SHORT REPORTS

Idiosyncratic reactions to carbamazepine mimicking viral infection in children

Adverse reactions to carbamazepine include rashes, lymphadenopathy, hepatosplenomegaly,[1] and bone marrow depression ranging from mild leucopenia to aplastic anaemia.[2] Such reactions are rare in children. Mild leucopenia does not indicate withdrawal of the drug, but more serious bone marrow and systemic effects do. We report two cases in which the initial presentation mimicked viral infection and was associated with profound neutropenia.

Case reports

Case 1—A 1 year old girl with poorly controlled myoclonic and complex partial epilepsy developed fever and cervical lymphadenopathy eight weeks after carbamazepine had been added to her treatment. Five days later her neutrophil count had fallen from $1{\cdot}72\times10^9$/l to $0{\cdot}25\times10^9$/l and the carbamazepine was stopped. After three further days the neutrophil count had returned to $1{\cdot}8\times10^9$/l and her clinical illness resolved. She was subsequently challenged with carbamazepine; after six days her neutrophil count had fallen to $0{\cdot}85\times10^9$/l, increasing to 3×10^9/l five days after the drug was stopped.

Case 2—A 6 year old girl with myoclonic and complex partial epilepsy developed an itchy maculopapular rash on her trunk, scalp, palms, and soles two weeks after her treatment was changed from phenytoin to carbamazepine. Palatal petechiae, cervical and inguinal lymphadenopathy, and (subsequently) hepatosplenomegaly were also found. A blood film showed "atypical lymphocytes," but there was no neutropenia (neutrophils $5{\cdot}78\times10^9$/l). Monospot and serial viral titres were negative, as were other indices of infection. A week later she became anorectic and lethargic. The rash had faded and become pigmented, but the lymphadenopathy and hepatosplenomegaly persisted. The neutrophil count fell to $0{\cdot}07\times10^9$/l. Carbamazepine was stopped, and over the following week her clinical condition and neutropenia resolved.

In both patients the haemoglobin concentration and platelet count remained normal, and because of this and the rapid response to withdrawal of the drug bone marrow examinations were not performed.

Comment

Both children's neutropenia was thought to have been caused by a viral illness, but their problems resolved when carbamazepine was stopped. The table summarises these and four other reported cases. In those children taking other anticonvulsant treatment the neutrophil count increased when only the carbamazepine was stopped. Challenge with carbamazepine produced recurrence of the leucopenia in our first case and of the clinical features in the case reported by Bertrand *et al* (case 6 in the table).[5] In all patients the symptoms were initially thought to be infective (streptococcal or viral) in origin, and malignancy was also suspected in one patient.

These reactions to carbamazepine are thought to be idiosyncratic and may be due to hypersensitivity and formation of immune complexes.[1] The exact prevalence of such reactions is not known; fewer than 20 cases of rash, lymphadenopathy, and fever have been reported in adults and children, and only two other cases of hepatosplenomegaly, both in adults.

It has been suggested that haematological reactions occur more commonly in adults, but Silverstein found an incidence of leucopenia of 17% in a group aged 0-12 years and 8% in a group aged 12-17.[2] This does not appreciably differ from the generally accepted incidence of 10% in all ages. He recommended undertaking blood counts monthly for six months and then every three months. An idiosyncratic reaction to carbamazepine causing a potentially serious haematological abnormality should be considered in patients presenting with clinical symptoms of viral or streptococcal infection or of lymphoma. In these cases haematological examination is essential, but routine blood counts are unlikely to be worth while.

We thank Dr B G R Neville and Professor R J Robinson for permission to report these cases and Mrs Deirdre Gillies for typing the manuscript.

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Department of Paediatrics, Guy's Hospital, London SE1 9RT
CAROLINE BRAIN, MRCP, paediatric senior house officer
BREEGE MAC ARDLE, MRCP, honorary registrar in paediatric neurology
SIMON LEVIN, MRCP, paediatric senior registrar

Correspondence to: Dr C Brain.

Doses of aminophylline given intravenously in casualty department and resulting serum theophylline concentrations

Aminophylline is commonly given intravenously as emergency treatment for asthma and acute bronchitis, even to patients already receiving theophylline treatment who have appreciable serum theophylline concentrations.[1] We noted doses of aminophylline used in a hospital casualty department, and measured the effect on serum theophylline concentrations.

