Physiologically the electroencephalographic changes comprised pronounced reduction in fast-wave activity as the drugs were withdrawn. This drug-related effect is the reverse of the increase normally seen after administration of benzodiazepines.[11] We have also observed that auditory-evoked responses to clicks increase from very small prewithdrawal values to normal values over the same time. These effects may reflect psychological variables such as attention and arousal, and could be regarded as objective indicators of the hypersensitivity reported by many patients.

Psychological performance improved with time, as shown by the Digit Symbol Substitution Test. This test is subject to some effect of practice but not usually beyond two or three occasions. Furthermore, the improvement was too large to be explained by this alone. More likely it implies psychological impairment during chronic benzodiazepine ingestion, which suggests that such chronic usage has its drawbacks.

Other reports have generally suggested little concern,[12] but most were on patients who had escalated their dosage. Our findings, like those of other recent reports,[9 13 14] show that patients taking benzodiazepines in therapeutic doses risk developing some form of dependence.[15] We emphasise, however, that our patients were long-term users of benzodiazepines and were self-selected, in that they were referred because of their inability to stop their medication. Hence the present cohort may not be representative of benzodiazepine users generally, an issue which will be resolved only with proper epidemiological studies. Nevertheless, detecting withdrawal symptoms in patients taking normal therapeutic doses increases the urgency of the problem and argues against regular daily medication for chronic anxiety. Many thousands of patients may be at risk, as some 2% or so of the adult population take benzodiazepines chronically.

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References

1 Balter MB, Levine J, Manheimer DI. Cross-national study of the extent of anti-anxiety/sedative drug use. *N Engl J Med* 1974;**290**:769-74.
2 Lader M. Benzodiazepines—the opium of the masses? *Neuroscience* 1978;**3**:159-65.
3 Skegg DCG, Doll R, Perry J. Use of medicines in general practice. *Br Med J* 1977;ii:1561-3.
4 Shepherd M, Cooper B, Brown AC, Kalton GW. *Psychiatric illness in general practice.* London: Oxford University Press, 1966.
5 Taylor Lord, Chave S. *Mental health and environment.* London: Longmans, 1964.
6 Hollister LE, Motzenbecker FP, Degan RD. Withdrawal reactions from chlordiazepoxide ("Librium"). *Psychopharmacologia* 1961;**2**:63-8.
7 Fruensgaard K. Withdrawal psychosis: a study of 30 consecutive cases. *Acta Psychiatr Scand* 1976;**53**:105-18.
8 Preskorn H, Denner LJ. Benzodiazepines and withdrawal psychosis. Report of three cases. *JAMA* 1977;**237**:46-8.
9 Hallstrom C, Lader M. Withdrawal from benzodiazepines. *Int Pharmacopsychiatry* (in press).
10 Skolnick P, Goodwin FK, Paul SM. A rapid and sensitive radio-receptor assay for benzodiazepine in plasma. *Arch Gen Psychiatry* 1979;**36**:78-80.
11 Bond A, James C, Lader MH. Physiological and psychological measures in anxious patients. *Psychol Med* 1974;**4**:374-80.
12 Marks J. *The benzodiazepines. Use, overuse, misuse, abuse.* Lancaster: MTP Press, 1978.
13 Tyrer PJ. Benzodiazepine dependence and propranolol. *Pharmaceutical Journal* 1980;**225**:158-60.
14 Tyrer P, Rutherford D, Huggett T. Benzodiazepine withdrawal symptoms and propranolol. *Lancet* 1981;i:520-2.
15 Petursson H, Lader MH. Benzodiazepine dependence. *Br J Addict* 1981; **76**:133-45.

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SHORT REPORTS

Calcification of radiolucent gall stones during treatment with ursodeoxycholic acid

Both chenodeoxycholic acid and ursodeoxycholic acid reduce the cholesterol saturation index of bile and induce the dissolution of cholesterol gall stones in man. Ursodeoxycholic acid has been described[1] as the treatment of choice because it is effective at a lower dose and is free from side effects such as diarrhoea. The solubility of conjugates of ursodeoxycholic acid in bile is inferior to that of conjugates of chenodeoxycholic acid, and Igimi *et al*[2] predicted that precipitation of glyco-ursodeoxycholic acid could occur during treatment with ursodeoxycholic acid. This phenomenon would probably be associated with the precipitation of calcium, possibly as calcium glyco-ursodeoxycholate. We report calcification of gall stones in six patients during treatment with ursodeoxycholic acid.

Patients, methods, and results

Altogether 178 patients with radiolucent stones in radiologically functioning gall bladders were treated with chenodeoxycholic acid (122 patients) or ursodeoxycholic acid (56) for six months or more. The response to treatment was assessed in all patients by repeating oral cholecystography at six-monthly intervals. Calcification of the gall stones was assessed by radiologists who were unaware of which treatment had been given.

Six of the 56 patients given ursodeoxycholic acid developed calcification: in four patients this occurred within six months and in two within 12 months. None of the patients treated with chenodeoxycholic acid showed any evidence of calcification; this difference between the treatments was significant ($p < 0.002$, Fisher's exact test).

