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Population pharmacokinetic study of benzathine penicillin G administration in Indigenous children and young adults with rheumatic heart disease in the Northern Territory, Australia

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Background: Benzathine penicillin G (BPG) is the cornerstone of secondary prophylaxis to prevent *Streptococcus pyogenes* infections, which precede acute rheumatic fever (ARF). The paucity of pharmacokinetic (PK) data from children and adolescents from populations at the highest risk of ARF and rheumatic heart disease (RHD) poses a challenge for determining the optimal dosing and frequency of injections and undermines efforts to develop improved regimens.

Methods: We conducted a 6 month longitudinal PK study of young people receiving BPG for secondary prophylaxis. Throat and skin swabs were collected for microbiological culture along with dried blood spot (DBS) samples for penicillin concentrations. DBSs were assayed using LC-MS/MS. Penicillin concentration datasets were analysed using non-linear mixed-effects modelling and simulations performed using published BMI-for-age and weight-for-age data.

Results: Nineteen participants provided 75 throat swabs, 3 skin swabs and 216 penicillin samples. Throat cultures grew group C and G *Streptococcus*. Despite no participant maintaining penicillin concentration >20 ng/mL between doses, there were no *S. pyogenes* throat infections and no ARF. The median (range) observed durations >20 ng/mL for the low- and high-BMI groups were 14.5 (11.0–24.25) and 15.0 (7.5–18.25) days, respectively.

Conclusions: Few patients at highest risk of ARF/RHD receiving BPG for secondary prophylaxis maintain penicillin concentrations above the target of 20 ng/mL beyond 2 weeks during each monthly dosing interval. These PK data suggest that some high-risk individuals may get inadequate protection from every 4 week dosing. Future research should explore this gap in knowledge and PK differences between different populations to inform future dosing schedules.

Introduction

Acute rheumatic fever (ARF), the autoimmune sequelae of inadequately treated pharyngeal or skin infections with *Streptococcus pyogenes*, can result in rheumatic heart disease (RHD), which affects 40.5 million people and causes 306 000 deaths annually.[1] Most RHD occurs in low–middle-income countries, but underserved communities in high-income countries, such as Aboriginal and Torres Strait Islander (hereafter Indigenous/Aboriginal) Australians, have among the highest reported rates.[1,2]

Rural and northern Australia within the Northern Territory (NT) have very high age-standardized rates of ARF (incidence = 413 per 100 000 population) and RHD (prevalence = 2666 per 100 000 population).[2] By comparison, ARF incidence amongst urban-dwelling Indigenous Australians is 8 per 100 000 population.[3]

Benzathine penicillin G (BPG) is the mainstay of secondary prophylaxis for ARF/RHD.[4] International guidelines recommend 1.2 million units (MU) of intramuscular (IM) BPG every 4 weeks to prevent recurrence of *S. pyogenes* infections.[5] After injection, BPG dissociates into benzathine and benzylpenicillin (penicillin) before absorption into the plasma.

It is widely accepted that the time plasma penicillin concentrations remain >20 ng/mL is a pharmacological correlate of protection.[6] Data informing current guidelines are derived from studies conducted over 60 years ago.[7] However, ethnic/racial differences, socioeconomic background, body composition, significant health conditions and environmental factors may all contribute to pharmacokinetic (PK)-pharmacodynamic variation between populations.[8] Recent population PK (popPK) studies in urban Indigenous Australians[9] and Ethiopian patients with RHD,[10] together with a cross-over comparison of IM and subcutaneous (SC) administration of BPG,[11] highlight body composition and site of delivery as key factors determining penicillin exposure.

The lack of data from populations at highest risk poses challenges for determining optimal dosing and frequency of BPG. Here, we conducted a popPK study of Aboriginal children and young adults in the NT receiving secondary prophylaxis for RHD.

Methods

Ethics

Ethical approval was obtained from the NT Department of Health and Menzies School of Health Research (2017-2900). Written informed assent/consent was obtained from participants and parents/guardians (ACTRN12622000136707).

Study design

This study was conducted through the Danila Dilba Health Service (DDHS) in Darwin, NT, which provides primary healthcare to Indigenous Australians. Patients aged 5–21 years receiving BPG for ARF/RHF were eligible. Trained DDHS nurses administered BPG (Bicillin® L-A Pfizer™, Australia; 1.2 MU) employing recommended practices to reduce pain,[12] every 21–28 days.

The methodology largely replicated our previous study.[9] Details for sample size justification and popPK analysis are also provided (see the Supplementary data available at *JAC* Online).

Results

Twenty participants were enrolled. Nineteen contributed samples for PK analyses [16 (89%) provided greater than 80% and 3 provided fewer than five samples] and 1 withdrew. A proportion (24/96) of doses occurred at 21 day intervals. All participants were Indigenous Australians. Baseline characteristics are shown (Table S1, available as Supplementary data at *JAC* Online).

