Postgonococcal urethritis: a double-blind study of doxycycline vs placebo

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Abstract

The occurrence of postgonococcal urethritis (PGU) was studied in heterosexual men who were randomly assigned to receive either oral doxycycline 100 mg or a placebo capsule twice daily for seven days in addition to routine single dose treatment of urethral gonorrhoea. Of 216 patients suitable for assessment, PGU was diagnosed in 54/104 (51.9%) in the placebo group and 30/112 (26.8%) in the doxycycline group. Symptomatic PGU was uncommon (6.7% in the placebo group, 2.7% in the doxycycline group). Persistence of chlamydial infection at first follow-up was associated with the development of PGU in the placebo group ($p < 0.05$). Although PGU developed in 10/12 (83%) patients in whom *Mycoplasma hominis* was isolated on entry to the study, the association was not statistically significant. The development of PGU was not associated with the isolation of *Ureaplasma urealyticum*. A significant reduction in the incidence of PGU was achieved by the addition of a course of doxycycline ($p < 0.001$), but there remained a considerable proportion of patients in whom the aetiology of PGU was unknown.

Postgonococcal urethritis (PGU) occurs after single dose treatment of urethral gonorrhoea in heterosexual men in 30% to 70% of patients,¹⁻³ but is less common in homosexual men.^{4,7} PGU may be associated with symptoms such as urethral discharge and/or dysuria, or may be asymptomatic when the diagnosis is based solely on the finding of excess polymorphonuclear leucocytes on a gram-stained urethral smear.

In the majority of studies the condition has been most commonly associated with the isolation of the

genital serotypes of *Chlamydia trachomatis* from the urethra, presumably due to concomitant chlamydial infection.⁶ Ridgway and Oriel have recommended the addition of a course of tetracycline to routine single dose treatment of gonorrhoea.⁷ The aetiology of PGU in chlamydia-negative cases has not been established. One possible contender, *Ureaplasma urealyticum*, was not found to be associated with PGU in two studies.^{2,8}

The aims of this study were to identify organisms which might be associated with the occurrence of PGU, and to observe the effect of doxycycline prescribed as a seven day course at the time of diagnosis and single dose treatment of urethral gonorrhoea in heterosexual men.

Patients and methods

STUDY POPULATION

Consecutive heterosexual men attending the Department of Genitourinary Medicine at West London Hospital for diagnosis and treatment of acute urethritis were invited to participate in the study and given an explanatory leaflet. Patients were selected by a provisional diagnosis of gonococcal urethritis on the basis of characteristic intracellular Gram-negative diplococci in a urethral smear, later confirmed by isolation of *Neisseria gonorrhoeae* in culture. Patients were excluded from the study if they had been taking antibiotics during the previous two weeks, if they were unlikely to reattend for follow-up tests, or if they were allergic to tetracycline.

At the initial visit urethral specimens were taken for microscopic examination and culture for *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma hominis*, *U. urealyticum* and *Gardnerella vaginalis*. Blood was taken for serological tests for syphilis.

PGU was diagnosed at first follow-up (day 14) if ten or more polymorphonuclear leucocytes were seen per high power field ($\times 100$ objective; average number of polymorphs seen in five fields) on microscopic examination of the Gram-stained urethral smear.

ISOLATION OF NEISSERIA GONORRHOEAE

Specimens were taken with a plastic loop for microscopic examination and culture for *N. gonorrhoeae*. Specimens were plated directly on to Modified New

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York City Medium (Oxoid) and cultured for 48 hours in a candle extinction jar. *N gonorrhoeae* were identified by colonial appearance, oxidase reaction, fluorescent antibody test (Difco) and carbohydrate utilisation tests when necessary. Penicillinase-producing *N gonorrhoeae* (PPNG) were detected using a chromogenic cephalosporin test (Nitrocefin, Oxoid Ltd.)

ISOLATION OF *CHLAMYDIA TRACHOMATIS*

A wire-mounted, cotton wool tipped swab was used to take a urethral specimen. The swab was placed in transport medium and stored at -70°C until it was inoculated on to McCoy cells. The preparation was centrifuged at 3000 *g* for one hour at 35°C and the cells were treated with cycloheximide, incubated at 37°C for 48 hours, fixed in methanol and stained with iodine. Microscopic examination for the characteristic inclusions was performed.

