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SEXUAL HEALTH

Could late-latent syphilis be treated with a single subcutaneous infusion of long-acting penicillin?

Thel K. Hla[A,B,C,*], Sam Salman[A,B,D], Joseph Kado[A,B], Brioni R. Moore[A,B,E] and Laurens Manning[A,B,C]

For full list of author affiliations and declarations see end of paper

***Correspondence to:**
Thel K. Hla
Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, WA, Australia
Email: thel.hla@telethonkids.org.au

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ABSTRACT

Syphilis is an important global health threat and little has changed in its treatment since the mid-20th century. For late-latent or syphilis infection of unknown duration, the standard treatment of multiple intramuscular injections of benzathine penicillin G (BPG) are associated with significant pain and distress to clients and caregivers, negatively impacting on treatment completion. Based on pharmacokinetic modelling from a Phase I study of subcutaneous infusion of high dose BPG (SCIP), we present its feasibility, safety and tolerability for treatment of syphilis in a single infusion. SCIP leads to more sustained penicillin concentrations above the desired target with less reported pain and reduced clinic visits.

Keywords: antibiotics, benzathine penicillin G, late latent syphilis, population pharmacokinetics, subcutaneous penicillin, syphilis, syphilis of unknown duration, treatment of syphilis.

An estimated 19.9 million people are living with syphilis globally.[1] The World Health Organization has set a key strategic target for elimination of congenital syphilis via mother-to-child transmission (MTCT) in 50 countries by 2025. Currently only 15 countries have achieved this, highlighting the need for improved treatments.[2] The Australian syphilis epidemic continues and a national target to eliminate congenital syphilis by 2022 was not achieved.[3]

For those with late-latent or syphilis infection of unknown duration, three intramuscular (i.m.) injections of benzathine penicillin G (BPG; 2.4 million units [MU]) given on consecutive weeks are recommended, a regimen which has changed little since the 1950s.[4] Data are scarce on multi-dose completion rates, but appear low (43–69%), likely owing to the associated pain and the need for multiple clinic visits, which impede the overall efforts to reduce global burden and MTCT of syphilis.[5,6] Pharmacokinetic modelling suggests that current three-dose regimen given a week apart (using Bicillin®L-A formulation, Pfizer) result in penicillin plasma concentrations above 18 ng/mL (a historical therapeutic target) for approximately 6 weeks (Fig. 1; orange).[7–9]

Subcutaneous (SC) delivery of BPG, delivered to the lower abdominal area using a SC catheter at a rate of 0.5–1 mL/min, delays systemic absorption of penicillin which could be exploited to deliver the entire treatment course at a single visit.[9] Here we show the pharmacological profiles following SC infusion of 7.2 MU BPG (SCIP), delivered in 10 healthy adult volunteers who participated in a Phase I study[9] (Fig. 1; blue), which focused on secondary prophylaxis for acute rheumatic fever, a condition for which BPG is also indicated. Compared with standard treatment, SCIP leads to increased time (7 extra days) above 18 ng/mL. There were no serious adverse events throughout the 16 weeks follow-up and majority reported minimal pain, substantiated via quantitative pain scores and qualitative interviews.[9,10]

Therefore, SCIP appears safe and tolerable for syphilis, potentially providing a more sustained therapeutic penicillin exposure and less pain compared to standard i.m. therapy. In late-latent or syphilis of unknown duration, it confers added benefit of treatment completion at a single visit, emphasising patient-centred delivery to improve treatment completion rates. Equivalent drug costs can be assumed as the total dose delivered is the same (7.2 MU), while the additional low cost of a SC catheter is offset by reduced demand on material and personnel resources from reduced number of visits. Further evaluation is currently underway in a Phase IIa trial to explore safety, tolerability, and treatment efficacy of SCIP in non-central nervous system syphilis (ACTRN12622000349741), the results of which have the potential to improve syphilis treatment and adherence.

