who have similar concerns, although perhaps from a different perspective. Dr Unsworth writes of the safety issues. We have more experience of the practical problems.

Thanks to the availability of prompt training for school staff by community personnel, it is now rare for a child to actually be excluded from school because they have an adrenaline injection device. However, they may very well be excluded from other activities such as guide camp or trips abroad.

There is also the increasing problem of young people with adrenaline injection devices moving on to college or work places. Who should train staff there?

Other problems with adrenaline injection devices in our local community include two being lost on the bus, and one being accidentally fired into the interphalangeal joint of a child’s thumb with the needle becoming bent like a fish hook.

There is also the issue of keeping them in date. Parents often forget to renew them, particularly those kept in school. Whilst it does not need to be kept in a refrigerator, adrenaline does deteriorate in warm conditions, and injection devices should be checked to make sure the adrenaline inside remains clear and colourless.

Often, an adrenaline injection device has been prescribed with no demonstration to the child or family on how to give it, nor when to give it. Surely adrenaline should also be prescribed in every case? In most children, it is the only medication which is going to be needed. It is also important to instruct them as to when to call an ambulance. They could easily make the mistake of trying to take a deteriorating child to hospital in their own car, instead of calling for a specific ambulance, or even assuming that they do not need to go to hospital at all if they have given adrenaline. As Dr Unsworth points out, the adrenaline injection does not always save the child’s life.

We would suggest that when an adrenaline injection device is prescribed it must be demonstrated to both the parent and child (if the child is old enough). A dummy pen is helpful for this. Demonstration should be repeated with each repeat prescription of the device. The child and their family should always have a written management protocol, including instructions on expected symptoms, when to give antihistamine, when to call an ambulance, and when to give adrenaline. Such a protocol can then be passed rapidly to the community paediatric team to support the prompt training of school staff.

It is worth remembering that clinical responsibility for the safe administration of a drug rests with the prescriber.

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1 Unsworth DJ. Adrenaline syringes are vastly over prescribed. Arch Dis Child 2001;84:110–11.

Controversies in paediatrics?

Error,—I was very disappointed to see that the first contribution to the Controversy series was not written by a paediatrician. There are plenty of controversial topics in paediatrics, including the one cited. There are also plenty of paediatricians perfectly qualified to write an informed debate about them, again including the topic cited. The absence of a contrasting viewpoint in the same issue suggested to me the feature should be called “Opinioneers vs most (but not all) practitioners” because the article is not a balanced review of the current state of allergy practice.

The BPA and latterly RCPCH have championed for decades the holistic approach to the care of children. Paediatricians are best placed to assess the integrated needs of a child with medical problems. This principle is very relevant to developing areas of specialisation in which there is short supply of expert advice, such as in allergy. Paediatric allergists assess the impact of the diagnosis on many non-medical facets of a child’s life, including family lifestyle, integration into schools and peer groups, and the facilitation of appropriate independence from parental supervision.

It is tiring to have to rehearse the arguments for the adequate protection of subjects at risk of anaphylaxis. Epinephrine (as all doctors should now be calling adrenaline) is not prescribed for either children or families with an allergic child. It is part of the integrated management plan, which appears to be effective though difficult to measure.

It is very hard to prove that epinephrine saves lives and I agree that the notional “number needed to treat” with epinephrine to prevent a death from anaphylaxis is very high. Unsworth’s title suggests that this “very high number” (my phrase) is too high. How has he measured that? What is too many? He quotes a prevalence of about 1/1000 of American children having peanut allergy. That is approximately 3 million subjects. We do not restrict insulin syringes to just a few insulin dependent diabetics because diabetes is so common that we cannot adequately care for all of them. Every allergic child has the right to become available, which is not restricted to the first 100 through the clinic door (if they can find an allergy clinic).

Laparotomy will not save every patient with a leaking aortic aneurysm. Anaphylaxis will not save every person who has anaphylaxis. Anaphylaxis is a critical situation in which prompt administration of epinephrine may (but occasionally may not) save a life. I think it unarguable that it is better to self treat and probably survive than not self treat and possibly die. Unsworth quotes one early paper about anaphylaxis from the USA and more recent British data. These papers all tell us more that anaphylaxis is used due to unavailability or inappropriate training and patient confusion, rather than that epinephrine is useless or dangerous. Most subjects did not have epinephrine available. Several of the deaths were due to enteral feeding and were due to incorrect use of available epinephrine. In addition, epinephrine appears to be more dangerous in the hands of doctors who give it IV than in the hands of allergy subjects who self treat. I recommend your readers look at the report on the latest series of food related deaths.

In the absence of any perfect predictive test, allergists are confined to basing risk of future severe reactions on just a few variables. The first is a history of previous severe reactions. The majority of peanut allergies have had a severe reaction in the past and more than 60% have asthma, the second known association with severe reactions. According to current opinion, then, even after just one reaction to peanut most subjects are considered at risk of severe future reactions. Many minor reactors to peanut progress to more severe reactions and could consider being on “epinephrine” for just this reason.

Doctors must remember epinephrine is prescribed to be available for response to infrequent exposure at an uncertain future date, not to be taken four times a day. I have referred to this in the past as analogous to wearing a seatbelt on every car trip, every day, even though a serious car accident is unlikely on any individual day.

Unsworth is not up to date in his comments about the diagnosis of IgE mediated allergy. There are strong data from huge series of challenges, about the negative predictive values of the tests used in allergy clinics. Unsworth does not even mention formal challenges, the cornerstone of modern food allergy practice. The allergist would prescribe epinephrine on the basis of a positive SPT in the absence of a significant history or formal challenge.