Patients, methods, and results

We studied 33 consecutive adults, 22 (16 women, 6 men) with asthma and 11 (all men) with chronic obstructive airways disease, who received aminophylline intravenously in the casualty department. Prior treatment with theophylline orally, rectally, or parenterally was recorded. The dose of aminophylline, given over at least 10 minutes, was at the discretion of the administering doctor. Blood was taken before and one to two hours after the completed injection for assay of theophylline by the enzyme multiplied immunoassay technique (Syva).

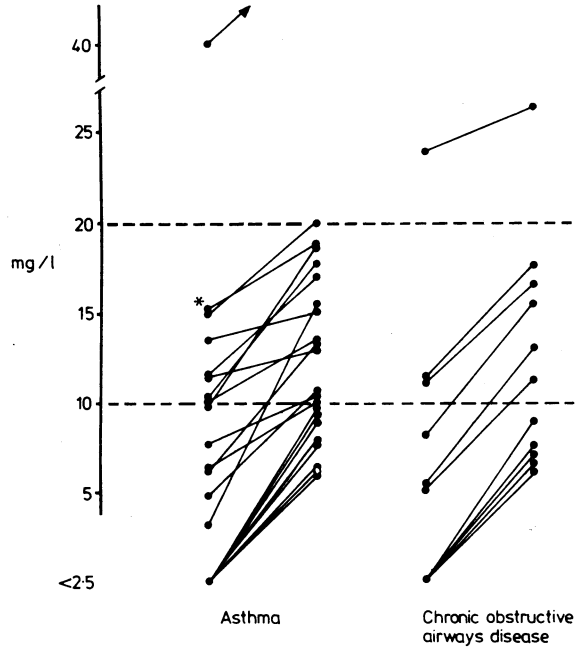
The 22 patients with asthma and 11 with chronic obstructive airways disease had mean (SD) ages of 45·1 (15) and 65·8 (5·3) years respectively and weighed 65·5 (15·8) kg and 65·2 (19·3) kg. Fifteen with asthma and seven with

Idiosyncratic reactions to carbamazepine in children

Case No and reference	Age (years)	Sex	Other drugs	Rash	Pyrexia	Lymphadenopathy	Hepatomegaly	Splenomegaly	Minimum neutrophil count ($\times10^9$/l)	Initial diagnosis	Response to stopping carbamazepine
1	1	F	Phenytoin, phenobarbitone, diazepam	–	+	+	–	–	0·25	Viral infection	Resolved*
2	6	F	None	+	+	+	+	+	0·06	Viral infection	Resolved
3[1]	8	M	None	+	+	+	+	+		Glandular fever	Resolved
4[3]	15	M	None	+	+	+	+	+		Streptococcal infection or lymphoma	Resolved
5[4]	11	F	Phenobarbitone	+	+	+	+	+	0	Viral infection, lymphoma, or systemic lupus erythematosus	Resolved
6[5]	14	M	Phenobarbitone, diazepam	+	+	+	–	+		Drug reaction or lymphoma	Resolved*

*Relapse after challenge with carbamazepine.

chronic obstructive airways disease had received theophylline (daily dose 9·8 (4·7) mg/kg and 8·1 (3·6) mg/kg) and one with asthma had received aminophylline 250 mg intravenously before arrival; their mean initial serum theophylline concentrations were 11 (9·1) mg/l and 9·3 (7·5) mg/l. The differences between these doses and initial concentrations were not significant, but outpatient doses and initial concentrations correlated significantly ($p<0·01$) but loosely ($r=0·59$). Serum theophylline concentrations were within the therapeutic range (10-20 mg/l) in nine, potentially toxic in two,



Serum theophylline concentrations before and one to two hours after intravenous injection of 250 mg (*125 mg) aminophylline (optimum therapeutic range between broken lines).

and undetectable in two. Five patients who gave no history of treatment with theophylline had positive assays; in three the history was unsatisfactory, and two were receiving a compound preparation (Franol) not realised to contain theophylline.

The admitting doctor gave 250 mg aminophylline intravenously to 32 patients and 125 mg to one. The mean increase in serum theophylline concentration was 6·3 (2·4) mg/l. The figure shows individual serum theophylline concentrations before and after the injection. No acute complications were recorded.