ISOLATION OF *MYCOPLASMA HOMINIS* AND *UREAPLASMA UREALYTICUM*

Mycoplasma agar base (Oxoid) and PPLO broth base (Difco) were supplemented by the addition of 10% yeast extract, 20% horse serum and 1000 I.U. penicillin per ml. The broth was further supplemented with either 0.2% arginine and 0.001% phenol red (arginine broth, pH 7.4) or 0.1% urea, 0.001% phenol red and 15 $\mu\text{g/ml}$ lincomycin (ureaplasma broth, pH 6.5). Thallous acetate (0.25%) was added only to the mycoplasma agar. Two urethral specimens were obtained using wire-mounted nasopharyngeal (calcium alginate) swabs. One swab was placed in transport medium and delivered to the laboratory within two hours. The swab was then plated on to mycoplasma agar before being expressed into arginine broth. Both cultures were incubated at 37°C for seven days, the agar in 5% CO_2 and the broth aerobically. The broth was subcultured on to mycoplasma agar if there was a colour change from orange to magenta. Typical "fried egg" colonies on the mycoplasma agar were regarded as positive for *M hominis*.

The second swab was expressed directly into ureaplasma broth and serial ten-fold dilutions made up to 1:1000. These were incubated aerobically at 37°C and examined over 72 hours for colour change from yellow to magenta. The highest dilution showing a colour change was subcultured on to blood agar to exclude contaminants. In the absence of contaminants such cultures were recorded as positive for *U urealyticum*.

ISOLATION OF *GARDNERELLA VAGINALIS*

Specimens were inoculated on to Human Blood Agar bi-layer plates with antibiotic selective supplement (gentamicin sulphate 4 mg/l medium, nalidixic acid 30 mg/l medium, amphotericin B 2 mg/l; Oxoid Ltd.,

Basingstoke, England) and incubated in an 8% CO_2 atmosphere for 48 hours. Colonies that consisted of Gram-variable bacilli, showing beta-haemolysis on human but not horse blood agar, were catalase-negative, susceptible to metronidazole 50 μg disc (Oxoid) and resistant to sulphonamide 1,000 μg disc (Oxoid) were identified as *G vaginalis*.

TREATMENT AND FOLLOW UP

Patients were given single dose treatment with oral ampicillin 3 g plus probenecid 1 g. Alternatively intramuscular spectinomycin 2 g was given if the patient was allergic to penicillin or infection with penicillinase-producing *Neisseria gonorrhoeae* (PPNG) was suspected on the basis of a history of sexual contact in an area with a high prevalence of PPNG infection, in particular the Far East or Central Africa. In addition patients were randomised by a computer generated code to receive either oral doxycycline 100 mg twice daily for seven days or one placebo capsule twice daily for seven days. This protocol was approved by the District Ethical Subcommittee.

Patients were asked to reattend for follow-up on the 14th day after initial presentation. Urethral specimens were taken for microscopy and for repeat cultures of *N gonorrhoeae*, *C trachomatis*, *U urealyticum*, *M hominis* and *G vaginalis*. A second follow-up was requested on day 28 when further urethral specimens were taken for microscopy and culture of *N gonorrhoeae* and serological tests for syphilis were repeated.

STATISTICAL ANALYSIS

Statistical correlates were calculated using the chi-square test with Yates's correction.

Results

Three hundred and thirty five patients were enrolled into the study. One hundred and nineteen of these were excluded from analysis because they failed to attend for initial follow-up tests (87), they failed to take the course of doxycycline or placebo capsules (11), or they were unable to be assessed for PGU because of persistence of gonococcal infection due to reinfection or treatment failure (21). Therefore 216 men were assessable for the presence of PGU at initial follow-up, 104 treated with placebo and 112 with doxycycline.

