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PENICILLIN CONCENTRATIONS IN CEREBROSPINAL FLUID AND SERUM AFTER INTRAMUSCULAR, INTRAVENOUS, AND ORAL ADMINISTRATION TO SYPHILITIC PATIENTS

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Abstract. Penicillin concentration in serum and cerebrospinal fluid (CSF) were estimated in 19 syphilitic patients given three different regimens: Penicillin G, 10 MIU i.v. three times a day (3 patients); procaine penicillin, 600 000 IU i.m. (11 patients); and penicillin V, 1.2 MIU by mouth four times a day (5 patients). Intravenous administration of penicillin G resulted in a penicillin concentration in CSF of 0.3–0.5 μg/ml; In contrast, procaine penicillin, i.m. and penicillin V by mouth did not result in any measurable CSF concentration, even in the presence of pleocytosis and/or barrier lesion. Penicillin V by mouth gave considerably higher serum concentrations than procaine penicillin intramuscular, however. In the light of these results, and reported treatment failures in neurosyphilis and demonstration of viable *Treponema pallidum* after treatment, we propose that neurosyphilis should be treated with high intravenous doses of penicillin to ensure treponemicidal concentrations in the central nervous system.

Key words: Syphilis; Penicillin; Cerebrospinal fluid; Neurosyphilis

The drug of choice for syphilis therapy is penicillin, given according to the World Health Organisation's (WHO) recommendations (11). In Scandinavia, aqueous procaine penicillin 600 000 international units (IU) by intramuscular (i.m.) injections once daily in a total dose of 10 million IU (MIU) has become the routine treatment for early as well as for late syphilis. The current therapeutic regimen does not reflect the penicillin doses used for treatment of other systemic infections. Knowledge concerning penicillin concentrations in different body fluids during syphilis therapy is sparse.

In recent years result of assays of penicillin in cerebrospinal fluid (CSF) have been reported and the currently recommended doses have been questioned (6, 14, 17).

Penicillin V by mouth has been used for many different infections but is not recommended for treatment of syphilis. However, in high doses, this treatment can give peak serum concentrations far above those achieved with procaine penicillin (2). No information has been presented concerning the concentration of penicillin V in CSF after oral administration.

The aim of this study was to compare the concentration of penicillin in serum and in the CSF when syphilitic patients were treated with procaine penicillin as recommended by the WHO with that after penicillin V by mouth and penicillin G in high doses by intravenous (i.v.) infusion.

PATIENTS AND METHODS

Patients

Nineteen patients (15 men and 4 women aged 28–63 years, mean age 41) with syphilis, seen and treated at the Department of Dermatology, Sahlgrenska Sjukhuset, Gothenburg between 1978 and 1980 were included in the study (Table I). Of these 19 patients, 8 (all men aged 30–44 years, mean age 38) were diagnosed as secondary syphilis (12), and 11 patients (7 men and 4 women aged 28–66 years, mean age 43) as latent syphilis defined as positive serology for syphilis but without clinical signs of the disease. Twelve of the patients were untreated when included in the study. Seven (nos. 2, 5, 11, 12, 13, 14, 16) of the 19 patients had been treated 4–12 months earlier and 4 (nos. 2, 11, 13, 14) had been subjected to lumbar puncture before that treatment. Because of abnormal CSF findings or remaining high antibody titre, a new lumbar puncture was indicated. All patients were informed about the study and accepted the administration of penicillin before CSF examination. None of the patients had overt clinical signs of central nervous system (CNS) involvement.

The serological tests for syphilis were the Wasserman reaction and the VDRL as non-specific tests and the *Treponema pallidum* immobilization (TPI) (16) and FTA-abs test (4) as confirmation.

The 8 patients with secondary syphilis were positive in all these serological tests. Of the 11 patients with latent syphilis, 5 were Wasserman negative but all were positive in the VDRL, FTA-abs, and TPI test.

