Results in the two treatment periods

	Clobazam	Placebo
<i>Mean No of seizures in treatment periods:</i>		
Generalised (n = 6)	16.7	24.2
Partial, with or without secondary generalisation (n = 14)	17.5*	32.4
All seizures (n = 20)	17.0**	29.9
<i>Mean serum concentrations, and ranges (μmol/l):</i>		
Carbamazepine	24.5 (14.8-34.7)	24.9 (14.4-39.3)
Phenytoin	51.5 (27.7-66.1)	49.1 (35.2-73.3)
Phenobarbitone	73.7 (18.5-115.5)	69.8 (18.5-94.8)
Sodium valproate	515.6 (159.4-907.8)	451.1 (256.4-817.7)
Clobazam	0.33 (0.13-0.99)	

* = 0.02; ** = 0.002.

Conversion: SI to traditional units—Carbamazepine: 1 μmol/l ≈ 0.24 mg/l. Phenytoin: 1 μmol/l ≈ 0.25 mg/l. Phenobarbitone: 1 μmol/l ≈ 0.23 mg/l. Sodium valproate: 1 μmol/l ≈ 0.14 mg/l. Clobazam: 1 μmol/l ≈ 0.30 mg/l.

Comment

These findings confirm the effectiveness of clobazam in the management of intractable seizures. Even when patients who withdrew from the trial because of side effects were included in the analysis significant differences compared with placebo were seen, and the complete disappearance of seizures in three of the 20 patients during active treatment was impressive. These data are comparable to the results of open studies by Gastaut,⁵ who reported a 76% improvement in patients with severe epilepsy. Moreover, the significance of our results in partial seizures, often so difficult to manage, was also in keeping with his results. Unlike Gastaut, however, we used lower doses, more in accordance with the regimen adopted by Martin.⁴

Our data are more directly comparable with the shorter double blind trial by Critchley *et al*³ who also reported significant benefits of low night time doses of clobazam on seizures. All data with this drug to date point to a rapid onset of anticonvulsant effects, minimal side effects, and development of tolerance in some patients. Although our active treatment period was nine weeks, open studies suggest that a sizable proportion of patients maintain improvement for 12 months or longer.⁴

The increased frequency of seizures on withdrawal is a potential problem with benzodiazepines, and our data suggest that, once started, clobazam should be tailed off with caution.

Our results suggest that further consideration should be given to the use of 1,5-benzodiazepines in epilepsy.

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α-Fetoprotein and ectopic pregnancy

Measuring maternal serum α-fetoprotein concentrations as a screening test for fetal neural tube defects is well established.¹ These and other birth defects, such as omphalocele and congenital nephrosis, result in increased concentrations of α-fetoprotein in the amniotic fluid owing to migration of the protein from the fetal serum through the congenital defects. From the amniotic fluid it crosses the fetal membranes into the maternal circulation. Raised serum α-fetoprotein concentrations may also be found after amniocentesis as a result of fetal serum leaking into the maternal circulation after breakdown in the fetal-maternal barrier.

We recently studied α-fetoprotein concentrations in five cases of tubal pregnancy. The protein was detected in all cases and the concentration was raised in two. To the best of our knowledge tubal pregnancy has not previously been associated with increased α-fetoprotein values.

Patients, methods, and results

Five women between seven and nine weeks of gestation (as computed from the first day of the last menstrual period) were clinically suspected to have an ectopic pregnancy. Ultrasonography showed adnexal masses in all cases (see table). α-Fetoprotein was detected in all cases using the Alphatek radioimmunoassay kit (Roche Diagnostics, Division of Hoffman-LaRoche Inc, Nutley, New Jersey). In two patients (cases 1 and 3) concentrations of the protein were raised—that is, above the 95th percentile. The concentrations were compared with the normal distribution of values in maternal serum at the New York Hospital-Cornell Medical Center based on 8217 samples tested.² Values above the 95th percentile were considered to be raised. Human chorionic gonadotrophin was determined by radioreceptor assay.³ Detectable concentrations were found in four cases (table). At operation tubal pregnancy was confirmed in all five cases.

Serum concentrations of α-fetoprotein and human chorionic gonadotrophin, results of ultrasonography, and operative findings in five patients undergoing surgery for ectopic pregnancy

Case No	Weeks of gestation	α-Fetoprotein (μg/l)	Human chorionic gonadotrophin (μg/l)	Ultrasonography	Operative finding
1	9	113.0*	20.0	Right sided mass including gestational sac by 6 by 4.5 cm	Partially aborted 6 by 8 cm right tubal pregnancy
2	6	11.6	6.2	Left sided mass 8 by 6 by 4.5 cm	Ruptured left ectopic pregnancy
3	8	46.9*	31.5	Enlarged left adnexa with small cystic component	Ruptured left ectopic pregnancy
4	7	11.1	<1.9	Intrauterine myoma 7 by 8 cm. Prominent right adnexa 3 by 3 cm with multiple small cysts	Right tubal pregnancy
5	7	12.5	92.1	Probable right adnexal mass	Right tubal pregnancy

*Raised value (above 95th percentile).