Of the 335 gonococcal isolates detected during the study period, 18 (5.4%) were PPNG, six in the placebo group and 12 in the doxycycline treatment group. Nine chlamydia results were not available owing to technical problems and in the remaining 326 cases *C trachomatis* was isolated in culture in 46 (14.1%), 20 in the placebo group and 26 in the doxycycline treatment group. There were no sig-

Table 1 Occurrence of PGU

	Placebo	Doxycycline	Total
PGU (> 10 PMNL/hpf) (%)	⁸⁴ / ₁₀₄ (51.9)	³⁰ / ₁₁₂ (26.8)	⁸⁴ / ₂₁₆ (38.9)
	$\chi^2y = 13.30; \quad p < 0.001$		
Symptomatic PGU (%)	⁷ / ₁₀₄ (6.7)	³ / ₁₁₂ (2.7)	¹⁰ / ₂₁₆ (4.6)
	$\chi^2y = 1.42; \quad 0.2 < p < 0.3$		

χ^2y = Chi square with Yates's correction
PMNL = Polymorphonuclear leucocytes

nificant differences in the initial isolation rates of PPNG nor *C trachomatis* in the doxycycline and placebo groups ($p > 0.05$ for both).

Of the 216 patients suitable for assessment at first follow-up, 84 (38.9%) were diagnosed by microscopy as having PGU, 54/104 (51.9%) in the placebo group and 30/112 (26.8%) in the doxycycline group (table 1). This difference was highly significant ($p < 0.001$). However, PGU associated with symptoms such as urethral discharge or dysuria was uncommon, occurring in 7/104 (6.7%) of the placebo group and 3/112 (2.7%) of the doxycycline group.

Of the 216 assessable patients, side effects related to treatment were uncommon, occurring in seven patients in the placebo group and nine in the doxycycline group. In the majority of cases side effects occurred within 24 hours of single dose ampicillin and were of less than 48 hours duration. One patient complained of nausea after spectinomycin. However, four of the nine patients in the doxycycline group stopped taking the capsules because of vomiting (2), nausea (1) or headache (1), while one patient discontinued placebo because of nausea.

ISOLATION OF CHLAMYDIA AND DEVELOPMENT OF PGU (table 2)

After exclusion of five patients in whom chlamydial isolation was not assessable owing to technical reasons, isolation of *C trachomatis* on entry in the

placebo group was associated with the occurrence of PGU in 12.1% (12/99) of cases. Seventy one % (12/17) of patients in whom *C trachomatis* was isolated on entry developed PGU. However, this association did not reach significance.

In the placebo group persistence of chlamydial infection at first follow-up was associated with the development of PGU in 8/90 (8.9%) patients, while one patient with persistence of the organism did not develop PGU. Therefore PGU developed in 8/9 (89%) patients with persistence of chlamydial infection. This association was significant ($p < 0.05$).

As expected, patients given doxycycline were less likely to develop PGU. Of 21 patients in whom *C trachomatis* was isolated on entry, six developed PGU, while persistence of the organism occurred in only one patient. (Data not shown in table).

ISOLATION OF *M HOMINIS*, *U UREALYTICUM* AND *G VAGINALIS* (table 2)

One hundred patients in the placebo group had initial cultures for *M hominis*, *U urealyticum* and *G vaginalis* and attended for follow-up. Ninety of these patients had second cultures for these organisms.

Of 12 patients in whom *M hominis* was isolated on entry, 10 developed PGU, suggesting an association between the isolation of this organism and the occurrence of PGU. However, the association did not reach significance ($0.1 > p > 0.05$). Three of these 12 patients were also positive for *C trachomatis* on entry, and exclusion of these three reduced the association with PGU further ($0.3 > p > 0.2$).

Of five patients in whom *M hominis* was isolated on entry and at day 14, four developed PGU. However, this association was not significant.

U urealyticum was isolated on entry in 38/100 patients in the placebo group and 22 of these 38 patients developed PGU. There was no association between isolation of this organism and development of PGU ($p > 0.6$).

Persistence of *U urealyticum* at day 14 occurred in 23/90 patients in the placebo group and was not

Table 2 Isolation of *C trachomatis*, *M hominis* and *U urealyticum* related to PGU in placebo group

Organism		PGU	No PGU	χ^2y	p value
<i>C trachomatis</i> day 0	+	12	5	1.88	0.2 > p > 0.1
	-	40	42		
<i>C trachomatis</i> days 0 and 14	+	8	1	4.16	0.05 > p > 0.02
	-	38	43		
<i>M hominis</i> day 0	+	10	2	3.48	0.1 > p > 0.05
	-	44	44		
<i>M hominis</i> days 0 and 14	+	4	1	0.59	0.5 > p > 0.4
	-	44	41		
<i>U urealyticum</i> day 0	+	22	16	0.16	0.7 > p > 0.6
	-	32	30		
<i>U urealyticum</i> days 0 and 14	+	13	10	0.01	p > 0.9
	-	35	32		

+ = organism isolated
- = organism not isolated
 χ^2y = Chi square with Yates's correction

associated with the development of PGU ($p > 0.9$).

