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Treatment of gonorrhoea in males in the Central African Republic with spectinomycin and procaine penicillin

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Gonorrhoea has become a problem in most parts of the world, and valid recommendations for treatment are important for control of the disease. In this study in Bangui, Central African Republic, 460 male patients with gonorrhoea were randomly assigned to treatment with either 4.0×10^6 units of procaine penicillin plus 1 g of probenecid, or 2 g of spectinomycin. Of these patients, 91% returned for follow-up; the failure rate was 4.8% with the penicillin schedule and 6.2% with spectinomycin (difference not statistically significant). Concomitant Chlamydia trachomatis *infection was found in 5% of patients, and almost all of this group developed postgonococcal urethritis.*

Of the 460 patients, 7 (1.5%) were infected with penicillinase-producing Neisseria gonorrhoeae *(PPNG) strains. Penicillin treatment failed in these cases, while spectinomycin was highly efficacious. The failure rate for penicillin was considerably higher in infections with strains that were less sensitive to penicillin* in vitro. *The failure rate for spectinomycin treatment was higher in patients who were infected with a strain that was highly sensitive to penicillin.*

It is concluded that, once PPNG strains have been found in a country, treatment of gonorrhoea should be based on an antibiotic that cures PPNG infections. Tetracycline can be used as second-line treatment, since it will also cure C. trachomatis *infection, which is much less frequently associated with gonorrhoea in Africa than in industrial countries.*

Gonorrhoea is one of the most common communicable diseases in the Central African Republic. National treatment recommendations were first made in 1980 on the basis of a gonococcal susceptibility study (*1*). Taking into account estimated treatment efficacy and cost, three regimens were recommended: procaine penicillin, 4.8×10^6 units, plus 1 g of probenecid; ampicillin, 3.5 g, plus 1 g of probenecid; and tetracycline, 500 mg, 4 times daily for 5 days. The first two regimens have been widely used and have proved highly efficacious (*2*). Tetracycline is rarely administered, mainly because of the problem of patient compliance with a 5-day regimen. As was feared, the prevalence of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) is increasing rapidly in Africa and PPNG strains have already been diagnosed in several countries (*2*, *3*); in the Central African Republic a PPNG strain was first diagnosed early in 1981.

To examine the possible need for revision of the treatment recommendations, a large clinical trial of the treatment of uncomplicated gonorrhoea was undertaken, using two regimens: procaine penicillin, 4.0×10^6 units, intramuscularly, plus 1 g of probenecid by mouth; and spectinomycin, 2 g, intramuscularly. The susceptibilities of *N. gonorrhoeae* to these (and three other) antibiotics were determined *in vitro* and the relationship between cure rate and susceptibility was studied.

MATERIALS AND METHODS

Male patients who attended the Centre for Sexually Transmitted Diseases in Bangui were considered for the study. Men with signs and symptoms of urethritis were eligible for the trial if they were not allergic to the drugs under study, had not received antimicrobial treatment within the preceding two weeks, and had no complication of the gonococcal infection. The objectives and procedures of the trial were explained and only subjects who gave free and informed consent were included.

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A short history was taken from each patient. With a calcium alginate swab, a specimen of the urethral discharge was plated directly on to modified Thayer-Martin medium and another was spread on a slide for Gram staining. Plates were placed in a candle extinction jar and incubated at 36 °C. A blood sample was taken for VDRL (venereal disease research laboratory) and TPHA (*Treponema pallidum* haemagglutination assay) tests. Patients who showed Gram-negative intracellular diplococci were randomly assigned to one of two regimens: procaine penicillin, 4.0×10^6 units, intramuscularly, plus 1 g of probenecid by mouth, or spectinomycin hydrochloride, 2 g, intramuscularly. (It was more convenient to administer 4×10^6 units of procaine penicillin rather than the recommended 4.8×10^6 units, as this could be achieved by diluting one vial of the commercial brand available locally in 10 ml of physiological solution. This resulted in easier administration of the drug with negligible effect on efficacy.) Patients were asked to bring their sexual contacts to the Centre for treatment, to abstain from any sexual activity, and to return for follow-up after 4–7 days.

At follow-up a short history was again taken, a clinical examination was done, a culture and smear were taken from the urethra with calcium alginate swabs, and details were obtained about sexual exposure and side-effects of treatment. Postgonococcal urethritis (PGU) was diagnosed if, at follow-up, gonorrhoea was excluded (smear and culture negative), but the Gram-stained smear showed 5 or more leukocytes in any microscopic field.

