Pyelograms from two identical twins. (a) Case 1, showing left chronic pyelonephritis; renal outlines have been pencilled in for clarity. (b) Case 2, showing normal appearances apart from a minor degree of duplex bilaterally.

Case reports

Case 1—This patient was investigated at the age of 18 for recurrent urinary infection. She had been aware of symptoms only for the preceding few months. The following year intravenous urography showed a normal right kidney and a shrunken left kidney with clubbing of the calyces (fig (a)) consistent with chronic pyelonephritis. On micturating cystography there was reflux up the left ureter as far as the renal pelvis but without dilatation of the renal tract. Cystoscopy showed a localized trigonitis. She was treated initially by urethral dilatation but, after a further recurrence of infection with haematuria, she underwent left nephrectomy at the age of 19. Histological examination confirmed the presence of severe chronic pyelonephritis. She continued to suffer from urinary infection and haematuria in the year after nephrectomy, at which point she was lost to follow up.

Case 2 is the twin sister of case 1. They were always regarded as identical, and identity was confirmed in 19 red cell types and the four HLA-A and HLA-B types (courtesy of Dr Ann Collins). She presented to one of us in general practice with a history of recurrent urinary infection, in which the first proved attack was at the age of 24. In view of the family history she was referred for investigation; no evidence of chronic pyelonephritis was seen on intravenous urogram (fig (b)). Micturating cystogram showed reflux up the left ureter of similar extent to that shown in her twin sister and also slight reflux up the right ureter. She was followed up as an outpatient for about three years, during which time she ceased to suffer from urinary infections. Repeat intravenous urography after five years confirmed the normality of the kidneys. Analysis of urine gave consistently normal results, and plasma urea and creatinine concentrations were within normal ranges.

Comment

The chronic pyelonephritis in case 1 was obvious on the intravenous urogram and its widespread presence in the kidney was confirmed by histological examination. Her twin sister’s left kidney was not, of course, examined histologically but it appeared entirely normal on two intravenous urograms giving a good demonstration of the calyceal system and on the nephrogram. The likeliest explanation for the different behaviour of the kidneys in two identical twins is that one contracted a urinary infection in infancy, when the kidneys were susceptible to reflux of infected urine, and the other did not. We cannot prove this hypothesis because our patient, like most of those in whom chronic pyelonephritis is diagnosed in adult life, had no recollection of infection in early childhood; at that age the symptoms are non-specific and they are often forgotten by the time the diagnosis is made 20 years later.


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Clobazam as adjunctive treatment in refractory epilepsy

The benzodiazepines have an established role in the treatment of epileptic seizures. Diazepam finds use either intravenously or per rectum in the management of status epilepticus, and several of the 1,4 structure have been evaluated for oral use in long term management of intractable seizures. More recently 1,5-benzodiazepines have been introduced, which are claimed to have fewer side effects but retain their therapeutic anti-convulsant potential. Clobazam has recently been evaluated as an anticonvulsant, and preliminary trials indicate its potential value as adjunctive treatment in epilepsy.1-4

We present the results of a double blind trial of clobazam versus placebo in patients with chronic poorly controlled epilepsy.

Patients, methods, and results

We studied 26 patients with a mean age of 34 (range 18-60) years. All were resident at the Chaffont Centre for Epilepsy and were having four or more uncontrolled seizures a month. Patients were given 30 mg clobazam nightly or an identically matched placebo capsule in a double blind cross over design. Half received the active treatment first, and each medication period was nine weeks. Between treatments there was an eight week washout period, and after treatment tablets were withdrawn over one week. Patients were seen at weekly intervals for assessment of side effects and dose adjustment. Early morning fasting blood samples were taken in each of the last three weeks of treatment for measurement of serum concentrations of clobazam, desmethyloclobazam, and concomitant antiepileptic drugs.

Six patients withdrew from the study, one during the placebo period. The table shows the frequency of seizures during each treatment period. There was a significant fall in frequency during the active treatment period (p= 0.002), especially of partial seizures. Three patients had no seizures and 12 had a 50% or more reduction with clobazam. When patients who withdrew were included as non-responders the number of patients showing a 50% or greater fall in seizures remained significant (χ²=14.3; p<0.001). Period or interaction effects were not seen.

Significantly more seizures were seen in the clobazam withdrawal period (p<0.002), but no significant tolerance to the drug effect was noted in those patients showing a response. (Tolerance was assessed by noting the frequency of seizures in the first and last halves of the active treatment period.)

Adverse effects occurred more often during the clobazam period: of the 20 patients staying in the trial, treatment was reduced because of side effects in six taking clobazam and two taking placebo. Mood changes recorded included irritability, depression, and disinhibition.

No significant changes in concentrations of other anticonvulsants were seen (table), although only a few patients were taking phenobarbitone, phenytoin, and sodium valproate. Serum concentrations of clobazam and desmethyloclobazam were not significantly related to the therapeutic response.

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, who reported a 76%, improvement in patients with severe epilepsy. Moreover, the significance of our results in partial seizures, so often 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.

Our data are more directly comparable with the shorter double blind trial by Critchley et al 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 on clobazam.

The increased frequency of seizures on withdrawal is a potential problem with benzodiazepines, and our data suggest that, once started, clobazam should be tailored 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. 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. Values above the 95th percentile were considered to be raised. Human chorionic gonadotrophin was determined by radioimmunoassay. 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

<table>
<thead>
<tr>
<th>Case No</th>
<th>Weeks of α-Fetoprotein</th>
<th>Human chorionic gonadotrophin</th>
<th>Ultrasonography</th>
<th>Operative finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>113*</td>
<td>20</td>
<td>Partially ruptured left</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>11.6</td>
<td>6.2</td>
<td>Partially ruptured left</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>46.9*</td>
<td>31.5</td>
<td>Enlarged left adnexa with no significant component</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>11.1</td>
<td>1.9</td>
<td>Intrauterine myoma 7.0 cm, Prominent right tubal pregnancy 3 cm by 3 cm with multiple small cysts</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>12.5</td>
<td>92.1</td>
<td>No abnormality</td>
</tr>
</tbody>
</table>

*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 (100000:1). In studying blood smears by the Kleihauer-Bethke technique, 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. Chard et al found raised values in maternal serum in 11 out of 65 cases after amniocentesis. 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. 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