later myoclonic jerking began in her arms; she felt frightened, and had episodes of panic. A nocturnal tonic-clonic seizure followed 48 hours after the last dose. Her family doctor gave her an anticonvulsant and referred her to the neurology outpatient clinic, where clinical examination and an electroencephalogram (EEG) showed no abnormality. The anticonvulsant was stopped gradually, and there have been no seizures in the four months since the single attack. Symptoms of anxiety continued for weeks, but she has not taken any tranquillisers.

Case 2—A 27-year-old woman had an eclamptic seizure after her first delivery seven years earlier. For four years she had been taking lorazepam 7.5 mg daily but it was stopped abruptly so that she might start a new tranquilliser. Twenty-four hours later, before she had taken the new drug, she had a tonic-clonic seizure and was admitted to hospital. Physical examination and an EEG were normal, and she was discharged without drugs. Once home she restarted lorazepam because of feelings of panic. Two months later she stopped the lorazepam, again abruptly, and 24 hours later had another tonic-clonic seizure. She was admitted under the medical firm who had managed her before, and an anticonvulsant was prescribed. It was weeks before she was able to leave her house because of anxiety and tremor. These symptoms settled spontaneously, the anticonvulsant has been withdrawn gradually, and there have been no seizures in the three months since her last attack.

Comment

Both these patients had been taking lorazepam for years but not in excessive doses. In each case abrupt withdrawal produced unpleasant symptoms and a seizure. The possibility that the seizures were due to drug withdrawal was not considered by the doctors who first saw the patients, and anticonvulsants were started.

In a study of abrupt withdrawal of chlorthalidone by placebo substitution all the patients experienced mild symptoms,³ but seizures seem more likely to occur after prolonged use or overdose. Although withdrawal seizures are not common, patients taking benzodiazepines should be warned to withdraw the drugs slowly. The possibility of drug withdrawal should be considered in any patient presenting with a seizure, for if this seems the likely cause prognosis and management will be radically altered.

I thank Dr S Currie, consultant neurologist, for permission to report these patients; and Mr J Cooke of the drug information unit, St James's Hospital, for his help in the preparation of the report.

¹ Hollister LE, Motzenbecker FP, Degan RO. Withdrawal reactions from chlorthalidone. *Psychopharmacologia* 1961;2:63-8.

² Kendall MJ. Hazards of abrupt withdrawal of drugs. *Prescribers J* 1978;18:25-34.

³ Covi L, Lipman RS, Pattison JH, Derogatis LR, Uhlenhuth E. Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatr Scand* 1973;49:51-64.

(Accepted 5 February 1980)

Department of Medicine, St James's University Hospital, Leeds LS9 7TF

J G HOWE, MB, MRCP, tutor in neurology

Meningitis caused by *Campylobacter fetus* ssp *jejuni*

Campylobacter fetus, formerly classified as *Vibrio fetus*, are bacteria well known to cause enteritis and, occasionally, systematic infections in man.¹ We report a case of meningitis caused by *Campylobacter fetus* ssp *jejuni*, a species not previously associated with this condition.

Case report

The patient was a 34-year-old American who had been operated on when aged 5 years for a neuroblastoma. He had suffered since from dysarthria and ataxia but his mental development was normal. In July 1979, when visiting Scandinavia, he developed fever and increasing ataxia and dysarthria. On admission to hospital after 24 hours he had signs of dehydration and meningitis. The cerebrospinal fluid (CSF) was clear and yellowish, and contained monocytes $184 \times 10^6/l$ ($184/mm^3$), polymorphonuclear leucocytes $155 \times 10^6/l$ ($155/mm^3$), protein 6.5 g/l, and glucose 0.5 mmol/l (9 mg/100 ml).

Concurrent blood glucose was 7.0 mmol/l (126 mg/100 ml). CSF microscopy was negative, but cultures yielded a spirochete-like organism that was later identified as *Campylobacter fetus* ssp *jejuni*. The organism was resistant to ampicillin but sensitive to chloramphenicol and metronidazole. On suspicion of a cerebellar tumour or abscess a computer-aided brain scan was performed. It showed a catheter running from the fourth ventricle through the ventricular system to the parenchyma of the right frontal lobe, a slight enlargement of the ventricular system, and a postoperative bone defect.

Treatment with chloramphenicol 1 g intravenously thrice daily for 11 days brought rapid recovery and a normal CSF. The patient was discharged and told to seek medical attention in the United States as soon as possible. For various reasons he did not do so until a week later and did not take any antibiotics during that period. He relapsed and was admitted to hospital with increased cerebellar symptoms and signs of meningitis. The CSF findings were almost identical to those described above, but cultures were sterile and microscopy did not show any micro-organisms. He did not respond to chloramphenicol 2 g intravenously twice daily, and his fever remained at about 39°C. The chloramphenicol was increased to 2 g four times a day. The symptoms then subsided and he recovered over the next seven days, after which he was afebrile and his CSF normal. Treatment was maintained for 14 days, and he was then followed up for six weeks without showing any further signs of relapse.

