

CLINICAL REPORT

Short-time, High-dosage Penicillin Infusion Therapy of Syphilis: An Alternative to Recommended Regimens?

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The optimal dosage and duration of penicillin treatment for the various stages of syphilis are not known. We present data on 20 patients with syphilis (primary, secondary or latent) treated with high-dose, short-time penicillin infusion therapy. Patients were given 10 MIU of penicillin G intravenously every 6 h up to a total dose of 90 MIU within 48 h. No adverse reactions were registered but 9 patients showed a Herxheimer reaction. Four patients were lost to follow-up and the remaining 16 were serologically and clinically followed for mean 18.5 months (range 3–36). During this period, the Wassermann reaction turned negative for 12 patients and was reduced more than fourfold for the rest, with one exception. None of the patients showed clinical signs of active syphilis following treatment. The cerebrospinal fluid penicillin concentration was measured in one patient during treatment and found to be much higher than the minimally treponemacidal concentration generally recommended. The treatment modality is reviewed and discussed and it may provide an alternative to conventional treatment regimens of early syphilis. **Key words:** penicillin; syphilis; *Treponema pallidum*.

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Penicillin therapy is a highly efficient treatment of syphilis and recommended treatment regimens have changed little since the introduction of long-acting penicillin preparations in the 1950s. Current treatment recommendations are based on inadequate scientific evidence (1), and the optimal dosage and duration of administration is not known (2).

For early syphilis (primary, secondary and latent up to 2 years) most treatment schedules involve intramuscular administration of either daily procaine penicillin for 10–14 days or benzathine penicillin G given as 1–3 weekly injections. Several studies suggest that these regimens provide inadequate concentrations of penicillin in the cerebrospinal fluid (CSF) to eradicate

Treponema pallidum (3–12). This may be important, because Lukehart et al. (13) detected *T. pallidum* in the CSF of 30% of patients with untreated early syphilis by culture on rabbit testes. Notably, the CSF from 4 of 16 of these patients appeared entirely normal, making it impossible to detect these patients by lumbar puncture (13). If left untreated, as in the Oslo study, 10% of patients with early syphilis developed symptomatic neurosyphilis (14).

German authors in the late 1970s and early 1980s reported successful use of high-dosage short-time i.v. penicillin G therapy for early syphilis. This treatment modality has the advantage of providing a treponemacidal level of penicillin in CSF, and being an inpatient treatment of short duration, and conceivably minimizes the risk of sensitization to penicillin (15–17).

Since these initial German experiences, there have been no reports on this potentially attractive treatment. We therefore believe it of interest to report results from a retrospective study on a limited number of Danish patients with syphilis given high-dose i.v. penicillin treatment and to review and discuss the treatment modality.

MATERIAL AND METHODS

Patients

Based on previous German experiences (15–17), high-dosage i.v. penicillin treatment for syphilis has been used since 1989 as a standard treatment at the Department of Dermatology and Venerology, University Hospital of Odense, Denmark, for patients with primary, secondary or latent disease without neurological signs. A total of 20 patients (8 women and 12 men), mean age 33.8 years (range 17–49), were treated with high-dosage i.v. penicillin for syphilis in the period 1989–2001. Patient characteristics are given in Table I. In summary, 2 patients had primary syphilis with chancre, 9 secondary syphilis with roseola, 2 early latent syphilis and 7 latent syphilis of unknown duration. Of the last-mentioned, two had asymptomatic neurosyphilis as indicated by positive Wassermann reaction (WR) in CSF, while the other five showed normal CSF. All 8 patients tested for HIV infection were negative. Of the two patients with primary syphilis, one was confirmed by *T. pallidum* in darkfield microscopy, the other by biopsy.

