

Treatment of Neurosyphilis: IV Penicillin G vs IM Procaine Penicillin/Oral Probenecid

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Background

The CDC recommends IV aqueous penicillin G (PenG) for 10-14 days to treat neurosyphilis (NS). Intramuscular (IM) aqueous procaine penicillin (APPG) plus oral probenecid “might be considered” as an alternative if compliance can be assured.¹ Many patients are treated with with APPG and probenecid due to the cost of PenG therapy or due to the ease of use of APPG since PenG requires use of a peripherally inserted central catheter (PICC) line or hospitalization. There is limited data directly comparing these two therapies.

We compare these two therapies for neurosyphilis treatment.

Methods

Participants were enrolled at the University of Washington from April 2003 to May 2014 in a study of CSF abnormalities in syphilis and were diagnosed and treated for NS. Only those with CSF WBCs >20/ul or CSF protein >50 mg/dl or reactive CSF-VDRL at entry and who had follow up were included in this analysis. Study visits included: medical history, neurological exam, venipuncture, and lumbar puncture (LP). LPs were repeated at weeks 12, 24 and 52 or until the CSF results normalized. Participants were followed for one year to evaluate clinical and laboratory responses to therapy.

Relationships between categorical variables were determined by Chi-square or Fisher’s exact test. Hazard ratios (HR) for normalization of CSF WBCs (decline to < 20/ul), CSF protein (decline to <50 mg/dL) and CSF-VDRL or serum RPR reactivity (4-fold decline in titer or reversion to nonreactive) were determined using Cox regression. P values <0.05 were considered significant.

Results

- Most patients were HIV infected, Caucasian men.
- Both groups were well matched except that more individuals treated with APPG/probenecid had early stage syphilis.

References

1. <https://www.cdc.gov/std/tg2015/syphilis.htm>
2. Marra CM, et al. *BMC Infectious Diseases*. 2007;7:37.

Results

Table 1. **Participant Characteristics**

	Pen G n=32	APPG/Probenecid n=118	P-value
Male	31 (97%)	118 (100%)	NS
HIV-infected	28 (88%)	88 (75%)	NS
Age	43 (32-52)	40 (33-46)	NS
Race:			
White	24 (75%)	97 (82%)	NS
Black	4 (12%)	14 (12%)	
Other	4 (12%)	7 (6%)	
Early syphilis	15 (47%)	84 (71%)	0.01
Late syphilis ^a	17 (53%)	34 (29%)	
Treated for uncomplicated syphilis prior to LP	8 (25%)	52 (44%)	NS
1/Serum RPR titer	128 (64-256)	128 (64-256)	NS
Reactive CSF VDRL	21 (66%)	69 (59%)	NS
CSF WBCs > 20/ul	23 (72%)	72 (61%)	NS
CSF Protein > 50 mg/dL	24 (75%)	68 (58%)	NS
Symptomatic NS ^b	16 (62%)	50 (48%)	NS
Asymptomatic NS	10 (39%)	54 (52%)	NS

Results are expressed as number (percent), or median (IQR)

^a Includes syphilis of unknown duration

^b Includes symptomatic meningitis, vision or hearing loss, or stroke

Table 2. **Normalization (Hazard Ratio, HR) of CSF and Serum Measures in HIV-uninfected Participants (95% CI)**

Variable	WBC > 20/ul	Protein > 50 mg/dL	Reactive CSF VDRL	Serum RPR
Treatment with APPG/probenecid	NS	NS	NS	NS
Pre-treatment measure =/> median	NS	0.2 (0.03 - 0.7)*	0.3 (0.01-1.2) [#]	2.0 (0.9 - 4.3) [#]
Uncomplicated syphilis treatment before LP	NS	NS	NS	NS
Late stage syphilis ^a	NS	NS	NS	0.2 (0.07 -0.5)**
Symptomatic NS ^b	NS	NS	NS	2.7 (1.1 – 6.1)*

