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Rheumatic fever prophylaxis in South Africa — is bicillin 1,2 million units every 4 weeks appropriate?

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Rheumatic fever is a major health problem in South Africa. Although intramuscular benzathine penicillin (bicillin) 1,2 million units (MU) every 4 weeks is widely used for secondary prophylaxis, studies in other countries have shown a recurrence rate of 3 - 8% over 5 - 6 years in patients on this regimen. It has been recommended that serum penicillin concentrations should be maintained above 0,02 mg/ml to prevent such recurrences. The World Health Organisation (WHO) and the American Heart Association have recommended since 1988 that patients in high-risk areas for the development of rheumatic fever should receive benzathine penicillin 1,2 MU every 3 weeks rather than every 4.

The aims of this study were, firstly, to determine the prevalence of serum penicillin concentrations below 0,02 µg/ml in rheumatic fever patients on benzathine penicillin 1,2 MU 4-weekly and, secondly, to study the effect of increasing the dose to 1,8 MU 4-weekly in patients with subtherapeutic concentrations.

Forty-five of 51 rheumatic fever patients (88%) in this study on benzathine penicillin 1,2 MU 4-weekly had low serum penicillin concentrations (< 0,02 µg/ml) at the end of the 4th week after the injection. Penicillin was detected in the urine of 30 of the 45 patients (67%) with low concentrations, suggesting that such patients have tissue-bound penicillin which might be important in preventing rheumatic fever. The 15 patients (33%) with subtherapeutic serum penicillin concentrations and no detectable penicillin in the urine could be at very high risk for recurrent attacks of rheumatic fever.

Fourteen of 29 patients (48%) given the higher dose of benzathine penicillin (1,8 MU 4-weekly) had subtherapeutic serum penicillin concentrations at the end of the 4th week after the injection, but in all 29 penicillin was detected in the urine.

Review of our present policy of secondary prophylaxis for rheumatic fever is necessary. Concentrated preparations of benzathine penicillin (600 000 U/ml) are not available in South Africa; administration of a higher dose (1,8 MU) 4-weekly would therefore require a double injection, which could affect compliance adversely. We recommend that rheumatic fever patients in our area should receive benzathine penicillin 1,2 MU 3-weekly as recommended by the WHO until strategies for secondary prophylaxis have been evaluated further.

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Rheumatic heart disease is the most common form of acquired cardiac disease in children worldwide. The prevalence of rheumatic fever and rheumatic heart disease in schoolchildren has been estimated to be less than 1/1 000 in developed countries and 11 - 22/1 000 in developing countries.[1] In 1972 McLaren *et al.*[2] reported a prevalence of rheumatic heart disease of 6,9/1 000 in 3 - 18-year-old children in Soweto, Johannesburg. Edginton and Gear[3] list rheumatic heart disease among the top 10 causes of death in the 15 - 24-year age group in South Africa. The financial burden on the country is reflected in the estimated costs (approximately R40 million annually) for valve replacement surgery at six major South African centres for the 5-year period 1982 - 1987.[4]

Secondary antibiotic prophylaxis against group A β-haemolytic streptococcus (GABHS) infection in patients with rheumatic heart disease will not only prevent recurrences but will improve healing of carditis.[5] Recurrent attacks of rheumatic fever usually result from non-compliance with prophylaxis. However, a disturbing recurrence rate of 3 - 8% over 5 - 6 years has been recorded in patients known to be compliant with the regimen of intramuscular benzathine penicillin (bicillin) 1,2 million units (MU) every 4 weeks.[5-7] Low as this rate may be, it is unacceptable because these patients run the risk of increased cardiac damage despite conscientiously arriving every month (often at great inconvenience) for treatment which is quite painful.

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Such 'prophylaxis failure' is thought to be associated with low serum penicillin concentrations in the 4th week after the injection.[7-10] It has accordingly been recommended by the World Health Organisation (WHO) and the American Heart Association (AHA) that rheumatic fever patients in high-risk areas should receive benzathine penicillin every 3 weeks.[8-9,11] Some authors have even recommended injections every 2 weeks.[12]

A potential disadvantage of giving benzathine penicillin more frequently is the risk that compliance may decrease. However, Lue *et al.*[8] found that changing from a 4-weekly to a 3-weekly regimen did not affect compliance. To avoid the potential problems arising from changing the frequency of injections, Ayoub[9] has suggested that therapeutic serum penicillin concentrations might be maintained on a 4-weekly regimen if the dose were to be increased.

