cardiac arrhythmia have been detected. These factors may, of course, contribute to the high cardiovascular vascular mortality. Population survey by postal questionnaire and checking of hospital and death records had demonstrated an association of snoring with angina pectoris and ischemic heart disease. Some of these snorers might actually have OSAS, and it has been suggested that OSAS is a possible risk factor for ischemic heart disease, but individual case studies or postmortem findings have rarely been described.

Our patient was initially diagnosed as having ischemic heart disease with a near-miss death event characterized by shock and pulmonary edema. However, subsequent investigations in daytime hours showed no evidence of cardiac dysfunction or myocardial ischemia, resembling the case reported earlier. We hypothesize therefore, that at least some fatalities in OSAS, labelled as cardiovascular deaths, may in fact, relate to extreme hypoxemia produced by OSAS rather than to underlying myocardial or coronary artery disease. We suggest that in patients with chest pain suggestive of angina, especially if the attacks are predominantly nocturnal, the diagnosis of OSAS should be considered, and in doubtful cases, formal sleep studies should be performed. More intensive investigations, including stress exercise testing, isotope scanning, coronary angiography, and, of course, detailed postmortem studies, are required to delineate the true incidence of coronary artery disease in patients with OSAS.

ACKNOWLEDGMENTS: We would like to thank Professor MG Nicholls for his review of our manuscript and his helpful suggestions.

REFERENCES
4 Smitz S. Endogenous opiates, pulmonary edema and sleep apnea syndrome. Chest 1983; 83:583-84

**From the Departments of Medicine, State University of New York Health Science Center at Brooklyn, Brooklyn Hospital, Brooklyn; The University of South Florida School of Medicine, Tampa, and the Department of Veterans Affairs, Bay Pines, FL

Amoxicillin-Clavulanic Acid for Treating Drug-Resistant Mycobacterium tuberculosis

Jeffrey P Nudler, M.D.; Judith Berger, M.D.; Jill A. Nord, M.D.; Richard Cofsky, M.D.; and Mridula Saxena, M.D.

This report describes two patients with multidrug resistant tuberculosis who were successfully treated with the addition of amoxicillin-clavulanic acid to second-line drugs. *Mycobacterium tuberculosis* possesses a beta-lactamase contributing to its resistance to beta-lactam antibiotics. The combination of clavulanic acid, a beta-lactamase inhibitor, and amoxicillin has been shown bactericidal for *M. tuberculosis in vitro*. These data suggest that resistant tuberculosis may warrant a trial of treatment including amoxicillin-clavulanic acid.

(Chest 1991; 99:1025-26)

Treatment of patients with resistant tuberculosis fails often, despite the prolonged use of multiple drugs. Therapy is complicated by the problems of increased toxicity, noncompliance, and a higher failure rate. New effective antituberculosis agents are needed for treatment of resistant tuberculosis.

The efficacy of amoxicillin-clavulanic acid for *M. tuberculosis* infections is suggested by several lines of evidence. *M. tuberculosis* possesses a beta-lactamase which may be responsible for its resistance to beta-lactam antibiotics. The combination of clavulanic acid, a beta-lactamase inhibitor, with amoxicillin, is bactericidal for *M. tuberculosis in vitro*. We report two patients with *M. tuberculosis* with multiple drug resistance who were treated successfully with the addition of amoxicillin-clavulanic acid.

CASE REPORT

**Case 1**

A 26-year-old woman was diagnosed as having symptomatic tuberculosis, with bilateral upper lobe chest x-ray infiltrates, and positive sputum smears and culture for *M. tuberculosis*. The patient's brother died of disseminated *M. tuberculosis* and was known to be noncompliant with therapy. Standard treatment with isoniazid, ethambutol, pyrazinamide, and streptomycin. Rifampin was discontinued because of side effects. Persistent fever, positive smears and cultures for *M. tuberculosis* were noted over the following year. Her physician was unaware that her initial mycobacterial isolate was resistant to all her current medications.

Symptoms continued to worsen and a bronchopleural fistula formed, necessitating chest tube placement. Smears and cultures continued positive. Bacterial cultures of blood and sputum were sterile. Culture results of the original isolates became available, indicating resistance to isoniazid, ethambutol, rifampin, and pyrazinamide. It was found to be sensitive to ethionamide and capreomycin, to streptomycin 10.0 but not 2.0 μg/ml, and to cycloserine, 60.0 but not 30.0 μg/ml. Oral ethionamide and cycloserine were added. After two weeks on this regimen, amoxicillin-clavulanic acid