*= P < 0.05, **= P < 0.01, ***= P <0.001, # P > 0.05, <0.10, NS = P > 0.10

^{a,b} See Table 1

Results

- In multivariate analysis in HIV-uninfected participants, there was no significant relationship between treatment and normalization of any measure
- In multivariate analysis in HIV-uninfected participants, taking into account variables significant at P < 0.10:
 - Serum RPR normalized faster in individuals with higher pretreatment RPR titer: HR = 3.0 (1.2 – 7.5, P = 0.02)
 - Serum RPR normalized more slowly in individuals with late stage syphilis: HR = 0.1 (0.03 – 0.60, P = 0.005)

Table 3. **Normalization (Hazard Ratio) of CSF and Serum Measures in HIV-infected Participants (95% CI)**

Variable	WBC > 20/ul	Protein > 50 mg/dL	Reactive CSF VDRL	Serum RPR
Treatment with APPG/probenecid	0.6 (0.3 – 1.0)*	NS	NS	NS
Pretreatment measure =/> median	NS	0.2 (0.1 – 0.4)***	NS	2.3 (1.4 – 3.6) ***
Uncomplicated syphilis treatment before LP	NS	NS	NS	NS
Late stage syphilis ^a	NS	NS	0.4 (0.2 – 0.7)**	0.5 (0.3 – 0.7)**
Symptomatic NS ^b	NS	NS	1.7 (1.0 – 3.0) [#]	NS
ARV Use	1.6 (1.0 – 2.8) [#]	NS	NS	NS
CD4 < 200/ul	2.1 (1.1 – 4.3)*	2.9 (1.2 – 6.9)*	NS	NS

*= P < 0.05, **= P < 0.01, ***= P <0.001, # P > 0.05, <0.10, NS = P > 0.10

^{a,b} See Table 1

Table 4. **Multivariate Analysis of Normalization (Hazard Ratio) of CSF and Serum Measures in HIV-infected Participants (95% CI)**

Variable	WBC > 20/ul	Protein > 50 mg/dL	Reactive CSF VDRL	Serum RPR
Treatment with APPG/probenecid	0.6 (0.3 – 1.0)*	NS	NS	NS
Pretreatment measure =/> median	-	0.1 (0.04 - 0.3)***	-	2.0 (1.3 – 3.2) **
Late stage syphilis ^a	-	-	0.3 (0.2 – 0.7) **	0.5 (0.3 – 0.8)**
Symptomatic NS ^b	-	-	NS	-
ARV Use	NS	-	-	-
CD4 < 200/ul	2.9 (1.4 – 6.2)**	3.0 (1.2 – 7.3)*	-	-

*= P < 0.05, **= P < 0.01, ***= P <0.001, # P > 0.05, <0.10, NS = P > 0.10

^{a,b} See Table 1

Summary

- Normalization of CSF and serum measures was not influenced by treatment in HIV-uninfected participants.
- Normalization of CSF WBCs was slower in HIV-infected individuals treated with APPG/probenecid compared to PenG.
- Normalization of CSF and serum measures was influenced by other factors.
- In multivariate analysis in HIV-uninfected participants
 - Serum RPR normalized faster in individuals with higher pretreatment titers and slower in those with late stage syphilis.
- In multivariate analysis in HIV-infected participants
 - CSF WBC and protein concentrations normalized faster in individuals with lower CD4 counts.
 - CSF protein normalized more slowly in those with higher pretreatment concentrations.
 - CSF-VDRL normalized more slowly in those with late stage syphilis.
 - Serum RPR normalized faster in individuals with higher pretreatment titers and slower in those with late stage syphilis.

Implications

- Slower normalization is not the same as treatment failure, but our data suggest that HIV-infected patients with NS who are treated with APPG/probenecid should be followed carefully to ensure adequate treatment response.
- Faster normalization of CSF WBCs and CSF protein concentrations in those with lower CD4 is surprising. HIV-related CSF pleocytosis is more common in individuals with CD4s >200/ul ². Thus faster normalization of CSF WBC and protein in those with lower CD4s may be due to the fact that these abnormalities are more likely to be due to syphilis alone, while in those with higher CD4 they may be due to syphilis and HIV.

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