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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.

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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.