The present study was motivated by the recurrence of rheumatic fever in a patient who had been on regular secondary prophylaxis (benzathine penicillin 1,2 MU 4-weekly) at Coronation Hospital, Johannesburg.

The aims of the study were, firstly, to determine the prevalence of subtherapeutic serum penicillin concentrations in patients on benzathine penicillin 1,2 MU 4-weekly and, secondly, to study the effect of increasing the dose to 1,8 MU 4-weekly in patients with subtherapeutic serum penicillin concentrations.

Subjects and methods

The study population consisted of patients with confirmed rheumatic fever and rheumatic heart disease as diagnosed by the revised Jones Criteria (1988)[13] who were being followed up in the Johannesburg area.

Penicillin concentrations on benzathine penicillin 1,2 MU

Consecutive patients were recruited over a 13-month period at either Baragwanath Hospital or Coronation Hospital and its related primary health care clinics. Patients were included if they had received benzathine penicillin 1,2 MU 28 days previously and were excluded if they had received any other antibiotics during that month.

Informed written consent was obtained from the parents of patients or from the patients themselves if they were older than 14 years. The study was approved by the Committee for Research on Human Subjects, University of the Witwatersrand.

Blood and random urine samples for penicillin assay were collected from each patient, and their age, sex and weight were recorded. All patients were then given benzathine penicillin (Penilente 1,8 g; Novo) 1,2 MU and their usual appointment date for 28 days later.

Blood samples were centrifuged and the serum separated within an hour after sampling. The serum and urine were then frozen at –20°C. Specimens were transported in batches, frozen on ice, to the central laboratory of the South African Institute for Medical Research (SAIMR) in Johannesburg. All specimens reached the central laboratory within 30 minutes.

Penicillin assays were performed using the agar diffusion microbiological method as described by Sutherland and Robinson.[14] Two replicate samples of each specimen were placed randomly in wells in an agar plate impregnated with the organism *Sarcina lutea*. Duplicate samples of five different standard concentrations of penicillin were also placed on each plate.

The plates were incubated overnight and the zones of growth inhibition around each well were measured. A graph was constructed by plotting the concentrations of each of the standard penicillin solutions against their inhibition zones on semi-logarithmic graph paper. The concentrations of penicillin in the patients' specimens were then determined from this graph.

Serum penicillin concentrations of 0,02 µg/ml or higher were defined as therapeutic and those lower than 0,02 µg/ml as subtherapeutic. This is an arbitrary therapeutic concentration as used by Kaplan *et al.*[7] The limit of sensitivity of the assay was 0,015 µg/ml and concentrations lower than 0,015 µg/ml were therefore defined as undetectable.

Serum creatinine levels were measured in all the specimens with detectable serum penicillin concentrations and were compared with serum creatinine levels measured in a random sample of 16 specimens from patients with undetectable serum penicillin concentrations. Urine penicillin/creatinine ratios were calculated to correct for varying volumes and concentrations of urine samples. An assessment of the accuracy and repeatability of the assay was made by analysis of the inhibition zones of the standard penicillin solutions.

Since penicillin is known to degenerate in stored specimens, even if they are frozen,[7,14] the time interval between collection of specimens and performance of the assay was recorded for correlation with the penicillin concentrations obtained. Furthermore, a trial was performed to document the rate at which penicillin degenerates over a 12-week period in specimens stored at –20°C. Serum and urine specimens were collected from 8 of the study patients. These specimens were used to prepare six 0,5 ml aliquots of serum and six 0,5 ml aliquots of urine for each patient. A single aliquot of serum and a single aliquot of urine from each patient were thawed at 2-weekly intervals and penicillin concentrations were measured.

In order to assess the susceptibility of local strains of GABHS to penicillin, a throat swab was taken from each patient and forwarded in appropriate transport medium to the local hospital laboratory for culture. Throat swabs were also sent from non-rheumatic fever patients who presented with follicular tonsillitis at the Paediatric Outpatient Department at Coronation Hospital between July and October 1990. A total of 16 positive cultures for GABHS were obtained. Penicillin minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) using the serial tube dilution method in 10% serum broth were determined for these 16 cultures.

Penicillin concentrations on benzathine penicillin 1,8 MU

Those patients who had subtherapeutic serum penicillin concentrations on benzathine penicillin 1,2 MU were entered into this part of the study. A dose of 1,8 MU was administered to these patients at their return clinic visit. Blood and urine samples were collected 28 days after administration of the higher dose.