Organisms were presumptively identified as *N. gonorrhoeae* if typical, oxidase-positive colonies containing Gram-negative diplococci grew after 24–48 hours' incubation in 4% CO_2. Sugar fermentation tests were performed only in doubtful cases. All isolates were screened for penicillinase production by the cephalosporin test.

Isolates were frozen at −20 °C and sent in dry ice to the Microbiology Department of the Institute of Tropical Medicine in Antwerp, Belgium, where they were confirmed as *N. gonorrhoeae* by sugar utilization tests, rescreened for penicillinase production, and tested for antimicrobial susceptibility using the agar plate dilution technique. Minimal inhibitory concentrations (MICs) were determined for penicillin, thiamphenicol, tetracycline, kanamycin, and spectinomycin.

Urethral swabs for the isolation of *Chlamydia trachomatis* were taken before treatment from 141 randomly selected patients; of these, 125 returned for follow-up and a further swab was taken. The specimens were transported to Antwerp in sucrose-phosphate buffer transport medium in liquid nitrogen. *Chlamydia* were isolated using cycloheximide-treated McCoy cells (*4*).

Only patients with a positive pretreatment culture for *N. gonorrhoeae* were included in the analysis. Patients with a persistent infection at follow-up were considered treatment failures and were given the alternative regimen (penicillin or spectinomycin).

RESULTS

In a 4-month period in 1981, a total of 460 patients entered the study, all with a pretreatment culture positive for *N. gonorrhoeae* (Table 1). Of these, 419 (91%) returned for follow-up, with similar follow-up rates in both treatment groups.

The mean age of the 460 patients was 23.9 years; 49% were students, 26% soldiers or policemen, and 25% belonged to other professional groups. The failure rate was 4.8% with the procaine penicillin regimen and 6.2% with spectinomycin. This difference is not statistically significant ($\chi_1^2 = 0.4$, $P > 0.5$).

Table 1. Results of treatment of uncomplicated gonorrhoea in males in Bangui, Central African Republic, with procaine penicillin and spectinomycin

Treatment regimen	No. of patients in study	Returned for follow-up		Treatment failures		Post-gonococcal urethritis		Side-effects	
		No.	%	No.	%	No.	%	No.	%
Procaine penicillin, 4.0×10^6 units, plus 1 g of probenecid	232[a]	209[a]	90	10[b]	4.8	51	24.4	16	7.7
Spectinomycin, 2 g	228[c]	210[c]	92	13	6.2	43	20.5	6	2.9

[a] 5 strains were PPNG.
[b] 4 strains were PPNG.
[c] 2 strains were PPNG.

Two patients in each treatment group who were not cured admitted sexual re-exposure and may have been reinfected. The frequency of postgonococcal urethritis (PGU) was not significantly different in the two groups ($\chi^2_1 = 0.93$, $P > 0.3$).

Only minor side-effects were seen, such as dizziness and pain at the site of injection; they were more frequent with procaine penicillin ($\chi^2_1 = 4.85$, $P < 0.05$).

C. trachomatis was isolated from 7 patients (5%), 5 of whom had a positive culture before and after treatment. Of these 7 *Chlamydia*-positive cases, 6 (85.7%) developed postgonococcal urethritis (4 treated with penicillin and 2 treated with spectinomycin), compared with 15 of 118 (12.7%) *Chlamydia*-negative cases ($P < 0.001$).

Of 460 patients, 7 were infected with a PPNG strain (1.5%). Five of these patients received procaine penicillin; 4 were not cured and 1 was lost to follow-up. The remaining 2 patients received spectinomycin treatment and were cured. The 10 patients who were not cured by penicillin (including 4 infected with PPNG strains) were retreated with spectinomycin; 7 were cured (including all 4 PPNG cases) and 3 were lost to follow-up. The 13 patients who were not cured by spectinomycin received procaine penicillin; 7 were cured and 6 were lost to follow-up.

Minimal inhibitory concentrations (MICs) of 5 antimicrobials were obtained for 246 pretreatment isolates (Table 2). Twenty-eight strains (11%) were highly sensitive to penicillin (MIC < 0.06 μg/ml), 75 strains (31%) had a slightly diminished sensitivity (MIC, 0.06–0.25 μg/ml), and 143 strains (58%) had a highly diminished sensitivity to penicillin (MIC ⩾ 0.5 μg/ml). In this last group were 4 PPNG strains with MIC ⩾ 8 μg/ml. All strains were sensitive to 16 or 32 μg/ml of spectinomycin; 54 strains (22%) had a diminished sensitivity to tetracycline (MIC ⩾ 2 μg/ml). Of 23 treatment failures, pretreatment MICs were available for 17 (8 failures in the penicillin group and 9 in the spectinomycin group). Fig. 1 gives the failure rates according to the pretreatment MIC for penicillin. The failure rate for penicillin treatment was considerably higher for strains that were less sensitive to penicillin.

