tion may also occur if the dose given is inadequate. The DHSS recommends a 50- μ g dose if abortion takes place at less than 20 weeks' gestation and a 100- μ g dose if it takes place at more than 20 weeks' gestation.³ The recommended dose in the USA after full-term delivery is 300 μ g, but smaller doses are used in Europe.⁴ The risk of sensitisation seems to be related at least partly to the volume of fetal blood entering the maternal circulation. Thus a standard dose of anti-D immunoglobulin may be inadequate if there are a high number of fetal cells. While examining Kleihauer counts after mid-trimester abortions using amniocentesis and intra-amniotic prostaglandin and urea one of us (RB) found some counts of more than 100. All Rh-negative patients who had had an abortion by amniocentesis had received a routine dose of 100 μ g of anti-D immunoglobulin; this may not be enough, especially as patients who have had an abortion leave hospital soon afterwards and are not always followed up. High Kleihauer counts may be caused by amniocentesis if the needle passes through placental tissue, and even diagnostic amniocentesis may cause Rh immunisation.

We carried out a prospective controlled study to investigate the incidence and cause of high Kleihauer counts.

Methods and results

Venous blood was collected after mid-trimester abortion from 100 patients who had undergone amniocentesis at Wistons Nursing Home, Brighton and from 100 patients who had not undergone amniocentesis at the Robert Nursing Home. All the patients at Wistons Nursing Home had had abortions by intra-amniotic urea and prostaglandin while patients at the Robert Nursing Home had had extra-amniotic prostaglandin introduced by a transcervical catheter. Samples were collected shortly after abortion during the day and at 9 am from patients who had aborted during the night. All specimens were examined in the laboratory at Selly Oak Hospital alongside routine specimens from normal full-term deliveries. Fetal cells were counted using Shepard's modification of the Kleihauer technique, and one film was examined from the blood of each patient. Fifty low-power fields were scanned using $\times 8$ eye pieces and a $\times 10$ objective lens.

Most of the films showed no fetal cells (table). In patients with a positive

Number of fetal cells in maternal blood after mid-trimester abortion

Fetal cells in 50 low-power fields	No of patients	
	Extra-amniotic (no amniocentesis) (n = 100)	Intra-amniotic (amniocentesis) (n = 100)
0	81	81
1	12	7
2	3	2
3	2	3
4		1
5		1
6	1	
7	1	
16		3
160		1
237		1

result the counts were significantly higher in the amniocentesis group ($p=0.028$ using a one-tailed Mann-Whitney t -test); this group contained five patients with unusually high counts, including two with very high counts. None of the patients who had had extra-amniotic prostaglandin had counts of more than seven.

Comment

It appears that differences in abortion technique may be reflected in the amount of fetal blood entering the maternal circulation. Results in this study suggest that in most cases the differences have no practical importance, but it is interesting that high Kleihauer counts were found only in the patients who had had abortions by amniocentesis. Experience at this laboratory shows that two out of every 100 specimens taken after full-term delivery would be expected to have counts of more than 100. A larger study would be needed to confirm the hypothesis that the absence of high counts in patients who had had extra-amniotic abortions is related to the method of abortion.

High Kleihauer counts clearly occur after abortion, and in some cases the normal doses of anti-D immunoglobulin may be inadequate. Since follow-up is uncertain it is important that patients with unusually high Kleihauer counts are detected and treated within 24 hours of termination. This may be achieved either by doing Kleihauer counts routinely after mid-trimester abortions and giving patients with unusually high counts an extra 100 or 200 μ g of anti-D immunoglobulin or by giving a

larger-than-normal dose to patients with high counts and also testing them before discharge for free anti-D. The presence of free anti-D would show that any fetal cells had been saturated with antibody, while its absence would show that a further dose was needed.

Smaller doses of anti-D immunoglobulin are probably adequate for patients who have first trimester abortions, and attention may be concentrated on the relatively few patients who have later abortions.

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British Pregnancy Advisory Service, Wootton Waven, West Midlands B95 6DA

COLIN BREWER, MB, MRCPsych, research fellow

Selly Oak Hospital, Birmingham B29 6JF

E W BALL, MD, MRCPATH, consultant haematologist

Brighton Health District

ROBERT BEARD, FRCS, MRCOG, consultant gynaecologist

The Robert Nursing Home, Birmingham

PETER GITTINS, MB, DOBStRCOG, medical director

Pancreatitis caused by methyldopa

Methyldopa is a widely used antihypertensive but has a high incidence of adverse effects.¹ We report on two patients in whom pancreatitis was associated with methyldopa.