A minimum of 11 patients was required for this part of the study to detect a difference of 0,02 µg/ml in serum penicillin concentrations (one-sided paired *t*-test: alpha = 0,05, beta = 0,05).

Statistical analysis

Statistical analysis was performed using a SAS computer package licensed to the University of the Witwatersrand. Differences between means were assessed with Student's *t*-test. Penicillin concentrations were not normally distributed and were therefore analysed using non-parametric tests. Differences between proportions were analysed with the χ^2-test or Fisher's exact test where appropriate. Correlation between variables was assessed by calculation of the Spearman rank correlation coefficient (r_s). Probability $P \leq 0,05$ was defined as significant.

Results

Penicillin concentrations on benzathine penicillin 1,2 MU

The analysis was performed on the results of 51 patients who had specimens collected exactly 28 days after administration of 1,2 MU benzathine penicillin. There were 24 males and 27 females (mean age 13 ± 3 years). The period between collection of specimens and performance of the penicillin assay was 23 ± 17 days.

Subtherapeutic serum penicillin concentrations (< 0,02 µg/ml) were found in 45 of the 51 patients (88%). All but 1 of these 45 patients had undetectable serum penicillin concentrations (< 0,015 µg/ml). The mean serum creatinine concentration of the 6 patients with therapeutic serum penicillin concentrations (≥ 0,02 µg/ml) was 50,0 ± 14,0 mmol/l. This value did not differ from the mean serum creatinine value of 49,9 ± 10,4 µmol/l for a random sample of 16 patients with subtherapeutic serum penicillin concentrations ($P = 0,77$).

Penicillin was detected in the urine of 5 of the 6 patients with therapeutic serum concentrations (83%) and in the urine of 30 of the 45 patients with subtherapeutic serum concentrations (67%) (Table I).

Table I. Relationship between serum and urine penicillin concentrations on benzathine penicillin 1,2 MU (51 patients)

Urine conc. (µg/ml)	Serum conc. ≥ 0,02 µg/ml	Serum conc. < 0,02 µg/ml	Total No. of patients
Detectable (≥ 0,015)	5	30	35 (69%)
Undetectable (< 0,015)	1	15	16 (31%)
Total	6	45	51

Serum penicillin concentrations did not correlate with urine penicillin/creatinine ratios ($r_s = 0,29$, $P = 0,17$), the time elapsed to performance of the assay ($r_s = -0,02$, $P = 0,15$), the weight of the patient ($r_s = 0,23$, $P = 0,18$) or the age of the patient ($r_s = -0,16$, $P = 0,15$). However, a higher proportion (36%) of patients aged 10 years or younger had therapeutic serum penicillin concentrations compared with the 11 - 15-year-olds (3%) or those aged 16 years or older (9%) ($P < 0,05$, Fisher's exact test). To eliminate the effect of the large number of undetectable serum and urine penicillin concentrations, the relationship between serum and urine inhibition zones was tested but no correlation was found ($P > 0,05$).

Urine penicillin/creatinine ratios did not correlate with the age of the patient ($r_s = -0,09$, $P = 0,15$), the weight of the patient ($r_s = -0,32$, $P = 0,20$) or the time which elapsed until performance of the assay ($r_s = -0,33$, $P = 0,13$).

Penicillin concentrations on benzathine penicillin 1,8 MU

Thirty of the 45 patients with subtherapeutic serum penicillin concentrations on benzathine penicillin 1,2 MU were given 1,8 MU. One patient did not come back for follow-up. She had been admitted with a recurrent attack of rheumatic fever 1 week after receiving benzathine penicillin 1,8 MU. The analysis was therefore performed on the data for the remaining 29 patients. There were 16 males and 13 females, aged 12 ± 3 years.

Fifteen of the 29 patients (52%) had therapeutic serum penicillin concentrations on bicillin benzathine penicillin 1,8 MU compared with only 6 of 51 (12%) on 1,2 MU ($P < 0,001$) (Fig. 1). Penicillin was detected in the urine of all 29 patients given 1,8 MU. The mean urine penicillin/creatinine ratio of 0,54 mg/µmol on the 1,8 MU dose was significantly higher than the ratio of 0,23 mg/µmol for the same 29 patients on 1,2 MU ($P < 0,005$, paired *t*-test).