Table I. *CSF findings in 19 patients with syphilis*

No.	Sex	Age	Diagnosis	Cerebrospinal fluid			
				Mononuclear cells (10^6/l)	Albumin quota[a]	IgG index[b]	WR, VDRL, TPI and/or FTA-abs
1	M	32	Secondary syphilis	1	2.82	0.44	NR
2	M	63	Latent syphilis	2	7.53	0.57	NR
3	M	43	Latent syphilis	0	4.70	0.59	NR
4	M	36	Secondary syphilis	1	4.30	0.50	NR
5	M	33	Secondary syphilis	1	8.29	0.48	NR
6	F	31	Latent syphilis	1	4.67	0.53	NR
7	M	44	Latent syphilis	2	3.87	0.52	NR
8	M	38	Latent syphilis	0			NR
9	M	30	Secondary syphilis	0	3.48	0.63	NR
10	F	66	Latent syphilis	1	4.38	0.54	NR
11	M	40	Secondary syphilis	1	3.95	0.43	NR
12	F	35	Latent syphilis	1	2.98	0.65	NR
13	M	45	Latent syphilis	9	6.37	0.57	NR
14	M	42	Latent syphilis	2	3.95	2.02	NR
15	F	28	Latent syphilis	1	4.12	0.62	NR
16	M	44	Secondary syphilis	0	4.7	0.44	NR
17	M	43	Secondary syphilis	2	7.07	0.58	NR
18	M	37	Latent syphilis	32	2.76	1.22	R
19	M	43	Secondary syphilis	16	5.46	0.56	NR

[a] Normal <6 (15–45 years), <7 (>45 years).
[b] Normal <0.7.

Analysis of CSF

Cells were counted and expressed in numbers, 10^6/l. Samples with significant blood contamination were not included. Albumin and immunoglobulin were determined according to Laurell in 1966 (13). The albumin ratio (alb. CSF/alb. serum) was quantified as sign of barrier lesion (20). The IgG index was calculated as

$$\frac{\text{CSF IgG}}{\text{serum IgG}} : \frac{\text{CSF albumin}}{\text{serum albumin}}$$

to eliminate the influence of blood-brain damage in evaluating local immunoglobulin production (20).

Treatment regimens

The following treatments were given: 1) Eleven patients (nos. 1–11) were given aqueous procaine penicillin 600000 IU by intramuscular injection once daily. 2) Five patients (nos. 12–16) were given penicillin V (phenoxymethylpenicillin potassium) 0.8 g (1 200 000 IU) by mouth four times a day. 3) Three patients (nos. 17–19) were given penicillin G 6 g (10000000 IU) intravenously three times a day.

Sample collection

CSF samples were taken on the treatment days indicated in Table II. Serum samples were drawn at the time of expected peak value, for procaine penicillin 2 hours after the intramuscular injection, for penicillin V 30 min after the oral dose, and for penicillin G immediately after completion of the intravenous infusion. One hour after this serum sample was drawn, lumbar puncture was performed and at the same time another serum sample was drawn. (The figures in parentheses in Table II indicate hours between treatment and serum or CSF sampling.)

Determination of penicillin concentration

Penicillin in serum and CSF was determined microbiologically on PDM-agar plates (AB Biodisk, Solna, Sweden) using punched holes as diffusion centres and a *Sarcina lutea* strain as the indicator organism. The antibiotics were received as dry powders of known potency. When assaying serum concentrations standards were prepared in pooled human serum and when assaying CSF concentrations standards prepared in physiological saline were used. Serum and CSF samples were kept at −20°C for a maximum period of 2 weeks before assay.

RESULTS

None of the 11 patients treated with procaine penicillin 600 000 IU i.m. had detectable penicillin in CSF. The penicillin concentration in serum 2 hours after the injection was 0.55–2.50 μg/ml, mean 1.1 μg/ml. At the time of the lumbar puncture, the serum concentration had decreased to 0.81 μg/ml. The mean penicillin concentration in serum 30 min after penicillin V 1.2 MIU by mouth in 5 patients was 4.8 μg/ml (range 2.4–7.0 μg/ml), and one hour later, when the lumbar puncture was performed, it was 2.12 μg/ml (range 1.2–2.8 μg/ml). None of the 5 patients treated with penicillin V had

detectable penicillin concentrations in CSF. When penicillin G 10 MIU was given intravenously to 3 patients the serum concentration immediately after the infusion varied between 20 and 100 μg/ml and one hour later, at the time of lumbar puncture, the mean concentration was 12.6 μg/ml (range 6–20 μg/ml). Measurable concentrations of penicillin were found in the CSF in all 3 patients (mean 0.38 μg/ml, range 0.3–0.5 μg/ml).