Case reports

CASE 1

A 61-year-old previously healthy woman was admitted because of high fever and pain in the back, arms, and legs, present for one week. She had no abdominal complaints. For three weeks preceding admission she had taken chlorthalidone 50 mg thrice weekly and methyldopa 250 mg thrice daily for hypertension. She had no evidence of biliary tract disease or alcohol abuse. Routine physical examination was normal. Temperature was 40.6°C, pulse regular at 90/min, and blood pressure 110/50 mm Hg.

Laboratory results included: normal urine analysis; erythrocyte sedimentation rate 68 mm in first hour; haemoglobin 12.4 g/dl; leucocytes $8.3 \times 10^9/l$ (96% neutrophils); potassium 3.0 mmol(mEq)/l (normal 3.5-4.8 mmol/l); calcium 2.09 mmol/l (8.4 mg/100 ml) (normal 2.25-2.60 mmol/l; 9.0-10.4 mg/100 ml); aspartate transaminase 25 U/l (normal <25 U/l); alanine transaminase 51 U/l (normal <30 U/l); alkaline phosphatase 92 U/l (normal <100 U/l); serum amylase 829 U/l (normal 70-300 U/l); protein 62 g/l; albumin 32 g/l (normal 36.5-51.0 g/l); direct Coombs negative. Blood and urinary cultures were negative. X-ray examination of the thorax, oral cholecystography, and ultrasonography of the upper abdomen were normal. All drugs were stopped and the temperature normalised within 24 hours. Serum amylase activity remained slightly raised.

She was rechallenged, with informed consent, with 250 mg methyldopa; in four hours she became feverish (39°C) and experienced the same pain as before admission. Physical examination was normal. Next day serum and urinary amylase activities were increased to 8190 U/l and 18 370 U/l (normal <2000 U/l) respectively; serum lipase activity was 4900 U/l (normal <80 U/l); erythrocyte sedimentation rate had increased to 104 mm in first hour. During the following weeks serum and urinary amylase and serum lipase activities gradually became normal.

CASE 2

A 69-year-old woman with cystic lung disease was admitted with increasing dyspnoea, fever, and abdominal pain over the preceding five days. For 24 hours she had been confused. She had been taking methyldopa 500 mg/day and frusemide 40 mg/day for two weeks; ampicillin had been started five days before admission because of the fever. On examination she was tachypnoeic, restless, and stuporous. Temperature was 39.2°C, pulse regular at 120/min, and blood pressure 100/60 mm Hg. Examination of the lungs showed no new abnormalities. The abdomen exhibited decreased bowel

sounds, and there was generalised rebound tenderness but no muscular rigidity or hepatosplenomegaly. Rectal and pelvic examination were painful but normal. Neurological examination showed no abnormalities.

Laboratory values were: erythrocyte sedimentation rate 5 mm in first hour; haemoglobin 15.3 g/dl; packed cell volume 47%; leucocytes $7.8 \times 10^9/l$, with a shift to the left; thrombocytes $128 \times 10^9/l$; serum amylase 1110 U/l (normal <340 U/l); aspartate transaminase 43 U/l (normal <17 U/l); alanine transferase 42 U/l (normal <21 U/l); lactate dehydrogenase 321 U/l (normal <200 U/l); direct Coombs negative. Electrolytes, blood glucose, renal function, and urine analysis were normal. Chest x-ray examination showed cystic abnormalities of the left lung; abdominal x-ray examination was normal. Pancreatitis caused by choledochal obstruction was suspected and all oral drugs stopped. Within two days the fever, confusion, and hyperamylasaemia had disappeared. Retrograde cholangiopancreatography showed two stones in the gall bladder but normal choledochal and pancreatic ducts.

Drug-related pancreatitis was suspected and with informed consent she was rechallenged with 250 mg methylodopa. Within three hours the same symptoms had developed. Serum amylase activity rose from normal to 2105 U/l in 12 hours, serum lipase activity rose to 1200 U/l, and a transient leucocytosis with left shift developed. All symptoms subsided in 36 hours; serum amylase and lipase activities normalised within five days.