In four of the patients receiving ursodeoxycholic acid who developed calcification bile samples were obtained before and during treatment. Before treatment ursodeoxycholic acid (measured by gas-liquid chromatography combined with enzymatic assay) constituted 0-3·8% of the total bile acids, and the proportion increased to 32·3-85·8% during treatment, 75-97% being conjugated with glycine. One gall stone that showed radiological calcification during treatment was removed surgically and subjected to chemical analysis. The different constituents of the stone expressed as the percentage of the total weight of the stone were cholesterol (94%), glyco-ursodeoxycholic acid (2·3%), other bile acids (2·3%), calcium salts (1%), and unidentified matter (0·4%). Glyco-ursodeoxycholic acid and calcium salts were found mostly in the outer surface of the stone. Further analysis by the *x*-ray powder diffraction method confirmed that most of the calcium was in the outer surface of the stone and that it was not in the form of calcium bilirubinate. It was not possible to confirm that it was in the form of calcium glyco-ursodeoxycholate.

Comment

Six out of 56 patients with radiolucent gall stones who received ursodeoxycholic acid but none out of 122 patients who received chenodeoxycholic acid developed gall-stone calcification. The possibility of calcification during treatment with ursodeoxycholic acid should therefore be borne in mind when choosing which bile acid to use for medical dissolution of cholesterol gall stones, since calcification of gall stones renders bile-acid treatment ineffective.[3]

We are grateful to our various radiological colleagues for assessing gall-stone calcification. We are also grateful to Dr June Sutor for analysing one of the gall stones by the *x*-ray powder diffraction method. We thank Weddel Pharmaceuticals for supplies of chenodeoxycholic acid (Chendol) and Giuliani Company, Tokyo Tanabe, and Lepetit Pharmaceuticals for supplies of ursodeoxycholic acid.

1 Williams G, Maton PN, Murphy GM, Dowling RH. Will ursodeoxycholic acid (UDCA) replace chenodeoxycholic acid (CDCA) as the medical treatment of choice for gallstone dissolution? *Gut* 1978;**19**:A974.

[2] Igimi H, Tamesue M, Ikejiri Y, Shimura H. Ursodeoxycholate in vitro cholesterol solubility and changes of composition of human gallbladder bile after oral treatment. *Life Sci* 1977;**21**:1373-80.
[3] Stiehl A, Raedsch R, Czygan P, *et al*. Effects of biliary cholesterol saturation in gallstone patients treated with chenodeoxycholic acid and/or ursodeoxycholic acid. *Gastroenterology* 1980;**79**:1192-8.

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Department of Medicine, Ninewells Hospital, Dundee
M C BATESON, MD, MRCP, lecturer (present appointment: consultant physician, General Hospital, Bishop Auckland, County Durham).
I A D BOUCHIER, MD, FRCP, professor

Manor Hospital, Walsall
D B TRASH, MRCP, consultant physician

Department of Medicine, St George's Hospital Medical School, London
D P MAUDGAL, PHD, MRCP, senior registrar
T C NORTHFIELD, MD, FRCP, consultant physician and senior lecturer

Production of treponemicidal concentration of penicillin in cerebrospinal fluid

In treating neurosyphilis penicillin regimens should be used that achieve, in the cerebrospinal fluid, at least the minimal acceptable treponemicidal concentration as recommended by the World Health Organisation—namely, 30 IU/l (0·018 mg/l). Otherwise, viable *Treponema pallidum* may persist in the cerebrospinal fluid despite treatment that produces adequate penicillin concentrations in the serum.[1] Commonly used treatment schedules—namely, daily intramuscular injections of procaine penicillin alone or with aluminium monostearate or of the depot preparation benzathine penicillin—achieve treponemicidal concentrations in blood but not cerebrospinal fluid.[1–4] Treponemicidal concentrations of penicillin may be produced in cerebrospinal fluid by benzylpenicillin alone, 4 MIU intravenously four hourly, or by 500 000 IU intravenously six hourly together with probenecid by mouth.[4] Indeed, it has been suggested that penicillin might have to be administered intravenously to produce adequate cerebrospinal fluid concentrations. Recently, however, we reported that an inpatient regimen of intramuscular benzylpenicillin and oral probenecid, both given six hourly, produced treponemicidal cerebrospinal fluid concentrations in all of 31 patients.[2] We now report similar results produced by a regimen suitable for outpatients.

Patients, methods, and results

Fifty patients with acquired or congenital syphilis who required lumbar puncture were admitted to hospital. They were informed about the study and agreed to undergo lumbar puncture after starting treatment instead of before. Thirty-eight patients received procaine penicillin 2·4 MIU by single daily intramuscular injections and 12 received similar injections of 1·8 MIU. Probenecid 500 mg was taken by mouth six hourly by all patients. Penicillin concentrations were measured in specimens of serum and cerebrospinal fluid taken at the same time, two to 10 hours after injection, two to nine days after the start of the treatment.

Penicillin concentrations were measured by standard microbiological assay using *Sarcina lutea* (NCTC 8340) as the test organism. The specimens of cerebrospinal fluid and serum were stored at −20°C if the assay could not be carried out immediately. The mean ± 2 SD percentage error of the assay was 30%.