In CSF, pleocytosis was found in 3 (nos 13, 18, 19) of 19 patients (normal <5 mononuclear cells · 10^6/l). A barrier lesion, defined as increased albumin quota, was demonstrated in 4 (nos. 2, 5, 13, 17) patients and 2 patients (nos. 14, 18) had a pathological IgG index. In only one patient (no. 18) were specific syphilitic antibodies detected with positive Wasserman, VDRL, FTA-abs and TPI test.

Table II. *Penicillin levels in serum and CSF of 19 patients with syphilis*

Hours after treatment in parentheses

Pat. no.	Treatment day	Penicillin concentration: Serum, μg/ml	CSF, μg/ml	
Pc G procaine 6000000 IU i.m.				
1	3	1.1 (2)	0.8 (3)	NM[a] (3)
2	2	0.62 (2)	0.55 (3)	NM (3)
3	4	0.62 (2)	0.62 (3)	NM (3)
4	2	0.7 (2)	0.60 (3)	NM (3)
5	2	2.5 (2)	0.9 (3)	NM (3)
6	1	1.0 (1)		NM (1)
7	1	1.0 (1)		NM (2)
8	7	0.8 (2)		NM (3)
9	5	0.55 (2)	0.4 (3)	NM (3)
10	2	1.6 (2)	1.8 (3)	NM (3)
11	2		2.1 (3)	NM (5)
Pc V 0.8 g (12000000 IU) by mouth 4 times a day				
12	2	2.4 (0.5)	1.2 (1.5)	NM (1.5)
13	2	4.2 (0.5)	2.8 (1.5)	NM (1.5)
14	2	7.0 (0.5)	2.3 (1.5)	NM (1.5)
15	3	4.2 (0.5)	1.8 (1.5)	NM (1.5)
16	7	6.0 (0.5)	2.5 (1.5)	NM (1.5)
Benzylpenicillin 6 g (10 MIU) 3 times a day				
17	7	20 (0)	20 (1)	0.5 (1)
18	7	90 (0)	12 (1)	0.3 (1)
19	8	100 (0)	6 (1)	0.35 (1)

[a] NM (not measurable) means less than 0.03 μg/ml.

DISCUSSION

A general aim of treating bacterial infections is to achieve bactericidal concentration in all tissues involved for a sufficient period of time. In the present study the method used for penicillin assay detected penicillin concentrations of 0.03 μg/ml. The recommendations given for penicillin treatment of syphilis are based on in vitro studies (15) and experiments performed in rabbits (8). The results obtained from these experiments has suggested that the penicillin concentration in serum has to be at least 0.018 μg/ml for 7–10 days in early syphilis for healing to occur. On the other hand in these studies the maximal immobilization (killing) of *Treponema pallidum* in vitro was achieved with a penicillin concentration of 0.1 μg/ml (15) and in vivo the most effective penicillin concentration was 0.36 μg/ml (8). Results from these experimental studies should be extended with caution to human syphilis and recommended effective penicillin concentrations ought to be given primarily on the basis of the human therapeutic trials. With recommended penicillin doses for syphilis the serum level mostly does not fall below 0.1 μg/ml (10), i.e. above the lower limit of the present assay.

It seems logical that a treponemicidal concentration should be achieved in all organs involved, including the CNS. The penetration of penicillin into the CSF is poor due largely to the low lipid solubility of the drug resulting in a CSF/plasma ratio assessed to 1–2% with normal meninges (1).

With currently recommended penicillin doses for syphilis it may be questioned whether consistently treponemicidal concentrations are achieved in CSF. Treatment failures in cases of primary and secondary syphilis are admittedly rare (11), but there are several reports indicating that the currently recommended doses are insufficient for neurosyphilis. Short & Knox (18) reported in 1966 a failure rate of approximately 10% within 2 years in active neurosyphilis. Wilner & Brody 1968 (22) found a failure rate of 39% in general paresis treated with penicillin doses of 3–30 MIU parenterally. Persistence of pathogenic *Treponema pallidum* in CSF and other tissues after treatment has also been reported (19, 21).