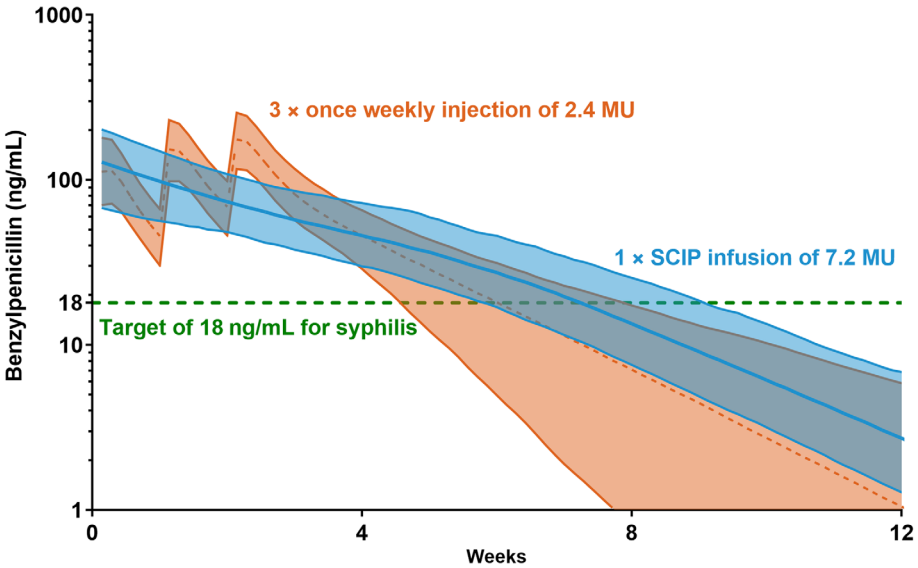

Fig. 1. Simulation of 7.2 MU subcutaneous infusion of benzathine penicillin (as Bicillin®L-A) compared to three separate weekly 2.4 MU intramuscular injections modelled from Kado *et al.*[9] MU, million units; SCIP, subcutaneous infusion of penicillin.

References

1 Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, *et al.* Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* 2019; 97(8): 548–562P. doi:10.2471/BLT.18.228486

2 World Health Organization. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. Geneva: World Health Organization; 2022.

3 Department of Health. Fifth National Aboriginal and Torres Strait Islander blood borne viruses and sexually transmissible infections strategy 2018-2022. Commonwealth of Australia; 2018.

4 Magnuson HJ, Thomas EW, Olansky S, Kaplan BI, De Mello L, Cutler JC. Inoculation syphilis in human volunteers. *Medicine* 1956; 35(1): 33–82. doi:10.1097/00005792-195602000-00002

5 Mangone E, Bell J, Khurana R, Taylor MM. Treatment completion with three-dose series of benzathine penicillin among people diagnosed with late latent and unknown duration syphilis, Maricopa County, Arizona. *Sex Transm Dis* 2023; 50(5): 298–303. doi:10.1097/OLQ.0000000000001775

6 Wu M, Seel M, Britton S, Dean JA, Lazarou M, Safa H, *et al.* Addressing the crisis of congenital syphilis: key findings from an evaluation of the management of syphilis in pregnancy and the newborn in South-East Queensland. *Aust N Z J Obstet Gynaecol* 2022; 62: 91–97. 10.1111/ajo.13424

7 Rein MF. Biopharmacology of syphilotherapy. *J Am Vener Dis Assoc* 1976; 3(2 Pt 2): 109–27.

8 Kampmeier RH. The introduction of penicillin for the treatment of syphilis. *Sex Transm Dis* 1981; 8(4): 260–265. doi:10.1097/00007435-198110000-00005

9 Kado J, Salman S, Hla TK, Enkel S, Henderson R, Hand RM, *et al.* Subcutaneous infusion of high-dose benzathine penicillin G is safe, tolerable, and suitable for less-frequent dosing for rheumatic heart disease secondary prophylaxis: a phase 1 open-label population pharmacokinetic study. *Antimicrob Agents Chemother* 2023; 67: e0096223. doi:10.1128/aac.00962-23

10 Enkel SL, Kado J, Hla TK, Salman S, Bennett J, Anderson A, *et al.* Qualitative assessment of healthy volunteer experience receiving subcutaneous infusions of high-dose benzathine penicillin G (SCIP) provides insights into design of late phase clinical studies. *PLoS ONE* 2023; 18(4): e0285037. doi:10.1371/journal.pone.0285037

Data availability. The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Conflicts of interest. The authors declare no conflicts of interest.

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Author affiliations

[A]Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, WA, Australia.

[B]Medical School, University of Western Australia, Perth, WA, Australia.

[C]Department of Infectious Diseases, Fiona Stanley Hospital, Perth, WA, Australia.

[D]Clinical Pharmacology and Toxicology Unit, PathWest, WA, Australia.

[E]Curtin Medical School, Curtin University, Perth, WA, Australia.