tween doses were similar to those seen on placebo. Thus hydralazine in a slow-release formulation may have a place in the management of patients with hypertension, particularly when non-compliance is a problem. Two patients reported blackouts with this formulation and more investigation is therefore required. It is reassuring, however, that a previous large open study has shown that the tolerability of once-daily slow hydralazine is similar to that of conventional twice-daily treatment.¹⁰

Our data support the view that acetylator phenotype is a major determinant of response to hydralazine¹¹⁻¹³ though this has been disputed.^{14, 15} Generally the fall in blood pressure in slow acetylators was twice that seen in rapid acetylators. The difference in response between the phenotypes was most pronounced 24 hours after treatment with conventional hydralazine as a single morning dose. At this time the response of slow acetylators was similar to that observed on the other active treatments. In contrast, the trough effect during once-daily conventional hydralazine was negligible in rapid acetylators. These findings in part have a pharmacokinetic basis. The bioavailability and half life of hydralazine in the conventional preparation are greater in slow acetylators.^{13, 16} Administration of the slow-release formulation makes little difference to hydralazine elimination in slow acetylators but the apparent half life and bioavailability are both increased in rapid acetylators.¹⁷ The duration of hypotensive effect is nevertheless much greater than that expected from plasma concentration data, presumably because of prolonged binding of hydralazine to arteriolar muscle wall.⁹

In conclusion, once-daily hydralazine in a slow-release form was as effective as conventional hydralazine given twice daily, and it may prove convenient to use provided that it is well tolerated. In slow acetylators the conventional once-daily and twice-daily regimens were equally effective. Once-daily treatment with conventional hydralazine was unsatisfactory in rapid acetylators.

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SHORT REPORTS

Emergence of resistance after spectinomycin treatment for gonorrhoea due to β -lactamase-producing strain of *Neisseria gonorrhoeae*

The aminocyclitol antibiotic, spectinomycin, is commonly used for the treatment of gonorrhoea caused by β -lactamase-producing strains of *Neisseria gonorrhoeae*. Although spectinomycin-resistant penicillin-sensitive gonococcal isolates have been found,¹ only one report of gonorrhoea caused by a spectinomycin-resistant β -lactamase-positive strain has been published. In that instance, the only isolate available for study was obtained after spectinomycin treatment had failed, presumably because treatment had produced chromosomal mutation leading to ribosomal changes and high-level resistance.²

We report here the isolation of β -lactamase-producing strains of *N gonorrhoeae* from the same patient on five occasions during November 1981. Although the first two isolates were sensitive to spectinomycin, the remainder were resistant after treatment with spectinomycin.

Patient, methods, and results

A 27-year-old North African postgraduate student presented at the Praed Street Clinic, St Mary's Hospital, with a five-day history of urethral irritation and a two-day history of blood-stained urethral discharge on 2 November 1981.

He admitted to a casual sexual exposure in October in Canterbury, Kent. On examination he had unilateral tender inguinal lymphadenopathy and an obvious meatitis, from which oozed a persistent purulent discharge. Gonorrhoea was diagnosed on microscopy and culture of the urethral discharge. He was initially treated with 3.5 g ampicillin and 1.0 g probenecid orally. The strain of *N gonorrhoeae*, however, produced β -lactamase.

On his next visit to the clinic four days later he still had a urethral discharge, from which a strain of spectinomycin-sensitive β -lactamase-producing *N gonorrhoeae* was grown. He was given spectinomycin 2 g intramuscularly. Five days later, although his discharge had stopped, Gram-negative diplococci were seen on microscopy and he was given a further 4 g spectinomycin. The strain of *N gonorrhoeae* isolated on this visit was, however, resistant to spectinomycin. Six days later he was free of symptoms. Since the previous isolate had been resistant to spectinomycin but was sensitive to tetracycline on disc testing, he was given a seven-day course of tetracycline 500 mg four times daily. A week later he was still free of symptoms but spectinomycin-resistant β -lactamase-producing strains of *N gonorrhoeae* were again isolated from his urethral exudate. He denied any further sexual contact since his first visit to the clinic. Because of the failure of treatment and the unusual resistance of the infecting strain, he was admitted to hospital on 1 December for further treatment and observation. His urethral discharge had recurred accompanied by dysuria. These symptoms resolved slowly when treated with cefuroxime (1.5 g with probenecid at once and 750 mg three times daily for three days). A week later he was finally discharged and has remained asymptomatic; follow-up cultures for *N gonorrhoeae* have shown no growth.