Comment

The leakage of small amounts of fetal serum into the maternal circulation may raise maternal α-fetoprotein values owing to the high concentration gradient of the protein across the placental barrier (100 000:1). In studying blood smears by the Kleihauer-Bethke techniques, Los *et al* found that spontaneous fetomaternal transfusions were significantly more common among 42 pregnant women with raised serum concentrations of the protein than among 42 pregnant women with normal concentrations.⁴ Chard *et al* found raised values in maternal serum in 11 out of 65 cases after amniocentesis.⁵

We previously found raised α-fetoprotein concentrations in maternal serum in three patients with placenta praevia and in a patient with molar pregnancy and a triploid fetus.² All were attributed to a breakdown in the fetal-maternal barrier.

The increased maternal serum α-fetoprotein concentrations in two of our patients with ectopic pregnancies can also be explained by breakdown in the fetal-maternal barrier. A normal placental implantation does not occur in tubal pregnancy but the villi grow freely, deep into the tubal tissue. This causes a breakdown in the barrier and fetal

α -fetoprotein can more easily reach the maternal circulation. Another possibility is absorption of fetal blood after tubal abortion.

Our findings support the use of Rh₀ (D) immune globulin in Rh-negative women with ectopic pregnancy. Determination of the α -fetoprotein concentration may also prove useful as an adjunct in the diagnosis of ectopic pregnancy.

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Acute meningitis in early childhood caused by *Aerococcus viridans*

Aerococcus viridans (syn *Gaffkya homari*, *Pediococcus homari*), which is commonly present in dust and air, has been isolated from patients with urinary tract infections,¹ endocarditis, and bacteraemia²; no reports exist on its causative role in meningitis. We report three cases of acute meningitis in children in which *A. viridans* was identified as the pathogen.

Patients, methods, and results

The table summarises the clinical and pathological data in the three patients. Cerebrospinal fluid, aspirated on admission, was plated directly at the bedside, with simultaneous smearing for Gram stains. The appearances of the smears from all three cases were similar, showing Gram positive discrete cocci which were extracellular as well as adherent to pus cells in fields with scanty organisms. Meningeal pus from the single fatal case (case 2) obtained at necropsy showed similar appearances.

Clinical and pathological features in *Aerococcus viridans* meningitis in early childhood

Case No and duration of illness before admission	Age (months), sex, history, symptoms, and signs	Peripheral blood		Cerebrospinal fluid			
		Leucocyte count	%, Neutrophils	Leucocyte count	Red cell count	%, Neutrophils	Protein glucose
1, one month	24, F; impaired head control, abnormal gait, decreased alertness, low fever, vomiting; flaccid limbs, decreased tendon reflexes, high stepping gait, truncal ataxia; history of leg impetigo one month before present illness	30 × 10 ⁹ /l	82	60 × 10 ⁶ /l	30 × 10 ⁶ /l	80	0.4 g/l 1.1 mmol/l
2, seven days	5, F; fever, refusal of feeds, generalised convulsions; bulging anterior fontanelle. Died	Not available	—	480 × 10 ⁶ /l	60 × 10 ⁶ /l	55	0.6 g/l 0.6 mmol/l
3, two months	7, F; jerky movements of limbs, irritability; bulging anterior fontanelle; history of upper respiratory tract infection at onset of present illness	11 × 10 ⁹ /l	78	6000 × 10 ⁶ /l	8 × 10 ⁶ /l	93	1.6 g/l 1.7 mmol/l

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Cultures of all three specimens of uncentrifuged cerebrospinal fluid (sheep blood agar, 37°C, two days in air) were pure and consisted of α -haemolytic optochin resistant colonies. Nutrient broth and Todd-Hewitt broth cultures of the isolates gave granular turbidity, with the cocci showing tetrads without chain formation. Growth occurred on media containing 40% bile salts, 10% NaCl, and 0.01% potassium tellurite and in media with a pH of 9.6. Growth was absent at 45°C; the cocci survived heating at 60°C for 30 minutes. All three strains from cerebrospinal fluid and a similar isolate from meningeal pus in case 2 gave identical cultural and biochemical reactions which conformed with typical reactions of *A. viridans*.²⁻⁵

Antibacterial drug sensitivity disc diffusion tests by the Kirby-Bauer method gave identical antibiograms with all three strains—sensitivity to tetracycline, streptomycin, penicillin, ampicillin, chloramphenicol, gentamicin, co-trimoxazole, sulphonamide, and erythromycin.

Identification of the isolates from the cerebrospinal fluid of cases 2 and 3 as *A. viridans* was confirmed by the National Collection of Type Cultures, London.

Two patients (cases 1 and 3) recovered completely with appropriate antibiotic treatment without residual lesions or abnormality in the cerebrospinal fluid. The remaining patient (case 2) developed an intercurrent intestinal and respiratory tract infection and died on the 12th day after admission. Necropsy showed basal and vertical pyogenic meningitis with greenish yellow pus.

Comment

In cases 1 and 3 impetigo and a respiratory tract infection, respectively, appear to have been the antecedent infections and possible sources of the organism. The relatively long history of the illness before admission in two of the three cases contrasts with the more acute meningitis caused by the usual pyogenic cocci and might suggest that *A. viridans* is of relatively lower pathogenicity. In the single death intercurrent intestinal and respiratory tract infections might have been a contributory factor.

The presence of cocci adherent to pus cells in the cerebrospinal fluid might suggest "adherence" properties which may be associated with the pathogenicity of this species.

We are grateful to Dr L R Hill (National Collection of Type Cultures, London) for examining two of our isolates of *A. viridans*.

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