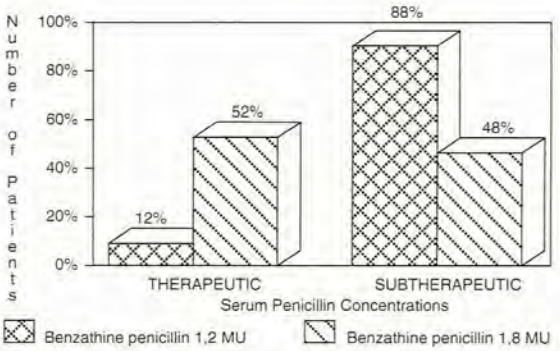

Fig. 1. Serum penicillin concentrations on benzathine penicillin 1,2 and 1,8 MU.

Serum penicillin concentrations on benzathine penicillin 1,8 MU did not correlate with urine penicillin/creatinine ratios ($r_s = 0,16$, $P = 0,20$), the age of the patient ($r_s = 0,14$, $P > 0,05$), the weight of the patient ($r_s = 0,05$, $P = 0,05$) or the time interval between specimen collection and assay ($r_s = 0,64$, $P > 0,05$).

Throat culture results

Throat swab results were available for 44 of the study patients. Results for the other 7 patients could not be traced. GABHS was cultured from the throat swabs of 2 patients. Both were asymptomatic and were not treated on antibiotics. Neither of them had a recurrence of rheumatic fever on follow-up for 2 months after these results.

Of the non-rheumatic fever patients with sore throats, 16 had throat swabs positive on culture for GABHS that were forwarded for penicillin MIC/MBC determinations. The MICs and MBCs were identical and ranged from 0,003 to 0,015 µg/ml, and the MBC/MIC ratios for all the organisms were equal to 1. Tolerance of the group A *Streptococcus* to penicillin would be suggested by MBC/MIC ratios of 10 or over.[15]

Assessment of penicillin assay

Penicillin assays on the patients' serum and urine specimens were performed on 11 different dates. An analysis was made of the variability of the zones of inhibition for the replicate samples of 69 serum and 119 urine standard penicillin solutions used in these assays.

The inhibition zones of the serum standard solutions ranged from 11,0 to 38,0 mm. The inhibition zones of replicate samples from each standard solution differed by a mean of 0,9 ± 1,0 mm (P = 0,46). There was also no difference between the inhibition zones of the replicate samples of the urine standard solutions (P = 0,65).

Rate of degeneration of penicillin in stored specimens

Penicillin was detected in serum of 3 of the 8 patients, and these results were consistent throughout the 84 days of the trial. There was no difference between the mean urine penicillin/creatinine ratio of 0,87 mg/µmol for the specimens assayed 14 days after collection and the mean ratio of 0,98 mg/µmol for those assayed 84 days after collection (P = 0,80).

Discussion

The role of antibiotic prophylaxis in the prevention of rheumatic fever has been well established.[16,17] Penicillin remains the most important therapeutic agent for both primary and secondary prophylaxis of rheumatic fever. Recurrences of rheumatic fever in patients known to be compliant with benzathine penicillin 1,2 MU every 4 weeks for secondary prophylaxis have led to doubts about the usefulness of this regimen.

The majority of our patients (88%) had subtherapeutic serum penicillin concentrations in the 4th week after administration of benzathine penicillin 1,2 MU. Eighty-six per cent of patients had undetectable serum concentrations on this dose. These results are similar to those of Ginsburg *et al.*,[18] who reported subtherapeutic serum penicillin concentrations (< 0,02 µg/ml) 18 days after doses of 0,6 MU and 1,2 MU in all of 13 children aged 11 years and younger. All these patients had undetectable serum penicillin concentrations 30 days after administration of benzathine penicillin. Kaplan *et al.*[7] also reported subtherapeutic serum penicillin concentrations (< 0,02 µg/ml) in 64% of 193 serum samples taken 28 days after administration of a 1,2 MU dose. Penicillin was undetectable in 56% of these samples.

Ayoub[9] has questioned the value of therapeutic serum penicillin concentrations in the management of rheumatic fever, since tissue-bound penicillin may be more important in preventing streptococcal infection in the pharynx. Nightingale[19] confirms that it is the quantity of antibiotic present at the site of infection (called the critical antibiotic concentration) that is important in killing infecting organisms and that serum antibiotic MICs/MBCs do not necessarily reflect such tissue concentrations. Konig *et al.*[20] noted that antibiotics with small differences in MIC values had vastly different bactericidal and bacteriostatic effects *in vivo*. They suggest that clinical decisions based largely on MIC values ignore the pharmacological properties of antibiotics and the role of the host immune system in eliminating organisms.

