Therapeutic Trial and Pharmacokinetics of Sulbactam for Uncomplicated Gonorrhea in Men

VIRGINIA A. CAINE,1,2 GEORGE FOULDS,3 AND H. HUNTER HANDSFIELD1,2*

Seattle-King County Department of Public Health, Seattle, Washington 98104;* Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195; and Pfizer Central Research, Inc., Groton, Connecticut 06340

Received 14 May 1984/ Accepted 13 August 1984

The efficacy of intramuscular sulbactam for uncomplicated gonorrhea was assessed in 20 men infected with β-lactamase-negative Neisseria gonorrhoeae. Ten subjects received 2.0 g of sulbactam given in a single intramuscular dose with 1.0 g of probenecid orally; 4 of 10 urethral infections persisted, as did one rectal infection. Ten subjects were treated with 0.5 g of intramuscular sulbactam given twice, 4 h apart; 3 of 10 urethral infections and 2 of 2 rectal infections persisted. The geometric mean MIC of sulbactam for 20 pretreatment isolates of N. gonorrhoeae was 1.37 μg/ml (range, 0.25 to 8.0 μg/ml). Serum levels of sulbactam, determined for nine subjects in the two treatment groups, fell below the MIC of some gonococci after <6 h with both regimens. In the regimens studied, sulbactam alone is not suitable as therapy for uncomplicated gonorrhea.

The emergence of penicillinase-producing strains of Neisseria gonorrhoeae (2, 6) has stimulated investigation of alternative treatments for gonorrhea. Sulbactam (CP-45899) is a β-lactamase inhibitor that enhances the activity of the β-lactamase-sensitive penicillins against penicillin-producing N. gonorrhoeae or other β-lactamase-producing organisms. In addition, sulbactam itself has significant in vitro activity against β-lactamase-positive and -negative N. gonorrhoeae, with reported MICs of 0.15 to 2.5 μg/ml (4, 8). This study was designed to assess the efficacy of sulbactam alone as single-session therapy for men with acute uncomplicated gonorrhea due to β-lactamase-negative N. gonorrhoeae and to correlate the results with serum levels of the drug.

MATERIALS AND METHODS

The study population consisted of men ≥17 years of age with acute uncomplicated gonococcal urethritis. Infection was initially documented by Gram-stained smears of urethral exudate and subsequently confirmed by isolation of N. gonorrhoeae. Anorectal and pharyngeal cultures also were performed on all subjects.

Two regimens were studied. Regimen A (12 subjects) was 2.0 g of sulbactam given in two simultaneous intramuscular (i.m.) injections (1.0 g each) plus probenecid (1.0 g orally). Regimen B (11 subjects) was two 0.5-g i.m. doses of sulbactam given 4 h apart, without probenecid. In five subjects treated with regimen A and four subjects given regimen B, blood specimens for determination of sulbactam serum levels were obtained at standardized intervals for 10 h. Smears and cultures of the urethra and cultures of the anal canal and pharynx were repeated 2 and 7 days after treatment. Subjects with persistent gonococcal infection were retreated with aqueous procaine penicillin G (4.8 MU i.m.) plus probenecid (1.0 g orally) or with spectinomycin (2.0 g i.m.).

Specimens for isolation of N. gonorrhoeae were inoculated directly onto modified Thayer-Martin medium and incubated at 35°C in an atmosphere of 5% CO2. N. gonorrhoeae was identified by routine methods, and isolates were stored at −70°C in horse serum and tryptic soy-yeast broth (1:1, vol/vol) for later antimicrobial susceptibility testing. β-Lactamase production was tested by the disc method (9). Agar dilution MICs of sulbactam, penicillin G, and tetracycline hydrochloride were determined by using twofold dilutions of antibiotic in GC agar base (Difco Laboratories, Detroit, Mich.) containing 1% hemoglobin and 1% IsoVitaleX (BBB Microbiology Systems, Cockeysville, Md.) as described previously (10). Serum specimens for the pharmacokinetic studies were stored at −20°C. Serum levels of sulbactam were determined by gas chromatography of the methyl ester with detection by mass spectrometry, as described elsewhere (5). The limit of detection of sulbactam with this method is approximately 0.3 μg/ml.

Written informed consent was obtained from all subjects. Statistical methods included Student’s t test and the two-tailed Fisher exact test.

RESULTS

Ten of 12 patients treated with regimen A and 10 of 11 treated with regimen B returned for follow-up examinations. These 20 men had a mean age of 30.3 years (range, 17 to 47 years). There were no significant differences in these characteristics between subjects treated with regimen A or regimen B. N. gonorrhoeae was eradicated from all infected sites in 5 of 10 patients treated with regimen A and 6 of 10 treated with regimen B (Table 1). All nine treatment failures were detected by culture at the first follow-up visit. All subjects denied interim sexual exposure.