Of 75 throat swabs collected during follow-up, 9 (12%) cultured group C *Streptococcus*/G *Streptococcus* (GCS/GGS), but none cultured *S. pyogenes* (Table S2). One *S. pyogenes* isolate was identified from a skin swab. This isolate had a penicillin MIC of 8 ng/mL, with corresponding penicillin concentration of 4 ng/mL. Two GCS isolates and one GGS isolate were resistant to penicillin by Etest and, while most of the penicillin concentrations measured at time of swab collection were below the measured MIC for group C and G *Streptococcus* (GCGS) that grew, one patient grew GGS despite the penicillin concentration being greater than the MIC. The median ratio of *in vitro* MIC to measured penicillin concentration was 8.5 (IQR = 1.9–14.2). There were no ARF recurrences.

PK modelling

There were 216 dried blood spot (DBS) penicillin measurements included in the PK analysis. A two-phase model of penicillin absorption resulted in the best model fit (Figure S1). These two phases were parameterized in terms of their respective half-lives, $t_{½,\ abs\text{-}1}$ and $t_{½,\ abs\text{-}2}$. Inter-individual variability (IIV) could be estimated on volume (*V*/F; 29%) and the slower absorption parameter ($t_{½,\ abs\text{-}2}$; 21%). Inter-occasion variability for $t_{½,\ abs\text{-}2}$ was 39%. The best size parameter for allometric scaling on volume was fat-free mass (FFM). A BMI cut-off of 26 kg/m^2 resulted in the best fit with a 64% increase in $t_{½,\ abs\text{-}2}$. No other significant covariate relationships were identified.

The final model parameter estimates and the bootstrap results are summarized (Table S3). PK parameters are summarized in Table 1. Goodness-of-fit plots demonstrated no bias (Figure S2) and prediction-corrected visual predictive check (pcVPC) plots stratified for BMI are shown (Figure 1). The actual 10th, 50th and 90th percentiles of observed data mostly fell within their respective 95% CI, demonstrating suitable predictive performance of the model.

Discussion

Our study of Indigenous Australians from the NT receiving BPG indicated that none maintained penicillin concentrations >20 ng/mL throughout the dosing interval, similar to previous studies in people with RHD.[6,9,10]

As with our previous study, FFM and BMI were key covariates in the popPK model. In the final model, FFM correlated best with

Table 1. PK parameters for penicillin following administration of BPG for RHD prophylaxis

	BMI <26 kg/m^2, n = 13	BMI ≥26 kg/m^2, n = 6
$t_{½,\ abs\text{-}1}$ (days)[a]	0.408	0.408
$t_{½,\ abs\text{-}2}$ (days)	8.63 (6.73–10.5)	14.3 (11.5–15.9)
C_{min} (ng/mL)	7.06 (3.50–15.5)	11.1 (7.00–13.1)
C_{max} (ng/mL)	55.5 (39.0–104)	37.6 (27.0–42.3)
T_{max} (h)	46 (42–47)	50 (44–52)
Time >20 ng/mL (days)	14.5 (11.0–24.25)	15.0 (7.5–18.25)
Time >20 ng/mL (%)	52 (39–87)	54 (27–65)
Time >10 ng/mL (days)	23.25 (17.75–28.0)	28.0 (21.25–28.0)
Time >10 ng/mL (%)	83 (63–100)	100 (76–100)

Data are median (range).
[a]IIV not included in final model.

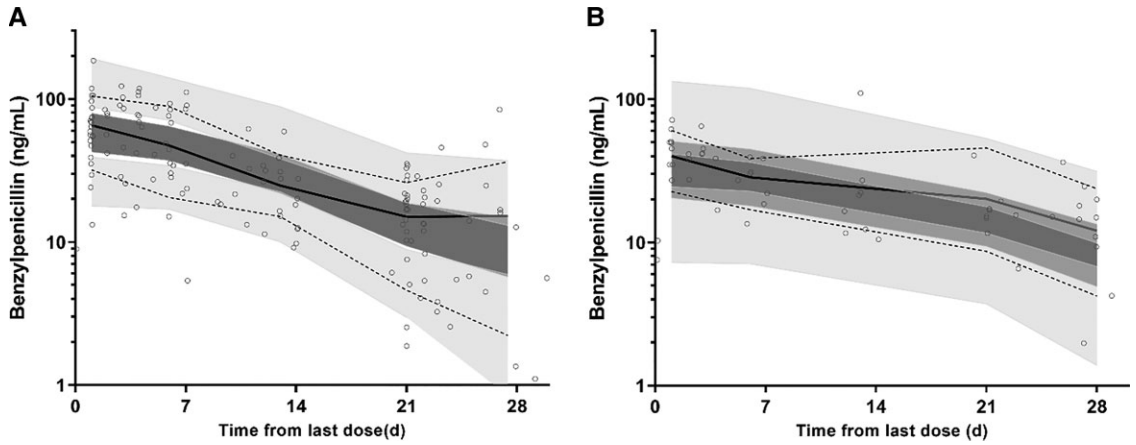

Figure 1. pcVPCs for penicillin concentrations (ng/mL on $\log_{10}$ scale) for low-BMI (<26 kg/m^2) (a) and high-BMI (≥26 kg/m^2) (b) patients. Observed 50th (solid line) and 10th and 90th (dotted lines) percentiles within their simulated 95% CI (grey shaded areas) are shown with overlying of the data points (open circles).