Comment

Campylobacter is well known to cause veterinary diseases and is one of the commonest causes of gastroenteritis in man.¹ A relatively large number of systemic infections caused by it, especially septicaemia, have been reported.¹ Most of these infections have been caused by *Campylobacter fetus* ssp *intestinalis*. The subspecies identified in our patient, *jejuni*, has only rarely been associated with systemic infections but seems to be the organism normally causing enteritis.¹ Our patient was compromised by his previous brain operation and by the resulting catheter in his ventricular system. Importantly, campylobacter systemic infections seem to be most prevalent in the type of patients who are at risk of developing infections caused by *Listeria monocytogenes*—that is, neonates and compromised adults. Since the clinical symptoms can be similar in these two infections, and since ampicillin is normally the drug of choice for treatment of listeriosis but is often inactive against *Campylobacter*,² this organism should be considered in the differential diagnosis in these patients.

We thank Dr M B Skirrow, Worcester Royal Infirmary, Worcester, England, for identifying the causative organism in this case.

¹ Rettig PJ. *Campylobacter* infections in human beings. *J Pediatr* 1979;94:855-64.

² Butzler JP, Dekeyser P, Detrain M, Dehean F. Related vibrio in stools. *J Pediatr* 1973;82:493-5.

(Accepted 1 February 1980)

Department of Infectious Diseases, University of Gothenburg, East Hospital, S-416 85 Gothenburg, Sweden

R NORRBY, MD, PHD, associate professor

Division of Infectious Diseases, Department of Medicine, Thomas Jefferson University, Philadelphia, USA

R V McCLOSKEY, MD, MS, professor of medicine

Department of Clinical Bacteriology, University of Gothenburg, Gothenburg, Sweden

GUNILLA ZACKRISSON, MD, registrar in clinical bacteriology
E FALSEN, PHD, civil engineer

Differences in serum ampicillin concentrations among patients under constant-rate infusion

Continuous infusion of a drug at a constant rate is supposed to maintain its serum concentration at a constant and predictable level. We investigated the truth of this in patients treated with ampicillin for severe purulent meningitis.

Patients, methods, and results

Twenty-four patients (15 men, 9 women) whose mean age ($\pm$ SE) was 37.6 ± 20.1 years (range 14-76) were treated for spontaneous bacterial meningitis with continuous intravenous infusion of ampicillin 150 mg/kg body weight/day. Ampicillin 50 mg/kg was diluted in 20 ml distilled water and infused at a constant rate with an intravenous perfusor pump. Under these conditions ampicillin remains stable for eight hours. No other drug was infused.¹ The serum antibiotic concentration was measured on treatment day 5. Three blood samples were drawn at one-hour intervals. Simultaneously with the second blood sampling the cerebrospinal fluid (CSF) antibiotic concentration was measured.² Assays were performed by microbiological methods using *Bacillus subtilis* as a test micro-organism. The sensitivity of the test was as high as 0.1 mg/l.

No significant difference was found in the concentrations in the different blood samples drawn at one-hour intervals in each patient. Thus it may be considered that in each individual the concentration of antibiotic remained constant during this period. But the differences in the concentrations among the 24 patients were large (from 9.4 mg/l to 92 mg/l). These differences could not be explained by the difference in the antibiotic doses received during 24 hours and recalculated for body weight. No correlation was found between blood concentration and sex or age. Since the rate of metabolism of ampicillin is relatively high (35 to 40%)³ hepatic metabolism is likely. Anticonvulsant drugs such as phenobarbitone and diazepam are hepatic enzymatic inductors⁴ and may modify serum ampicillin concentrations. In fact, nine of our patients were taking an anticonvulsant but there was no significant difference between their serum ampicillin concentrations and those of the remaining 15 patients. On the other hand, there was a significant correlation between the creatinine clearance and serum antibiotic concentration (figure). But the creatinine clearance variations may only partly explain the range of serum concentrations.

Relations between serum ampicillin concentrations and creatinine clearance in 24 patients under constant-rate infusion.

Comment

No definite conclusions can be reached from this study. Too many complex factors are concerned, and there is probably more than one reason for the differences in serum ampicillin concentrations, including variation in antibiotic distribution, protein binding of the drug, extrarenal metabolism, and differences in tubular function.⁵

Three considerations must be borne in mind. Firstly, though the serum concentration of a drug infused continuously may be estimated accurately in a normal healthy subject, this may not be the case in a critically ill patient. Secondly, when the dose-dependent toxicity of an antibiotic is small large doses must be given even against very sensitive micro-organisms (as for ampicillin in treating pneumococcal or meningococcal meningitis). Thirdly, when the minimum inhibitory concentration of an antibiotic is close to the available concentration the concentrations in serum and in situ must if possible be checked.