Comment

In these two patients increased serum and urinary amylase activities accompanied by fever occurred after administration of methylodopa and reappeared on rechallenge. Although the first patient did not show the classical symptoms of acute pancreatitis, the increased serum amylase and lipase activities were suggestive of clinically mild pancreatitis. The second patient suffered from serious symptoms of pancreatitis. Although she had concomitant cholelithiasis, this is unlikely to have caused the pancreatitis because the choledochal duct was normal.

Drug-induced pancreatitis has occurred with several drugs, such as chlorthalidone and frusemide,² but these were stopped in our patients and could not have caused the pancreatitis after rechallenge. We could find reports of only two other cases of possible methylodopa-associated pancreatitis^{3,4} but believe that this may be more common than is generally thought.

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Deakness Hospital, Hilversum, the Netherlands

H VAN DER HEIDE, MD, resident physician (present address: Wilhelmina Gasthuis, Amsterdam)

M A TEN HAAFT, MD, resident physician (present address: Onze Lieve Vrouwe Gasthuis, Amsterdam)

Netherlands Centre for Monitoring of Adverse Reactions to Drugs, Leidschendam, the Netherlands

B H CH STRICKER, MB, medical officer

Withdrawal reaction from clobazam

Prolonged benzodiazepine treatment may lead to physical dependence and a characteristic withdrawal syndrome.¹⁻³ Clobazam (Frisium) is the first 1,5-benzodiazepine to be marketed, supported by the claim that therapeutic doses do not impair psychomotor performance,^{4,5} and the drug has not been reported to cause dependence. We report two cases from our studies of withdrawal reactions from long-term, low-dose benzodiazepine treatment.

Case reports

Case 1—A 36-year-old man with chronic anxiety had been treated with benzodiazepines for two and a half years. He had been taking clobazam 20-30

mg daily for a year, but lately he had complained that the clobazam was having little effect. He therefore tried several times to discontinue the medication but could only stay off the capsules for a few days, becoming increasingly tense and anxious; his sleep was disturbed and he had had shakes and perspired profusely. The symptoms disappeared on restarting the medication. He was gradually withdrawn from clobazam under supervision in our benzodiazepine withdrawal clinic using placebo-controlled double-blind conditions and assessment with several biochemical, physiological, and clinical measures. Plasma benzodiazepine concentrations were estimated using a radioreceptor binding assay.

Case 2—A 58-year-old man had a long history of anxiety and bouts of depression for which he had been prescribed benzodiazepines, mainly diazepam, up to 30 mg daily, for the past 16 years. He had been told that his affective disturbances might be due to diazepam addiction and hence he had tried several times to discontinue the medication but found that he could not tolerate the withdrawal symptoms, which subsided on restarting treatment. Clobazam 30 mg daily was substituted for the diazepam, and after six months he was referred to our withdrawal clinic. The clobazam was withdrawn in the same manner as in case 1.

In each case the withdrawal syndrome from clobazam was the same as that from other benzodiazepines—namely, a severe insomnia, tension, restlessness, anxiety, panic attacks, hand tremor, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, palpitations, blurring of vision and photophobia, and muscle pains and stiffness. The symptoms started soon after the drug was stopped, lasted for 8-10 days, and improved rapidly. Both patients experienced several more episodes of anxiety and tension, which gradually subsided over the next few weeks.

The figure shows some changes in relevant variables. Clobazam (and its active metabolites) was still detectable in the plasma one week after stopping the drug, in accord with the long half life of *N*-desmethyl clobazam. The electroencephalographic fast-wave activity (13.5-26 Hz) diminished as withdrawal proceeded. Psychological performance (digit symbol substitution test) improved and the Hamilton anxiety scale ratings increased to a peak after withdrawal, returning to prewithdrawal level as the syndrome subsided.

Reaction to withdrawal from clobazam. Case 1 —●—●; case 2 —●—●. Plasma drug activity in diazepam equivalents plotted against a time scale: weeks 1-2, full dose; 3-4, half dose; medication stopped at the end of fourth week. Electroencephalographic fast-wave activity (13.5-26 Hz) is expressed as a percentage of total electroencephalographic activity. Digit symbol substitution is expressed as items completed in 90 seconds.

Comment

In the past 18 months we have withdrawn 26 patients from low-dose, long-term benzodiazepine treatment. All suffered from anxiety as either a neurotic state or a personality disorder; none were alcoholic or took other drugs. All had received benzodiazepines for at least a year, and all experienced some form of withdrawal reaction comprising anxiety and dysphoria and usually also perceptual changes. Anxiety