In the doxycycline group there was no association between the development of PGU and isolation of *M hominis* on entry ($p > 0.5$), persistence of *M hominis* at day 14 ($p > 0.5$), isolation of *U urealyticum* on entry ($p > 0.5$) nor persistence of *U urealyticum* at day 14 ($p > 0.5$). (Data not shown in table).

Of 103 patients treated with doxycycline, 13 had persistence of *U urealyticum* at day 14.

G vaginalis was isolated on entry in only one patient in the study.

Discussion

The incidence of PGU in the placebo group was 52%, which falls within the range of 30 to 70% reported in previous studies.¹⁻³ PGU was associated with symptoms in only 13% (7/54) of cases in this group. Failure to perform a urethral smear at day 14 and chlamydial testing on presentation would have resulted in 47 of 54 (87%) patients with microscopic PGU being untreated due to the absence of symptoms. Forty seven of 104 (45%) patients with gonorrhoea in the placebo group had asymptomatic PGU diagnosed at day 14. Therefore PGU will pass undiagnosed unless it is carefully sought, particularly in departments without adequate chlamydial diagnostic facilities.

A course of doxycycline 100 mg taken twice daily for one week was associated with a highly significant reduction ($p < 0.001$) in the incidence of PGU (51.9% in the placebo group vs 26.8% in the doxycycline group). This supports the findings of Ridgway and Oriel who compared the effect of adding a course of oxytetracycline 500 mg orally four times daily for 7 days to single dose oral treatment for gonorrhoea with a historical group treated with ampicillin and probenecid alone.⁷ In their study PGU was diagnosed in nine (20%) of 45 patients treated with oxytetracycline in addition to ampicillin and probenecid. In our study 30 (27%) of 112 patients treated with doxycycline in addition to single dose treatment for gonorrhoea developed PGU. Therefore although the addition of doxycycline resulted in a significant reduction in the development of PGU, there remained a considerable proportion of patients who still developed PGU. In both studies the addition of a tetracycline resulted in almost complete elimination of *C trachomatis* at follow-up in patients positive on entry, so it would appear likely that PGU in this group is due to a cause other than *C trachomatis*.

The chlamydial isolation rate of 14% on entry to the study was lower than we had expected, but fell within the range of 11 to 34% reported in earlier studies.^{5,9} Similarly the chlamydial isolation rate of 23% (12/52) on entry in patients in the placebo group who went on to develop PGU was lower than in some studies but within the reported range of 15 to 81%.¹⁵

Isolation of *M hominis* on entry to the study was

associated with the development of PGU in 83% (10/12) of patients in the placebo group, but the association was not significant, and was reduced further after exclusion of three patients in whom *C trachomatis* was also isolated. Persistence of *M hominis* at follow-up was associated with PGU in 80% (4/5) of cases, but the small numbers involved were not compatible with the demonstration of a significant difference.

The addition of doxycycline was associated with a lower incidence of PGU (3/13, 23%) in patients with *M hominis* and persistence of the organism occurred in only two cases, neither of whom developed PGU.

These figures suggest an association of *M hominis* with PGU but statistical significance could not be shown. A larger group of patients would have to be studied in order to establish whether the association would reach significance.

Neither the initial isolation of *U urealyticum* nor the persistence of the organism was associated with the development of PGU. This finding is in accordance with earlier studies.² *G vaginalis* was isolated in only one patient in the study.

We did not routinely examine urethral specimens for the presence of *Trichomonas vaginalis* as previous work has shown that this organism is rarely isolated in these patients.⁸

This study confirms that a significant reduction in the incidence of PGU may be achieved by the addition of a course of tetracycline to standard single dose treatment for urethral gonorrhoea. There remains a considerable proportion of patients in whom the aetiology of PGU is unknown.

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