All specimens of urethral exudate were cultured directly on to a selective medium consisting of GC agar base supplemented with 1% IsoVitalex (Difco), vancomycin, colistin, trimethoprim, and nystatin³ and identified by Gram staining, oxidase reaction, and their ability to utilise glucose but not maltose, sucrose, or lactose. Their auxotype was determined by the method of Catlin *et al*⁴ and β -lactamase activity by the nitrocefin chromogenic cephalosporin test.⁴ The minimum inhibitory concentrations of six

TABLE—Changing susceptibility of sequential *N gonorrhoeae* isolates to six antibiotics using high (10^8 cfu) and low (10^3 cfu) inocula. (Figures with the lower inoculum are given in parentheses)

Date of isolation	Minimum inhibitory concentrations (mg/l)					
	Penicillin	Ampicillin	Spectinomycin	Streptomycin	Tetracycline	Cefuroxime
2.11.81	8 (4)	> 64 (32)	32 (16)	> 512 (> 512)	16 (8)	0.12 (0.06)
6.11.81	> 64 (16)	> 64 (32)	32 (16)	> 512 (> 512)	16 (8)	0.12 (0.06)
1.11.81*	> 64 (16)	> 64 (32)	> 512 (512)	512 (512)	16 (8)	0.12 (0.06)
7.11.81*	> 64 (16)	> 64 (32)	> 512 (> 512)	512 (512)	16 (8)	0.12 (0.06)
14.11.81*	> 64 (16)	> 64 (32)	> 512 (> 512)	512 (512)	16 (8)	0.12 (0.06)

*After spectinomycin treatment.

antibiotics for all five isolates were determined using sensitivity agar (DST, Oxoid) supplemented with 1% IsoVitalax and 5% lysed blood inoculated with 10^8 and 10^3 colony forming units (cfu). After 24 hours' incubation at 36°C in 7% CO₂ the minimum inhibitory concentration was determined as the point of complete inhibition. All isolates were screened for plasmids using a rapid screening method.⁵ The samples were electrophoresed in 0.6% agarose and stained with ethidium bromide.

Neisseria gonorrhoeae isolates from the urethral exudate were oxidase-positive, Gram-negative cocci, utilising glucose alone, and requiring proline for growth. The minimum inhibitory concentrations of benzyl penicillin, ampicillin tetracycline, spectinomycin, streptomycin, and cefuroxime for these strains, using high (10^8 cfu) and low (10^3 cfu) inocula, are shown in the table. Although penicillin-resistant, the first isolate (obtained before treatment with ampicillin) had a minimum inhibitory concentration of benzyl penicillin lower than the other four. The chromogenic cephalosporin test, performed after one subculture, showed that β -lactamase was produced by only 7% of the colonies from the first isolate but by all the colonies from the other four. The first two isolates showed zones of inhibition to a 30 μ g disc of spectinomycin while the remaining isolates did not. This difference in disc sensitivity to spectinomycin was reflected in the minimum inhibitory concentrations (see table). Although disc testing suggested sensitivity to tetracycline, all isolates had relatively high minimum inhibitory concentrations. On plasmid analysis three plasmids with molecular weights of 2.6, 4.4, and 24.5 megadaltons were found.

Comment

Only one other report of a spectinomycin-resistant β -lactamase-producing strain of *N gonorrhoeae* has been published.² In that report and in our own both spectinomycin-resistant strains were isolated after spectinomycin treatment, both contained plasmids of 2.6, 4.4, and 24.5 megadaltons, and both required proline for growth. Although we have no further information about the source of the strain the initial infection was probably caused by a mixed population of *N gonorrhoeae*, only some of which produced β -lactamase. Treatment with ampicillin and probenecid selected the β -lactamase producers, which resulted in the increase in the minimum inhibitory concentration of benzyl penicillin for the subsequent isolates.