¹ Brodlie P, Henney C, Wood AJJ. Problems of administering drugs by continuous infusion. *Br Med J* 1974;i:383-5.

² Bouvet E, Gibert C, Witchitz J, et al. Diffusion méningée de deux bêta-lactamines du groupe A au cours des méningites purulentes. *Ann Med Interne (Paris)* 1978;129:657-60.

³ Von Simon C, Malerczyk V, Zierott G, Lehmann K, Thiesen U. Blut-, Harn- und Gallepiegel von Ampicillin bei intravenöser Dauerinfusion. *Arzneim Forsch* 1975;25:654-6.

⁴ Heubel F. Interferenz von Diazepam und Phenobarbital and der rattee und am Menschen. *Arch Exp Pharmacol* 1969;264:246-9.

⁵ Whelton A. Intrarenal antimicrobial distribution modulating factors, therapeutic and toxicologic implications. In: JP Fillatre, ed. *Nephro-toxicity*. New York: Masson, 1978:95-126.

(Accepted 23 January 1980)

Departement de Pharmacologie Clinique et Clinique de Réanimation Médicale. Hôpital Claude Bernard, 10 Avenue de la Porte d'Aubervilliers, 75019 Paris

E BOUVET, MD, chef de clinique assistant

C GILBERT, MD, professeur agrégé

C GAUDEBOUT, MD, maître de recherches

F VACHON, MD, professeur

Hydrallazine-induced hepatitis?

Hydrallazine has been widely used for treating hypertension, and its toxic effects are well known. Hepatotoxicity in the form of acute hepatic necrosis has only recently been reported¹ to be associated with its use. We report on a patient in whom we believe the drug was implicated in otherwise unexplained asymptomatic disturbance of liver function.

Case report

A 37-year-old woman presented with epistaxis. Her blood pressure was 215/150 mm Hg, and initial treatment with oxprenolol and a diuretic failed to achieve adequate control. She was found to be a rapid acetylator, and treatment with hydrallazine 25 mg twice daily was started. At this stage routine liver function tests were normal. Blood pressure was controlled at 175/110, but two weeks later she returned to the clinic complaining of malaise and palpitations. Hydrallazine was stopped and attempts were made over the next three months to control her hypertension with methyldopa and prazosin. Because of inadequate control and complaints of side effects she was readmitted for restabilisation of hypertension. Oxprenolol and bendrofluazide were continued and hydrallazine 25 mg twice daily reintroduced. Routine liver function tests done immediately before this were normal (see table). Three days after starting treatment with hydrallazine tests showed a

Results of liver function tests after treatment for hypertension

Date	Medication (total daily dose)	Liver function tests*		
		γ -glutamyl transpeptidase (IU/l) (normal range 0-35)	Alanine transferase (IU/l) (normal range 0-35)	Alkaline phosphatase (IU/l) (normal range 60-260)
20 Mar 1979	Bendrofluazide 5 mg	18	17	184
16 Aug 1979	Bendrofluazide 5 mg	11	11	161
17 Aug 1979	Oxprenolol 480 mg Prazosin 20 mg Prazosin replaced by hydrallazine 50 mg	12	11	153
20 Aug 1979		121	504	733
23 Aug 1979	Hydrallazine 100 mg	165	234	995
24 Aug 1979	Hydrallazine 150 mg	162	177	1077
31 Aug 1979	Hydrallazine stopped, prazosin started	—	—	—
4 Sept 1979		63	23	422
17 Sept 1979		32	12	222

*Serum total bilirubin remained within normal limits ($<17 \mu\text{mol/l}$; 0.99 mg/100 ml) throughout.

mixed hepatocellular-cholestatic picture of liver function abnormality with normal total bilirubin. The dose of hydrallazine was increased over the next four days to 150 mg daily. The liver function tests were still grossly abnormal but the patient remained asymptomatic and blood pressure was well controlled at 150/90. All other investigations including HBsAg were normal. After 10 days hydrallazine treatment was replaced again by prazosin. Liver function tests performed at follow-up 9 days and 5 weeks later had returned to normal.

This patient showed biochemical evidence of liver function abnormality within three days of starting on a low dose of hydrallazine. Liver enzymes were persistently raised throughout the two weeks of treatment but fell over the next two weeks after hydrallazine was discontinued. No other pathological causes of liver dysfunction could be found from viral and autoantibody studies. The patient had no evidence of pre-existing liver disease.