Comment

To achieve therapeutic theophylline concentrations rapidly in untreated patients an initial dose of aminophylline 6 mg/kg intravenously has been recommended.[2 3] Despite this advice, our findings suggest that the dose of aminophylline given intravenously in casualty was determined by the size of the ampoule (250 mg), which represented 4·1 (0·7) mg/kg in our untreated patients, and resulted in a mean serum theophylline concentration of only 7·5 (1·4) mg/l after one hour. Although peak serum concentrations occur immediately after the injection, we chose this interval to reflect the therapeutic appropriateness of the dose by allowing for redistribution of the drug and variations in the speed of injection.

In 17 patients treated with theophylline, only one received a modified dose of aminophylline; the doctor did not realise that theophylline had been taken by a further five. These findings underline the need for careful inquiry before administering intravenous aminophylline and for awareness of the composition of compound bronchodilator preparations.

Initial serum theophylline concentrations in those on treatment were mainly in the low or subtherapeutic range. The dose given (mean 3·8 (1) mg/kg) resulted in serum concentrations of over 20 mg/l in only the two patients with already high concentrations, although concentrations may have been higher immediately after the injection. In a recent study 14 (12%) of 113 outpatients in a stable condition receiving theophylline had serum concentrations over 20 mg/l.[4] During exacerbations clearance of theophylline can fall, but patients often increase their rectal or oral intake. In one of our patients the result was an initial serum concentration of 40 mg/l.

Our results indicate the need to estimate aminophylline dosage more carefully to achieve optimum therapeutic concentrations and avoid overdosage. They support the current recommendations of a loading dose of 6 mg/kg in those who have not taken theophylline within 24 hours.[5] A loading dose may be inappropriate in patients already being treated but, in the absence of evidence of toxicity, 3 mg/kg can be administered with relative safety if intravenous aminophylline is considered to be essential.

We thank all participants, Dr R C Strange and his staff for performing the assays, and Miss Mary Ash for typing the manuscript.

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Department of Respiratory Physiology, City General Hospital, North Staffordshire Hospital Centre, Stoke on Trent ST4 6QG
C S MUNRO, MB, MRCP, medical registrar
K PROWSE, MD, FRCP, consultant physician

Correspondence to: Dr C Munro.

Can Trichomonas vaginalis cause pneumonia in newborn babies?

The differential diagnosis of respiratory distress in the newborn baby is often difficult. The clinical and radiological picture of conditions such as bacterial and aspiration pneumonia may be similar to those of delayed absorption of lung fluid.[1 2] Many babies are therefore treated empirically with antibiotics. We describe a patient who was considered to have one of the above conditions until microscopical examination of a wet preparation of tracheal aspirate showed many *Trichomonas vaginalis* organisms.

Case report

A boy weighing 3690 g was born at 40 weeks' gestation after an uneventful pregnancy. A mild vaginal discharge had occurred early in pregnancy; microscopical examination for *Trichomonas vaginalis* gave negative results, but *Candida albicans* was cultured. The membranes broke 15 hours before delivery. There was no passage of meconium and no sign of fetal distress. The baby was, however, asphyxiated at birth (Apgar scores were: 1 at 1 minute, 3 at 5 minutes, and 7 at 10 minutes). He was immediately intubated and placed on a ventilator. Thick white sputum was aspirated from the trachea. Microscopical examination of wet preparations of tracheal aspirate and gastric content[1] showed scanty leucocytes and numerous organisms with motile flagella which resembled *Trichomonas vaginalis*. The identification was confirmed by the department of microbiology. A chest radiograph showed widespread patchy infiltrates in both lungs. A full blood count showed $7·1\times10^9$ leucocytes per ml with 21% band forms. The child was given ampicillin and tobramycin intravenously. Bacterial cultures of blood, cerebrospinal fluid, and aspirates of the trachea and gastric contents were sterile. As there was a rapid improvement in the clinical signs and blood gases we decided not to start treatment with metronidazole.

Assisted ventilation was stopped at 36 hours. The tachypnoea and radiological changes, however, persisted until day 7. The patient was well when discharged at 14 days of age and was thriving at follow up two weeks later.

Comment

We had previously found *Trichomonas vaginalis* in the gastric contents of two other babies with respiratory distress, but had not considered this contamination to be clinically important. McLaren *et al*[3] have now suggested, however, that this parasite may cause neonatal pneumonia. They reported on two babies who required ventilation for their respiratory disease for which bacterial and viral causes were excluded. *Trichomonas vaginalis* was not seen on Gram's stain of the tracheal aspirate, and diagnosis was delayed until the organism was found growing on the viral culture medium. The babies responded