The serial serum concentrations of sulbactam in five subjects treated with regimen A and four subjects given regimen B are shown in Table 2. The serum concentrations observed in patients who were cured were not significantly higher than in those whose treatment failed. The serum half-life (t1/2) of sulbactam (mean ± 1 standard deviation) was 1.57 ± 0.47 h after regimen A and 1.12 ± 0.53 h after the second 0.5-g dose of regimen B.

Table 3 shows the MICs of sulbactam and penicillin G for 20 pretreatment urethral isolates of N. gonorrhoeae. The geometric mean MIC of sulbactam was 1.37 μg/ml, and that for penicillin 0.17 μg/ml. The geometric mean MIC of
subbacamp for the pretreatment isolates from patients who were cured was 1.12 \( \mu \text{g/ml} \), compared with 1.83 \( \mu \text{g/ml} \) for the isolates from patients whose treatment failed, not a significant difference \((P > 0.2)\). \( N. \text{gonorrhoeae} \) was eradi-
cated from all infected sites in 7 of 10 patients infected with
strains with subbactam MICs of \( \leq 1.0 \mu \text{g/ml} \), compared with
4 of 10 infected with strains with MICs of \( \geq 2 \mu \text{g/ml} \) \((P =
0.4)\). After the injection of sulbactam, 11 (48%) of the 23
subjects complained of mild to moderate pain that lasted 5 to
30 min. No other adverse effects occurred.

**DISCUSSION**

The pharmacokinetics of sulbactam in this study were
similar to those reported elsewhere \((3,5)\). Foulds et al. \((5)\)
documented a \( t_{1/2} \) of 0.97 h, and Emmerson et al. \((3)\) reported
extension of the \( t_{1/2} \) to 1.3 h after administration with
probenecid, compared with 1.12 and 1.57 h, respectively, in
our small sample. We found the in vitro activity of sulbactam
against \( \beta \)-lactamase-negative \( N. \text{gonorrhoeae} \) to be some-
what less than that reported by other investigators \((4,8)\),
with 8 (40%) of 20 isolates requiring \( \geq 4.0 \mu \text{g/ml} \) for inhibi-
tion.

In the regimens studied, sulbactam eradicated only 13
(65%) of 20 urethral and none of 3 anorectal gonococcal
infections due to \( \beta \)-lactamase-negative \( N. \text{gonorrhoeae} \), an
unacceptably low cure rate. With two 0.5-g doses 4 h apart,
the mean peak serum sulbactam level barely exceeded the
MIC for some infecting strains of \( N. \text{gonorrhoeae} \) (8.0
\( \mu \text{g/ml} \)), and two of four subjects had peak serum concentra-
tions below this level. With a single 2.0-g dose combined
with probenecid, higher peak serum levels were achieved,
but the mean serum level fell to <8.0 \( \mu \text{g/ml} \) within 4 h. Jaffe
et al. \((7)\) showed that the efficacy of single-dose penicillin
therapy for gonorrhoea is correlated with maintenance of a
serum penicillin level at least fourfold greater than the MIC
of the infecting strain of \( N. \text{gonorrhoeae} \) for \( \geq 7 \text{h} \), a standard
not achieved with the sulbactam regimens used in this study.
However, too few patients were studied to demonstrate a
definite relationship between the MIC of sulbactam for the
infecting gonococcus and the response to treatment.

The combination of sulbactam or a related \( \beta \)-lactamase
inhibitor, with penicillin, ampicillin, or amoxicillin may have
value for the treatment of penicillinase-producing \( N. \text{gonor-
rhoeae} \) infections. Using a single-dose regimen of 2.0 g of
sultamicillin (a congener of sulbactam and ampicillin) with
1.0 g of probenecid, Atta et al. \((1)\) cured 91 (97%) of 94 men
with gonococcal urethritis, including 6 of 6 infected with
penicillinase-producing strains of \( N. \text{gonorrhoeae} \). In the
regimens that we studied, however, sulbactam alone is not
suitable for the treatment of gonorrhea.

**ACKNOWLEDGMENTS**

This study was supported by a grant from Pfizer Central Research,
Inc., and by Public Health Service program project grant AI-12192
from the National Institutes of Health.
We are grateful to Ferne Beier for preparing the manuscript.

**LITERATURE CITED**

1. Atta, W. A., A. M. Emmerson, and D. Holmes. 1983. Sultami-
cillin in the treatment of gonorrhea caused by penicillin sensitive
and penicillinase producing strains of \( Neisseria \text{gonorrhoeae} \).
2. Centers for Disease Control. 1982. Global distribution of penicil-
linase-producing \( Neisseria \text{gonorrhoeae} \) (PPNG). Morbid. Mortal.
netics of sulbactam and ampicillin following oral administration
4. English, A. R., J. A. Reisena, A. E. Girard, J. E. Lynch, and
W. E. Barth. 1978. CP-45699, a \( \beta \)-lactamase inhibitor that
extends the antibacterial spectrum of \( \beta \)-lactams: initial bacteri-
5. Foulds, G., J. P. Stankewich, D. C. Marshall, M. M. O'Brien,
S. L. Hayes, D. J. Weidler, and F. G. McMahon. 1983. Pharma-