In all 50 patients treponemicidal penicillin concentrations were achieved in serum and cerebrospinal fluid. The table shows the concentrations in the 38 patients who received 2·4 MIU of procaine penicillin intramuscularly with probenecid by mouth. The remaining 12 patients treated with procaine penicillin 1·8 MIU intramuscularly daily achieved concentrations of 0·06-1·8 mg penicillin/l cerebrospinal fluid (giving a more than adequate margin above 0·018 mg/l to allow for possible error in the assay method). In these 12 patients the cerebrospinal fluid was normal in three, contained red blood cells in seven, and was abnormal in two. (In one of the last two the cerebrospinal fluid contained 50 000 red and 10 000 white blood cells/l and had a protein concentration of 0·65 g/l and a Venereal Disease Research Laboratory test was positive 1 in 2; in both, fluorescent treponemal antibody-absorption and treponemal haemagglutination tests were positive.) In these three groups the cerebrospinal fluid penicillin concentration was 4·1%, 3·6%, and 6·1% respectively of the serum penicillin concentration.

In the 38 patients treated with 2·4 MIU the nine patients who weighed over 80 kg had an average serum penicillin concentration of 9·1 mg/l and cerebrospinal fluid concentration of 0·28 mg/l and the cerebrospinal fluid concentration was 3·1% of the serum concentration. The corresponding values in the eight patients who weighed less than 60 kg were 13·8 mg/l, 0·5 mg/l, and 5·5% respectively.

Comment

Specimens of cerebrospinal fluid from 10 of the 38 patients who had received procaine penicillin 2·4 MIU intramuscularly and probenecid contained 3000-300 000 red blood cells/l. This amount of contamination would have had little effect on the penicillin concentrations detected in cerebrospinal fluid, because the specimen for estimation of penicillin was collected last, immediately after the specimen for estimation of cell count, and must have been even less contaminated.

The lowest concentration of penicillin achieved in the cerebrospinal fluid was 0·06 mg/l in one of the 12 patients who received 1·8 MIU procaine penicillin intramuscularly daily in addition to probenecid by mouth. This gave a more than adequate margin above 0·018 mg/l to allow for possible error in the assay method and still ensure a treponemicidal concentration of penicillin.

Thus procaine penicillin 2·4 MIU and 1·8 MIU by daily intramuscular injection, together with probenecid by mouth, produced treponemicidal concentrations in cerebrospinal fluid and serum and are suitable for the treatment of outpatients with neurosyphilis.

[1] Tramont EC. Persistence of Treponema pallidum following penicillin G therapy. Report of two cases. *JAMA* 1976;**236**:2206-7.
[2] Dunlop EMC, Al-Egaily SS, Houang ET. Penicillin levels in blood and CSF achieved by treatment of syphilis. *JAMA* 1979;**241**:2538-40.
[3] Mohr JA, Griffiths W, Jackson R, Saadah H, Bird P, Riddle J. Neurosyphilis and penicillin levels in cerebrospinal fluid. *JAMA* 1976;**236**:2208-9.
[4] Polnikorn N, Witoonpanich R, Vorachit M, Vejjajiva S, Vejjajiva A. Penicillin concentrations in cerebrospinal fluid after different treatment regimens for syphilis. *Br J Vener Dis* 1980;**56**:363-7.

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Whitechapel Clinic and Department of Medical Microbiology, The London Hospital, London E1 1BB
ERIC M C DUNLOP, MD, FRCP, consultant venereologist
SAFWAT S AL-EGAILY, MB, CHB, senior registrar in venereology (now consultant venereologist, Royal Infirmary, Huddersfield HD3 3EA)
ELIZABETH T HOUANG, MRCPATH, consultant microbiologist

Penicillin concentrations (mg/l) in serum and cerebrospinal fluid (CSF) after 2·4 MIU procaine penicillin given intramuscularly

CSF group	No of patients	Serum concentrations		CSF concentrations		CSF concentration as % of serum concentration
		Range	Average	Range	Average	
Normal	21*	2·8–22·4	11·1	0·07–1·2	0·3	3·2
Normal + red blood cells	10	2·9–21·0	10·7	0·13–1·15	0·46	4·4
Abnormal	4†	1·7–22·0	11·9	0·12–1·5	0·57	8·35
Incomplete data	3‡	1·5–30·4	16·0	0·12–0·8	0·53	3·3
Total	38‡	1·5–30·4	11·3	0·07–1·5	0·4	3·5

*Normal CSF: lymphocytes 0–4 × 10^3/l; protein ≤0·4 g/l. Negative standard tests (reagin tests) for syphilis and negative fluorescent treponemal antibody-absorption (FTA-ABS) and *T pallidum* haemagglutination (TPHA) tests.
†Protein 0·6 g/l in one patient and 0·7 g/l in another; TPHA test positive in a third; TPHA and FTA-ABS tests positive in the fourth; all other tests normal.
‡Cells not counted in two patients, serum penicillin concentration not estimated in one.