Cocaine Hydrochloride and Benzoylecgonine Have No In Vitro Inhibitory Effect against Neisseria gonorrhoeae

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We evaluated 72 clinical Neisseria gonorrhoeae isolates for in vitro susceptibility to cocaine hydrochloride and its metabolite benzoylecgonine and to penicillin, tetracycline, erythromycin, ceftriaxone, and ofloxacin. Although there was a wide range of susceptibilities to the antimicrobial agents, cocaine and its major metabolite, benzoylecgonine, had no demonstrable ant gonococcal activity. Cocaine use is frequently associated with outbreaks of sexually transmitted disease. We hypothesized that the dramatically decreasing incidence of gonorrhea over the past 15 years may be in part due to pharmacological effects of cocaine. However, since cocaine and its metabolite have no in vitro ant gonococcal activity, this hypothesis is unlikely.

In the past decade, cocaine abuse has become epidemic in the United States, possibly as a consequence of the availability of inexpensive cocaine formulations (such as "crack"). Self-reported cocaine use has been associated with a variety of public health problems. Recent studies in New York found toxicological evidence of recent cocaine use in 18% of persons who died in motor vehicle accidents (10) and in 76% of males arrested for criminal offenses (3). In addition, cocaine use has been associated with risk of human immunodeficiency virus infection in intravenous drug abusers (1) and with the increased frequency of self-reported sexually transmitted diseases (STDs) (6). Among men attending the Baltimore City Health Department STD clinics for evaluation of new problems, 8% have evidence of recent cocaine use by urine assay (unpublished data).

Recently, changes in the epidemiology of syphilis and gonorrhea have also been attributed in part to cocaine use. Between 1985 and 1988, the incidence of primary and secondary syphilis increased 66%, reaching the highest level in 40 years (4). Although there are probably many reasons for these increases, behaviors associated with cocaine use, especially use of crack cocaine, such as "sex for drugs," have been implicated as important risk factors for syphilis acquisition in adults in Connecticut and Philadelphia (1) and among the mothers of babies with congenital syphilis in New York City (2).

While the incidence of reported gonococcal infections has decreased over the past 10 years, gonorrhea (4) and particularly outbreaks of antibiotic-resistant gonorrhea have also been increasingly associated with cocaine use. Nonetheless, considering the explosive increase in the incidence of syphilis, the declining number of patients with gonorrhea has not been fully explained. The decreased incidence of gonorrhea appears to be real, as it cannot be explained by changes in reporting procedures. Although behaviors leading to increases in occurrence of one STD might be expected to lead to increased risk of another STD, host susceptibility might also be altered by the presence of drugs such as cocaine. For example, lidocaine and other local anesthetics have been demonstrated to have in vitro bactericidal effects against both gram-positive and gram-negative organisms (9, 15). Thus, we hypothesized that cocaine hydrochloride or its metabolite(s) might have an inhibitory effect on Neisseria gonorrhoeae at concentrations in serum commonly attained by frequent users. Since cocaine use is highly prevalent in the population at risk for STDs, this would potentially help explain the observed decreases in gonorrhea incidence.

We evaluated 72 gonococcal isolates for in vitro susceptibility to cocaine hydrochloride, benzoylecgonine (the major metabolite of cocaine found in plasma and urine [7]), penicillin, tetracycline, erythromycin, ofloxacin, ceftriaxone, and spectinomycin. All isolates were tested by using the agar dilution method and twofold dilutions of antibiotics, cocaine HCl, and benzoylecgonine (8) with GC-II Agar Base supplemented with IsoVitaleX (Becton-Dickinson, Cockeysville, Md.). Cocaine hydrochloride and benzoylecgonine were evaluated over a dilution range of 0.001 to 4.0 \( \mu \text{g/mL} \) (10 times the peak concentration observed in human plasma). In humans, peak concentrations of cocaine in plasma vary with the route of administration. Smoking 100 mg of cocaine paste results in peak concentrations in plasma of 0.478 \( \mu \text{g/mL} \) in less than 5 min (12); when administered intranasally, the same dose yielded a peak concentration of 0.161 \( \mu \text{g/mL} \) in 45 to 90 min (14). Levels of cocaine metabolites in plasma or urine have not been well characterized.

The organisms for this study were selected from isolates which were systematically collected as part of a national gonococcal isolate surveillance program (13) and from studies conducted in the Baltimore STD clinics. Twelve isolates had plasmid-mediated antibiotic resistance (2 were penicillinase-producing \( N. \ gonorrhoeae \) isolates, 9 isolates had plasmid-mediated tetracycline resistance, and 1 was a penicillinase-producing tetracycline-resistant isolate), and none of the other isolates had MICs of penicillin of \( >1.0 \mu \text{g/mL} \) (clinically significant chromosomally mediated penicillin resistance).

Although a wide range of susceptibility to antibiotics was demonstrated in these organisms (Table 1), neither cocaine hydrochloride nor benzoylecgonine had any demonstrable ant gonococcal activity. The stability of cocaine and its metabolites in agar medium has not been determined. However, the melting points of cocaine (195°C) and benzoylcegonine (154°C) are above the temperature at which the agar medium solidifies, suggesting that these compounds may be effective against gonococci in vivo.

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TABLE 1. Susceptibility characteristics of 73 N. gonorrhoeae isolates

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/ml)</th>
<th>Range</th>
<th>Geometric mean</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.015-32.0</td>
<td>0.24</td>
<td>0.25</td>
<td>1.00</td>
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</tr>
<tr>
<td>Tetracycline</td>
<td>0.060-32.0</td>
<td>0.79</td>
<td>1.00</td>
<td>16.00</td>
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<tr>
<td>Erythromycin</td>
<td>0.015-2.0</td>
<td>0.30</td>
<td>0.25</td>
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<tr>
<td>Ceftriaxone</td>
<td>0.001-0.03</td>
<td>0.005</td>
<td>0.008</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.004-0.03</td>
<td>0.009</td>
<td>0.008</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Cocaine HCl</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>Benzoylcegonine</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
<td>&gt;4.0</td>
</tr>
</tbody>
</table>

* Isolates tested include 2 penicillin-producing N. gonorrhoeae isolates, 1 penicillin-producing tetracycline-resistant isolate, and 9 tetracycline-resistant isolates.

** 50% and 90%, MICs for 50 and 90% of the isolates tested, respectively.

nine (86 to 92°C) (11) are substantially higher than the 50°C used in our agar preparation procedure.

The possibility that there is a pharmacological basis for the association of cocaine use with the decrease in incidence of gonorrhea is unlikely. Whether the decreased incidence of gonococcal infections is due to changes in sexual behavior among populations at risk needs to be further evaluated.

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REFERENCES