Children and adults at risk of food related anaphylaxis have enough of life’s pleasures denied to them. The provision of epinephrine
kits allows normal life to go on, involving school, overnight stays at friends, camping, and other normal activities of childhood. Anecdotally, parents seem to me less stressed when they leave clinic with information (however awful the scenarios described) and response strategies than when they arrive. I have never met a parent who reported being more scared of the epinephrine kits than of the prospect of allergen exposure (with or without epinephrine available).

Families must be taught when to use epinephrine and how to use autoinjectors. Until doctors can tell families that anaphylaxis will never happen we should continue to empower families, ensuring they are ready to respond as best they can to the disaster that allergen exposure represents. When anyone develops a real treatment for food related anaphylaxis I can stop prescribing epinephrine kits to people who currently need them.

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Appropriate prescription of epinephrine remains the best available treatment

EDITOR,—Epinephrine kits enable a food allergic child at risk of anaphylaxis to lead a normal life and participate in childhood activities that could easily be denied by a parent terrified of another allergen exposure. Avoidance of allergens rather than rescue epinephrine therapy is the basis of current management of food allergy. However, unexpected exposures are inevitable. Fifty eight per cent of children followed for five years experienced adverse reactions from accidental peanut exposure.5 Peanut is the most common food allergen causing anaphylaxis and perved as the most often used, in food processing. Anaphylaxis related to foods most commonly occurs in patients who have had previous severe reactions. However, minor initial reaction does not exclude a subsequent severe reaction to peanuts. Any person with anaphylaxis deserves the best available protection. It is reasonable to always have two Epipens available both at home and at school. And a second Epipen provides back up if a faulty technique is used or one syringe is damaged. Anaphylaxis may be biphasic, recurring in 3% of children admitted with anaphylaxis.6

As advocates of children, paediatricians are unlikely to hand out epinephrine syringes without due consideration of the impact on the child and his or her family. A comprehensive plan with written information is essential for any child seen with a food allergy whether or not epinephrine is prescribed. Sicherer et al showed 20% of children did not carry epinephrine outside the home and only 55% had unexpired epinephrine on them. However, successful demonstration was associated with repeat prescriptions, membership of a lay organisation for food allergy, and being reviewed by a specialist. Training packages for schools such as devised that by Vickers in Cambridge1 are valuable.

Unsworth states that “Community use should be much more restricted with increased involvement and training of the medical staff”. Food allergy is the most common cause of anaphylaxis in children outside hospital. Early recognition and use of epinephrine is vital for successful outcome. The median time to respiratory or cardiac arrest was thirty minutes and hence occurred anaphylaxis in one series.7 Surely this implies that the community is the setting where epinephrine should be given by appropriately trained carers and carers to a food allergic child with signs of anaphylaxis. Parents should be empowered as limited resources prevent medical staff being present immediately. Indeed, epinephrine IV by trained medical staff also appears to be more hazardous than the use of epinephrine by lay caregivers.8

In the absence of any other treatments for food related anaphylaxis, the considered use of epinephrine kits as part of an integrated management plan is the best choice.

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Reply

EDITOR,—I was pleased to see that my article provoked lively discussion of this important issue. I am not surprised therefore that some are concerned about poor compliance. I agree with Wolff and Runney that adrenaline should never be the sole prescription. In addition to antihistamines, prednisolone has a place. The idea of a writing group meeting to write these guidelines is a good one.

Hourihane contrasted prescription of adrenaline with provision of insulin syringes in diabetes mellitus. We do not restrict provision of insulin syringes in that context because to do so would inevitably result in hypoglycaemia and ill health in all cases, ranging from coma to retinopathy. The risk benefit ratio is clearly in favour of daily insulin use. By contrast, the “very high” number of adrenaline prescriptions is not. Surelly this implies that the risk benefit ratio.

In our clinics, where we see large numbers of both adults and children, reviewing the last few years we have seen one fatal and two near fatal episodes related to adrenaline usage (submitted for publication). Admittedly, all three were in adults. Hourihane describes “epinephrine” to “most (but not all) subjects who have reacted to peanuts”. He also implies that some patients do not get the prescription.

Those with a previous history of only mild reactions can go on to suffer severe life threatening episodes,9 so all anaphylaxis related fatalities will surely demand adrenaline. He would not prescribe adrenaline in the absence of a significant clinical history of true nut allergy, (and I applaud that) but others regrettably do, and I know from personal experience that once the mistake is made, it is hard to reverse. I like the seat belt analogy, but seat belts have few side effects. Regarding positive and negative predictive values of IgE based allergy blood tests, my point is that often these tests are misleading. Patients with eczema, (a common finding in those presenting with possible nut or food allergy) typically have high background IgE levels and false positives are common.

Dr Abay reminds us that the prescribing medical staff including doctors may administer adrenaline incorrectly. That fact does not justify delegating responsibility to the general public in these cases. They are surely less likely to make errors, despite training and/or management plans. Expecting the public to confidently decide whether to use the adrenaline or not, is expecting a lot. Fatal episodes do in fact tend to occur within minutes of allergen exposure and can evolve to anaphylaxis rapidly, even in cases where previous reactions have been benign. Families may well misjudge and/or err on the side of caution, giving adrenaline early for what was likely to turn out to be another benign reaction. Hence my keenness for restriction of community use and increased reliance on trained medical staff.

I was also impressed that within the community many thousands of children and adults experience unpleasant but essentially benign reactions each year, very few very prove fatal.10 In the community context, focusing on the higher risk groups including asthmatics would be my preference.

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1 Unsworth DJ. Adrenaline syringes are vastly over prescribed. Arch Dis Child 2001;84:410–11
Hypoglycaemia and hypothermia due to nimesulide overdose

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