Treatment and serology

The patients were hospitalized and treated with 10 MIU penicillin G i.v. every 6 h until a total dose of 90 MIU within

Table I. Clinical data on 20 syphilis patients treated with high-dose penicillin infusion therapy

Gender/age	Syphilis/stage WR at start	Months: After treatment WR			
M/43	2nd	0.5	2.5	6.5	24
	17	17	7	0	0
M/20	2nd	0.5	9	11	18
	12	12	0	0	0
M/33	2nd	1	24	36	
	8	5	0	0	
F/41	2nd	1	2	3	5
	17	12	5	5	2
M/44	Early latent	1	3	6	34
	12	8	0	0	0
F/38	2nd	0.5	1.5	3.5	6
	13	11	8	1	0
F/39	2nd	1	3.5	4.5	30
	12	11	2	0	0
F/49	Early latent	1	2	3.5	5.5
	3	2	2	2	2
M/47	Latent, AN	2	4	12	18
	8	8	6	2	5
M/41	2nd and 1st	1.5	17		
	11	2	0		
F/27	Latent	0.5	1	3	
	5	3	2	0	
M/27	1st	0.5	1.5	3	8
	14	11	8	0	0
F/25	Latent	2			
	6	5	(Lost to follow-up)		
M/23	Latent	0.25	2	3	
	5	1	0	0	
F/27	Latent	1.5			
	0	0	(Lost to follow-up)		
M/34	1st	1			
	0	0	(Lost to follow-up)		
M/17	Latent	3	6	7	14
	15	8	8	9	8
M/27	Latent, AN	4			
	4	2	(Lost to follow-up)		
M/36	2nd	2	15		
	12	5	0		
F/38	2nd	3	12	18	
	11	8	0	0	

AN = asymptomatic neurosyphilis.

48 h. Herxheimer reactions were registered. Before and after treatment, patients were followed serologically by serum analysis at Statens Serum Institut, Copenhagen, Denmark, for WR, automatic reagin test, anti-flagellum IgG and IgM ELISA and fluorescent treponemae antibody absorption (FTA-Abs). The WR was used to follow the non-treponemal antibodies after treatment and the result is given as a logarithmically expressed titre expressed in arbitrary units of degree of strength calculated as follows: the amount of antibodies in the sample = $3^{n/3}$, where n is the degree of strength. The unit therefore goes up by 3 if the number of antibodies is triplicated. A difference of ≥ 3 in tests from the same patient is considered significant.

Penicillin measurement in the central nervous system

In one patient, an epidural catheter was placed and 2 ml of spinal fluid was obtained by aspiration immediately before the

fifth and ninth penicillin infusions, and 12 h after the last infusion. At the same sampling times, 2 ml of blood was obtained and centrifuged to isolate serum. All samples were immediately frozen and stored at -60°C until analysis. The penicillin concentrations in CSF were measured by the agar diffusion technique using *Micrococcus luteus* ATCC 9341 as test organism. Aqueous dilutions of penicillin G were used as standards.

RESULTS

At the time of treatment, 18 of 20 patients were positive in a specific serologic syphilis test (FTA-Abs) and in WR. The exceptions were one patient with primary syphilis and *T. pallidum* observed in the lesion, who was negative in all serological reactions, and one patient with latent syphilis only positive in FTA-Abs. Both patients were lost to follow-up shortly after treatment. None of the patients showed adverse reactions to the treatment, and 9 patients experienced a Herxheimer reaction.

Unfortunately, four patients were lost to follow-up shortly after treatment because they moved to another country. The remaining 16 patients were followed serologically for a mean of 18.5 months (range 3–36). Serological results are given in Table I. For 12 patients, WR returned to zero during the follow-up period. Among the remaining 4 patients, all except one with early latent syphilis showed a more than fourfold decline in WR titre. None of the patients showed clinical signs of active syphilis after treatment.

In one of the patients with secondary syphilis and normal CSF parameters the penicillin concentration in spinal fluid was measured during treatment. The CSF/serum penicillin concentration in $\mu\text{g/ml}$ was 1.7/2.2 after 24 h, 0.45/3.7 after 48 h and finally 0.076/0.089 after 60 h.

DISCUSSION

In the present retrospective study the number of patients was limited and the follow-up period relatively short. However, all patients became free of symptoms after treatment and the serum WR titre was reduced more than fourfold in all except one, suggesting that the high-dose penicillin infusion therapy was successful. The exceptional patient with early latent syphilis showed a continuous low-titred value of WR during 11 months of follow-up. It is known that patients with early latent disease may show a slow decline in titre after apparently successful cure and not all show seroreversion even when followed for 3 years (18). However, treatment failure in this patient may not be entirely ruled out.