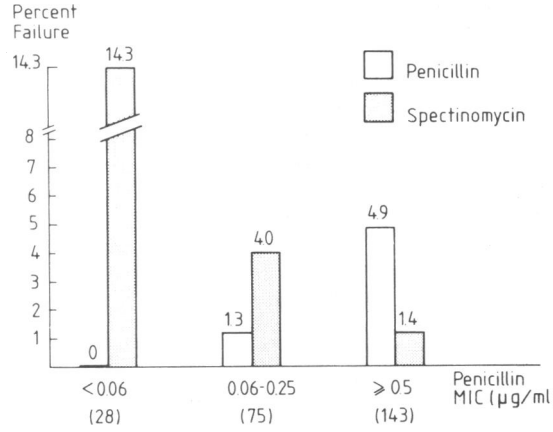

Fig. 1. Failure rate with procaine penicillin and spectinomycin in the treatment of gonorrhoea, according to the MIC of penicillin for the pretreatment isolates of *N. gonorrhoeae*. The number of isolates tested is given in parentheses.

For spectinomycin a reverse relationship was found, with a high failure rate for the strains that were highly sensitive to penicillin. Post-treatment MICs were available for 11 strains from the 23 treatment failures. Both pre- and post-treatment MICs were available for only 8 of these strains; there was no significant difference between the two values.

DISCUSSION

Both regimens studied were highly efficacious for the treatment of uncomplicated gonorrhoea. The failure rates were similar to those seen in the United States of America, where the rates were 3.2% with procaine penicillin and probenecid, and 5.2% with

Table 2. Antimicrobial MICs for 246 strains of *N. gonorrhoeae* isolated in Bangui, Central African Republic

Antimicrobial	Minimal inhibitory concentration (μg/ml)												
	0.0078	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Penicillin	5	14	9	13	36	26	35	67	36	1	4[a]		
Thiamphenicol				2	5	59	12	81	84	3			
Tetracycline					3	19	86	84	36	18			
Kanamycin										3	27	113	103
Spectinomycin												26	220

[a] MIC ⩾ 8 μg/ml; all 4 strains were PPNG.

the spectinomycin regimen (*5*). This could be expected from the susceptibility pattern of *N. gonorrhoeae* in the Central African Republic which, for both antibiotics, is very similar to that in the USA (*6*).

Few carefully conducted trials of gonorrhoea treatment have been done in Africa. The available data show failure rates of 1.0–6.8% for high-dose benzyl or procaine penicillin–probenecid schedules (*7–10*), and 3.9–5.4% for spectinomycin (*10*, *11*).

In agreement with a study carried out in the USA (*6*), we found a clear relationship between pretreatment susceptibility and failure rate for penicillin; such a relationship was not found for spectinomycin (all strains were susceptible to 16 or 32 μg/ml). There are no other African data available for comparison. It is interesting that failure rates with spectinomycin were higher with strains that were more sensitive to penicillin. These data need to be interpreted with caution because they are based on a relatively small number of subjects. Although not analysed in the publication, the raw data from the USA showed that, for strains with a penicillin MIC $\leqslant$ 0.06 μg/ml, the spectinomycin failure rate was 7.5%, while for penicillin MICs of 1.0 and 0.5 μg/ml, the failure rate was 0–3% (*6*). Later results from the USA did not show any relationship between failure rate with spectinomycin and the pretreatment MIC for penicillin (*12*).

A gonococcal susceptibility study was done on 70 strains isolated in the Central African Republic in 1979–80 (*1*) and our results 15 months later show a slightly higher percentage of strains with diminished sensitivity to penicillin and tetracycline. Predicted failure rates were 4.3% for procaine penicillin–probenecid and 4.6% for spectinomycin (*1*), which are very close to the rates determined in this study.

An important new finding is the 1.5% prevalence of PPNG strains, isolated for the first time in the Central African Republic in 1981. In the first 8 months of 1982, the prevalence increased to 3.1% (R. Widy-Wirski, unpublished data, 1982).

At this low prevalence, the efficacy of penicillin treatment is not yet significantly affected. Procaine penicillin can still be recommended as first-line treatment and spectinomycin for patients allergic to penicillin and for all treatment failures and their contacts (*10*). Once the prevalence of PPNG strains reaches 10% or more, it is generally accepted that penicillin should be abandoned as the first-line treatment (*13*).