volume of distribution (V), whilst a BMI cut-off of 26 kg/m^2 was the only other significant covariate in the model resulting in an increase in the absorption half-life ($t_{½,\ abs\text{-}2}$) of 66.3%, which we hypothesize is a surrogate for inadvertent SC dosing.[11]

This study mirrors the structure of our recent urban popPK model.[9] Importantly, $t_{½,\ abs\text{-}2}$ was similar (8.70 versus 8.88 days). Despite this, there were differences between the two cohorts. A small difference in BMI cut-off was observed (25 versus 26 kg/m^2) and the slower absorption half-life ($t_{½,\ abs\text{-}2}$) was increased by 66.3% for the higher BMI group, compared with 86.5% in the Perth cohort. Minimum and maximum concentrations were both higher due to a lower population estimate of V (50.4 versus 72.2 L/70 kg).

These differences impact penicillin time–concentration profiles. The median (range) observed durations >20 ng/mL for the Darwin low- and high-BMI groups were 14.5 (11.0–24.25) and 15.0 (7.5–18.25) days, respectively, noticeably longer than the Perth cohort [9.8 (3.5–18.5) and 0 (0–23.3) days]. Unlike the Perth study, the difference in median time >20 ng/mL between normal- and high-BMI groups was minimal. These differences likely reflect study population characteristics, with the Darwin cohort on average being younger (13.0 versus 14.1 years), lighter (56.8 versus 62.9 kg) and with a lower BMI (21.4 versus 23.6 kg/m^2; Table S4). Remote-living Aboriginal people are likely to be younger,[2] experience more economic deprivation and have a lower BMI,[13] hence these results may more closely reflect the situation for the largest group at risk of RHD in Australia.

Despite not maintaining penicillin concentrations >20 ng/mL, no participants experienced a *S. pyogenes* throat infection or ARF recurrence. This suggests that the target concentration need not be maintained for the entire dosage interval or that intermittent 'presumptive' treatment may prevent colonization.[6] This contrasts with a larger NT cohort, which showed that, despite adherence to every 4 week BPG, recurrences of ARF still occur.[14] Alternatively target concentrations based on susceptibility breakpoints across *S. pyogenes* isolates may not directly reflect the concentrations required to prevent colonization. Our simulations, using a clinically plausible lower breakpoint target of >10 ng/mL indicated higher median (range) percentages of time above the lower target between injections, for both the low- and high-BMI groups of 83% (63%–100%) and 100% (76%–100%), respectively. Adapting a recently published *S. pyogenes* human challenge model[15] will better define the minimum required therapeutic concentrations to prevent infection and will underpin new regimens and reformulation.

The presence of GCGS parallels previous reports in populations at risk of RHD.[16,17] While there were no ARF recurrences, a role for GCGS throat infections and *S. pyogenes* skin infections in the pathogenesis of ARF has been proposed.[18,19]

Pharyngeal colonization with GCGS also provides insights into pharmacological correlates of protection for β-haemolytic streptococci. *S pyogenes* has a lower MIC_{90} than GCGS. The median ratio of *in vitro* MIC to measured penicillin concentration was ~9. One interpretation is that the penicillin concentrations with current BPG regimens were adequate to prevent *S. pyogenes*, but not GCGS, pharyngeal colonization. These lines of evidence raise the possibility that the threshold concentration is lower than 20 ng/mL.

One limitation of our study was a smaller sample size than planned. Nevertheless, the number was similar to previous reports. We did not undertake ultrasound to confirm IM delivery of BPG. Thirdly, we used DBS sampling to avoid repeated venesections in this vulnerable population, without parallel plasma samples for internal validation. We have previously demonstrated good correlation between DBS and plasma concentrations.[11] Although DBS assays may display systematic bias with extremes of haematocrit,[20] there was a narrow haemoglobin range in our study. Finally, we were unable to measure creatinine levels to estimate glomerular filtration rate, noting that the clearance of penicillin from the central compartment needed to be fixed in the PK model. However, there was no established renal dysfunction amongst participants.

Conclusions

Few patients receiving BPG for secondary prophylaxis achieve target concentrations beyond 2 weeks for each dosing interval. This study is concordant with our previous popPK study in a different

predominantly Indigenous Australian population, but important differences were also highlighted.

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Transparency declarations

None to declare.

The funders had no role in: study design; data collection, analysis or interpretation; or writing of the report.

Supplementary data

Supplementary data, including Tables S1 to S4 and Figures S1 and S2, are available at *JAC* Online.

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