Furthermore, sub-bactericidal concentrations of penicillin have been shown to minimise streptococcal virulence by inducing loss of the organism's hyaluronic acid capsule and M-proteins.[16,21] Rheumatogenic strains of GABHS tend to be highly virulent.[13,16] It is therefore possible that serum penicillin concentrations below the MBCs for GABHS might be effective in secondary prophylaxis of rheumatic fever.

Ginsburg *et al.*[18] found penicillin in the urine of all 13 patients with undetectable serum penicillin concentrations 30 days after being given benzathine penicillin 1,2 MU. Urinary excretion of penicillin in these patients suggests that there is penicillin in the tissues even though serum penicillin is not measurable.[18] Serum penicillin concentrations may therefore be an inadequate measure not only of tissue-bound penicillin but also of the risk for development of rheumatic fever. Penicillin was not detected in the urine of one-third of the patients in our study with subtherapeutic serum penicillin concentrations on benzathine penicillin 1,2 MU. If absent urinary penicillin excretion represents lack of tissue-bound penicillin, these patients must be considered to be at very high risk for recurrent attacks of rheumatic fever.

Fifty-two per cent of patients given benzathine penicillin 1,8 MU had therapeutic serum penicillin concentrations, as opposed to only 12% of patients given 1,2 MU. All the patients who were given 1,8 MU had detectable penicillin concentrations in the urine. This suggests that patients on 1,8 MU 4-weekly still have tissue-bound penicillin 28 days post-injection. This higher dose may well be adequate to prevent rheumatic fever despite the high proportion of patients with subtherapeutic serum penicillin concentrations. Preparations of benzathine penicillin with concentrations of 600 000 U/ml[12,22] would require a single injection of 3 ml to administer 1,8 MU. Such preparations are not readily available in South Africa. The use of a double injection to administer 1,8 MU, as was used in this study, is not feasible for long-term prophylaxis because it may adversely affect compliance.

One of the patients entered into the second part of the study was admitted with a recurrent attack of rheumatic fever 1 week after benzathine penicillin 1,8 MU was administered. She had received 1,2 MU 4-weekly for at least 6 months preceding this recurrence. Her clinical presentation fulfilled both the 1982 and the more liberal 1988 revised Jones Criteria for a rheumatic fever recurrence. She had no evidence of infective endocarditis on clinical or echocardiographic examination. The patient was hospitalised for 2 months and is now receiving benzathine penicillin 1,2 MU 3-weekly.

In view of the documented prophylaxis failure in our study population and the fact that a large number of patients could be at high risk for recurrences of rheumatic fever, we recommend that the regimen of benzathine penicillin 1,2 MU

4-weekly used by our local hospitals and clinics be changed to 1,2 MU 3-weekly as recommended by the WHO. This latter regimen has been shown to protect against recurrences in clinical trials. Further studies should be performed to clarify which are the best antibiotic regimens for secondary prophylaxis of rheumatic fever. The findings of this study suggest that benzathine penicillin 1,8 MU 4-weekly may protect against recurrences even though patients may not have therapeutic serum penicillin concentrations. Such studies should include measurement of both clinical and pharmacological parameters in the same cohort of patients followed up for at least 5 years to document recurrence rates.

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Is ward evacuation for uncomplicated incomplete abortion under systemic analgesia safe and effective?

A randomised clinical trial

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Objective. To compare evacuation under systemic analgesia (fentanyl and midazolam) in a treatment room (ward group) with evacuation under general anaesthesia in theatre.

Design. A prospective randomised clinical trial.

Setting. A tertiary medical centre serving a black urban population.

Subjects. One hundred and forty-two patients with uncomplicated incomplete abortions.

Intervention. Randomisation into two groups, those for evacuation under systemic analgesia and those for evacuation under general anaesthesia.

Main outcome measures. Both groups were compared in terms of safety, efficacy, acceptability, blood consumption and time delay between admission and evacuation.

Results. Significantly less blood was used in the ward group (37 units for 13 patients) than in the theatre group (65 units for 24 patients) ($P < 0,03$). Significantly less time was taken between admission and evacuation in the ward group (median 7 hours 15 minutes) than in the theatre group (median 12 hours 38 minutes) ($P < 0,0003$). Evacuation under fentanyl and midazolam was safe, effective and acceptable for the majority of patients compared with evacuation under general anaesthesia.

Conclusion. Patients with uncomplicated incomplete abortions (uterine size equivalent to a pregnancy of 14 weeks' duration or less) can undergo evacuation safely and effectively under fentanyl and midazolam and have a significantly smaller chance of requiring a blood transfusion.

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