After the emergence of PPNG strains in south-east Asia and West Africa, most countries continued to use penicillin as the first-line treatment, with an antibiotic curative for PPNG as back up, mainly for economic reasons. They hoped to contain the PPNG problem at a low level for as long as possible. However, this policy failed and there has been a steady and rapid increase in the prevalence of PPNG strains in both areas. The current prevalences of PPNG strains are 55–60% in the Western Pacific region and 50% in Nigeria (A. Osoba, unpublished data, 1982).

An alternative policy would be to use an antibiotic active against PPNG strains as soon as these strains occur in a given area, as first-line treatment for cases and contacts. For most developing countries, the cost of treatment is very important, but spectinomycin has been shown to be not more expensive than unit-dose procaine penicillin (*14*). Treatment failures with spectinomycin could be retreated with tetracycline, procaine penicillin–probenecid, thiamphenicol, kanamycin, or cefoxitin.

A concomitant infection of *C. trachomatis* was found in only 5% of males with gonorrhoea, which is considerably less than the 20–30% isolation rate for *Chlamydia* in gonorrhoea patients in western Europe and North America (*15*). However, similar studies in Gambia, Kenya, South Africa, and Swaziland also found fairly low isolation rates (3–13%) for *C. trachomatis* in males with gonorrhoea (*16–19*). These low isolation rates contrast sharply with the high prevalence of anti-chlamydial antibodies in the same populations, including the patients in this trial (results not shown) (*17*, *18*). Further studies are required to elucidate the epidemiology of genital chlamydial infections in Africa.

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RÉSUMÉ

TRAITEMENT DE LA GONOCOCCIE PAR LA SPECTINOMYCINE ET LA PROCAÏNE PÉNICILLINE CHEZ DES PATIENTS CENTRAFRICAINS DE SEXE MASCULIN

A des patients de Bangui de sexe masculin porteurs d'une gonococcie aiguë confirmée par culture, on a administré, selon une distribution aléatoire, l'un des deux traitements suivants: *a*) $4{,}0 \times 10^6$ unités de procaïne pénicilline par voie intramusculaire plus 1 g de probénicide *per os*; *b*) 2 g de spectinomycine v.i. Quatre cent soixante patients au total ont été recrutés pour cette étude et 419 (91%) se sont présentés pour la visite de contrôle.

Le taux d'échec a été de 4,8% avec le schéma basé sur la pénicilline et de 6,2% avec la spectinomycine; la différence n'est pas statistiquement significative. De même, la fréquence de l'uréthrite post-gonococcique s'est montrée assez semblable dans les deux groupes mais le traitement par la pénicilline a provoqué sensiblement plus d'effets secondaires tous mineurs, tels que douleurs à l'injection et vertiges. Cinq pour cent des patients présentaient simultanément une infection à *Chlamydia trachomatis* et presque tous ont contacté une uréthrite postgonococcique.

Parmi les 460 malades de l'étude, 7 (1,5%) étaient porteurs d'une souche de NGPP. Cinq se trouvaient dans le groupe traité par la pénicilline et le traitement a échoué; ils ont toutefois été guéris par la suite à l'aide de la spectinomycine; les deux autres, traités par la spectinomycine, ont été guéris. Les épreuves de sensibilité aux antibiotiques effectuées par dilution en milieu solide ont montré que 11% des souches étaient très sensibles à la pénicilline (CMI < 0,06 µg/ml), 31% avaient une sensibilité légèrement atténuée (0,06 µg/ml < CMI < 0,25 µg/ml) et 58% une sensibilité très atténuée (CMI ⩾ 0,5 µg/ml). Toutes les souches étaient sensibles à 16 ou 32 µg/ml de spectinomycine et 22% des souches présentaient une sensibilité abaissée à la tétracycline (CMI ⩾ 2 µg/ml). Le taux d'échec avec le traitement par la pénicilline s'est avéré considérablement plus grand chez les patients infectés par des souches de sensibilité réduite vis-à-vis de la pénillicine. L'échec de la chimiothérapie par la spectinomycine a été plus fréquent chez les malades porteurs de souches très sensibles à la pénicilline.

On admet souvent que, tant que les NGPP n'atteignent pas un niveau critique (une fréquence de 10% par exemple), le traitement de première intention de la gonococcie peut s'appuyer l'administration de forte doses de pénicilline. Il est proposé, dans le présent article, qu'une fois les souches de NGPP introduites dans un pays, le traitement de première intention des cas de gonococcie et des contacts soit fondé sur l'emploi d'antibiotiques efficaces contre les infections à NGPP, par exemple la spectinomycine. La tétracycline peut être recommandée en seconde intention, car elle permet de traiter simultanément l'infection à *C. trachomatis*, qui est beaucoup moins souvent associée aux gonococcies en Afrique que dans les pays industrialisés.

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