The emergence of spectinomycin resistance could be the result of either selection or induction, although the increasing minimum inhibitory concentration suggested induced resistance. We investigated neither the mechanism of spectinomycin resistance in our isolates nor its genetic control, but the similarity of the plasmids to those of the recently reported strain² indicated a chromosomal change.

Tetracycline treatment was unsuccessful in our patient, as in the previous instance.³ The discrepancy between sensitivity results by disc testing (by the Stokes method) and minimum inhibitory concentrations highlighted the difficulty in interpreting this disc method with *N gonorrhoeae*. The most suitable antibiotics for these strains are probably the second and third generation β -lactamase-resistant cephalosporins. They are, however, relatively expensive and have been rarely used in gonorrhoea, particularly in single-dose regimens.

The emergence of spectinomycin resistance in *N gonorrhoeae* after treatment may not in fact be a rare event but rather a reflection of laboratory procedures. Since continuity of care in sexually transmitted diseases can be limited both clinicians and laboratory workers may easily fail to recognise resistant strains. The number of β -lactamase-producing isolates detected in the Praed Street Clinic has increased and will lead to a greater use of spectinomycin. Surveillance programmes are needed to determine the prevalence of spectinomycin resistance among strains of *N gonorrhoeae* by presumptive disc sensitivity techniques.

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Diclofenac hepatitis

Diclofenac (Voltarol, Geigy Pharmaceuticals), a derivative of phenylacetic acid, is a non-steroidal anti-inflammatory agent. It is at least as effective as indomethacin in relieving symptoms of inflammatory arthritis in clinical trials and is generally well tolerated.¹ Some patients, however, have developed abnormalities of serum liver function tests during treatment with diclofenac,² but there have been no documented cases of acute hepatitis caused by this drug. The Committee on Safety of Medicines and the manufacturer have received a few reports of hepatocellular damage in patients taking diclofenac, but none where other causes could be excluded.

Case report

A 52-year-old man began taking diclofenac for painful pseudogout in the right knee in November 1980. His pain was relieved, but in March 1981 he developed nausea and vomiting, followed within a few days by dark urine, pale stools, and jaundice. He was admitted to his local hospital and found to have an enlarged liver, palpable 4 cm below the right costal margin; serum liver function tests gave results consistent with acute hepatitis. Serum bilirubin concentration was 126 μ mol/l (7.4 mg/100 ml) (normal 5-17 μ mol/l (0.3-1.0 mg/100 ml)) and aspartate aminotransferase activity 1375 IU/l (normal 15-40). There was no history of blood transfusion, tattoos, injection, or recent foreign travel, and he was not homosexual. He did not abuse alcohol and took no regular medication besides diclofenac. Tests for hepatitis B surface antigen and hepatitis A IgM antibody yielded negative results. Diclofenac was withdrawn, and the jaundice resolved completely over seven days, although he remained weak and lethargic.

It was assumed that he had recovered from an acute viral hepatitis when he began treatment with diclofenac again in late April. Five weeks later he started to vomit and again became jaundiced. On admission to this hospital his liver was enlarged 2 cm below the right costal margin but there were no signs of chronic liver disease. Serum bilirubin concentration was 201 μ mol/l (11.8 mg/100 ml) and aspartate aminotransferase activity 1150 IU/l. Hepatitis B surface antigen and hepatitis A IgM antibody were again undetectable by radioimmunoassay, and serological tests for recent infection with Epstein-Barr virus and cytomegalovirus again yielded negative results. Liver biopsy specimens showed a moderately severe acute hepatitis with canalicular cholestasis and Kupffer-cell proliferation, and plasma cells and eosinophils in the inflammatory infiltrate.

Diclofenac was stopped, and his symptoms again resolved over a few days. Results of serum liver function tests returned to normal within six weeks and were still normal three months later.