Previous evidence for the efficacy of high-dose i.v. therapy stems from two German studies. In the 1970s Wecke et al. (15) reported on 130 syphilis patients with primary, secondary, early and late latent syphilis.

Patients were treated with 60 MIU penicillin G i.v. infused during 12 h twice with a 12 h night rest in between. Thus a total of 120 MIU was administered during 36 h. Patients were followed for more than 2 years and all turned negative in conventional serological reactions during this period. Interestingly, electron microscopic examination of infected tissue showed complete disappearance of *T. pallidum* within 24 h of therapy. In the 1980s, Sönnichsen et al. (16, 17) reported on 104 syphilis patients (10 primary, 76 secondary and 18 reinfections) using the same treatment schedule with the addition of a single dose of 75 mg prednisolone. They found no significant difference in fourfold reduction of Venereal Disease Research Laboratory (VDRL) as compared to 1 MIU penicillin G i.m. once daily for 30 days. It is not clear for how long these patients were followed. Taken together, the two studies on a relatively large number of patients suggest that this treatment modality was efficient. The treatment protocol in the present study was not identical to, but quite similar to the German protocols.

Traditional treatment schedules rely on substantially longer-lasting treponemacidal penicillin concentrations in serum, and according to the World Health Organisation effective treatment of early syphilis requires the maintenance of a minimal serum concentration of 0.03 IU of penicillin/ml (0.018 µg/ml) for 7–10 days without interruption for more than 24 h (2, 19). The long duration of syphilis treatment is partly based on the finding that *T. pallidum* has a relatively long time for division, estimated to be approximately 30–33 h in early infection (20), and animal studies have suggested that in longer-lasting infections the division time may be even longer (21). Interestingly, Eagle et al. (22) demonstrated that the minimally effective treponemacidal penicillin concentration killed treponema in a rabbit testicular chancre after 72–96 h, whereas a 50-fold higher dose killed the organisms within only 6 to 9 h. No further decrease in killing time was registered for higher penicillin doses. This difference between maximally and minimally effective penicillin concentration is substantially higher than the 2–4-fold difference found for most other bacteria (22). Therefore short duration of therapy is potentially enough if the concentration of penicillin is sufficiently high.

This is the first report on CSF penicillin concentration measurement during high-dose treatment. The one patient in which CSF penicillin concentrations were measured during therapy showed CSF penicillin levels from 1.7 µg/ml falling to 0.076 µg/ml after 60 h, i.e. all values well beyond the 0.018 µg/ml considered the gold standard (2, 19). The reason that the CSF penicillin concentration was found to be lower after 48 h as compared to after 24 h of treatment is not clear. Several studies on the CSF penicillin concentration after i.v. penicillin G infusion following various schedules all

showed CSF concentrations in the range 0.21–2.4 µg/ml (7, 9, 23, 24). Interestingly, Schoth & Walter (25) performed a careful study on patients treated with i.v. penicillin G 2 MIU × 6. After 8 days of treatment the CSF penicillin concentration was measured every hour for 8 h. The maximum penicillin concentration shortly after administration was 0.064–3 µg/ml (mean 0.98); the minimum concentration after 4 h was 0.062–0.98 µg/ml (mean 0.33). Taken together, these results suggest that high-dose therapy provides a CSF penicillin concentration well above minimal inhibitory concentration for at least 50 h.

Is this treatment modality more attractive than traditional treatment? Traditional treatment of early syphilis with one or two i.m. injections of benzathine penicillin G is definitely cheaper and easier. Although treponemas are known to be present in the CSF of a substantial proportion of these patients, and CSF treponemacidal penicillin concentrations are not reached with this regimen, many authors nevertheless argue that this treatment historically has been successful in the majority of patients (2). Treatment failures are easily detected serologically, such that retreatment seems to prevent late sequelae (26). Long experience and few side effects may indicate that there is no reason to change schedules (27, 28). In Denmark, 15 days of daily procaine penicillin injections is considered the standard treatment because this provides higher CSF penicillin concentrations, although not always above minimal recommended concentration. This regimen is painful and cumbersome for the patient. High-dose therapy constitutes a fast, inpatient treatment (good compliance) with potentially sufficient CSF penicillin concentration to kill *T. pallidum* and prevent late neurologic sequelae. It may thus be an alternative to conventional treatment regimens of early syphilis.

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