Of the three treatment schedules tested in this study, only procaine penicillin is recommended for syphilis by the WHO. Intravenous administration of penicillin G in high doses resulted in a concentration in the CSF which should probably be considered treponemicidal. In contrast, administration of penicillin V or procaine penicillin did not result in measurable CSF concentrations.

Table III. *CSF concentrations with different penicillin regimens*

Author (year)	Treatment regimen		No. of patients with measurable pc. concentration in CSF (μg/ml)
	Drug	Dose	
Boger et al. (1948)	Pc. G.	500 000 IU (i.v.)	8/11 (range 0.014–0.054, m=0.019)
Yoder (1975)	Procaine pc.	600000 IU (i.m.)	0/1
	Pc. G	4 MIU (i.v.) ×6	1/1 (0.186)
Mohr et al. (1976)	Benzathine pc.	3.6 MIU (i.m.)	1/13 (0.1)
	Pc. G	5–10 MIU (i.v.)	2/2 (0.3, 2.4)
Dunlop et al. (1979)	Procaine pc.	600000 IU (i.m.)	0/4
	Procaine pc.	600000 IU (i.m.) + probenecid 500 mg ×4	2/3 (0.033, 0.29)
	Pc. G	500 000 IU (i.m.) ×4+ probenecid 500 mg ×4	31/31 (range 0.02–1.5, m=0.35)
Polnikorn et al. (1980)	Benzathine pc.	2.4–7.2MIU (i.m.)	0/6
	Pc. G	400000 IU (i.v.) ×6	0/2
	Pc. G	4 MIU (i.v.) ×6	1/1 (0.579)
	Pc. G	500000 IU (i.v.) ×4+ probenecid 500 mg ×4	4/5 (range 0.35–2.838)
Dunlop et al. (1981)	Procaine pc.	1.8 MIU (i.m.) + probenecid 500 mg ×4	12/12 (range 0.06–1.8)
	Procaine pc.	2.4 MIU (i.m) + probenecid 500 mg ×4	38/38 (range 0.07–1.5, m=0.4)
Ducas et al. (1981)	Benzathine pc.	2.4–4.8 MIU (i.m)	0/19
	Benzathine pc.	2.4 MIU (i.m.) + probenecid 500 mg ×4	0/8
	Benzathine pc.	4.8 MIU (i.m.) + probenecid 500 mg ×4	2/6 (0.024, 0.048)

With inflamed meninges the CSF/plasma ratio of penicillin penetration is increased, assessed to 2–6% (1).

In this study only 3 (nos. 13, 18, 19) of the patients had pleocytosis as a sign of slight meningeal infection. Two (nos. 18, 19) of them were treated with penicillin G i.v. and the concentrations in CSF were estimated to be 2.5 and 6% respectively of their peak penicillin serum concentrations. The third patient (no. 13) was treated with penicillin V by mouth. The peak serum concentration was estimated to be 2.4 μg but no measurable penicillin was found in the CSF. Four patients (nos. 2, 5, 13, 17) had an increased albumin quota indicating a barrier lesion, but this was obviously not of such magnitude as to give diffusion of penicillin from the plasma to the CSF. We have thus found that even if there is pleocytosis and/or a barrier lesion, there is no measurable penicillin in the CSF when procaine penicillin 600 000 IU or penicillin V 1.2 MIU by mouth is administered.

Our results indicate that standard doses of penicillin may give penicillin concentrations insufficient to eradicate *Treponema pallidum* in the CSF and are in accordance with other studies compiled in Table III (3, 5, 6, 7, 14, 17, 23). Both Dunlop (6) and Polnikorn (17) have achieved treponemicidal concentrations in CSF by combining penicillin G i.v. with probenecid. Dunlop (7) has tried to simplify the treatment and proposed procaine penicillin 1.8–2.4 MIU i.m. in combination with probenecid by mouth as an alternative treatment for neurosyphilis. An objection to this regime are experimental data indicating that probenecid may compete with penicillin for entry to the brain tissue, resulting in a higher penicillin level in the CSF but a lower level in the brain tissue (9).

The results of this study, in combination with reported treatment failures in neurosyphilis, indicate that the currently recommended penicillin doses for syphilis with CNS engagement are insufficient. Penicillin V by mouth is not a satisfactory alternative. In our opinion, neurosyphilis should be treated with high intravenous doses of penicillin to ensure a treponemicidal effect in the CNS.

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