*From the Departments of Medicine, State University of New York Health Science Center at Brooklyn, Brooklyn Hospital, Brooklyn; The University of South Florida School of Medicine, Tampa, and the Department of Veterans Affairs, Bay Pines, FL
at a dosage of two 500 mg tablets every 6 h was begun with discontinuation of ethambutol and pyrazinamide. Three days after the addition of amoxicillin-clavulanic acid, her temperature abated. Her cough resolved and she began to gain weight. Eleven days after beginning therapy with amoxicillin-clavulanic acid, capreomycin was substituted for streptomycin. Eight days later, the air leak closed. Drug-induced hepatitis prompted discontinuation of isoniazid and ethambonamide, but the patient was successfully maintained on amoxicillin-clavulanic acid, capreomycin, and cycloserine for 18 months. Her x-ray film showed improvement; the cavity resolved. Acid-fast smears and cultures became negative at two and three weeks, respectively, after the addition of amoxicillin-clavulanic acid and remained negative.

Case 2

A 34-year old man was admitted with tuberculosis of six months’ duration with bilateral lung involvement and left supraclavicular lymphadenopathy, with cavitating granulomas on biopsy. Treatment with isoniazid, rifampin, and oral ethambutol was begun. Cultures grew M tuberculosis.

Systemic symptoms and positive sputum cultures persisted for two months. Rifampin was discontinued and pyrazinamide and streptomycin were added. Sensitivity testing from a reference laboratory became available revealing resistance to isoniazid, rifampin, and pyrazinamide, sensitivity to streptomycin, ethambonamide, and cycloserine. The patient was treated with isoniazid, streptomycin, ethambonamide, and cycloserine for two months with persistent symptoms, unchanged chest roentgenogram, and continued positive sputum culture. Amoxicillin-clavulanic acid was added at a dose of 500 mg every six hours. Within one month, his sputum culture became negative, symptoms resolved and his chest x-ray film improved. At 11-month follow-up, he had gained 2 kilograms and remained clinically well.

Methods

Clinical isolates from our patients were tested in vitro for susceptibility to amoxicillin-clavulanic acid by broth dilution methods. The method is previously described. A strain known to be sensitive to amoxicillin-clavulanic acid was run concurrently. The concentration of amoxicillin-clavulanic acid (in µg/ml) was as follows:

32:16, 16:8, 8:4, 4:2, 2:1, 1:0.5.

Results showed that the known sensitive strain grew in the negative control and only in the 1:0.5 dilution. Both our isolates showed growth in the negative control, but not in any of the amoxicillin-clavulanic acid-containing tubes.

Discussion

Our patients, infected with multiresistant M tuberculosis, showed apparent sustained clinical and bacteriologic response when amoxicillin-clavulanic acid was added to their drug regimen. The combination of a penicillin with an irreversible inhibitor of beta-lactamase expands the clinical spectrum to include organisms whose resistance to penicillin is mediated by beta-lactamase. Inherent difficulties in evaluating a response to a single drug in a multidrug regimen limit the conclusions we can draw from our data. Nevertheless, the failure of conventional therapy and the marked clinical response after the addition of amoxicillin-clavulanic acid suggests that this combination played an important role in the response of these patients. Our data taken together with in vitro studies indicate that amoxicillin-clavulanic acid may have a role in the treatment of M tuberculosis infection.

Cynamon and Palmer studied the in vitro susceptibility of M tuberculosis to amoxicillin-clavulanic acid in 1983. All 15 clinical isolates tested had beta-lactamase activity. Clavulanic acid alone did not inhibit any of the strains. Amoxicillin alone inhibited four isolates at 8 µg/ml or less, but was not bactericidal for any of the isolates at that concentration. Importantly, in contrast to either drug alone, amoxicillin-clavulanic acid was bactericidal for 14 of these isolates at levels which are achievable in serum.

The theoric basis for use of amoxicillin-clavulanic acid comes from studies done as early as 1941, when Abraham et al observed that M tuberculosis was not inhibited in vitro by high concentrations of penicillin. In 1949, Iland and Bains and in 1952, Solty's identified penicillinase activity in M tuberculosis. In 1965, Kasik showed that the penicillinase was a beta-lactamase, which plays a role in the resistance of M tuberculosis to penicillins in studies on the effect of beta-lactamase susceptible and resistant antibiotics on the nephelometrically assayed growth of the R1rv strain of M tuberculosis. He showed that a combination of beta-lactamase stable oxacillin with penicillin was more effective than either drug alone in inhibiting mycobacterial growth. This penicillin-sparing effect was shown to be due to beta-lactamase inhibition. This increase in M tuberculosis susceptibility to a penicillin-beta-lactamase inhibitor combination was also demonstrated in a murine model of tuberculosis.

Further studies will be required to assess the efficacy of amoxicillin-clavulanic acid for M tuberculosis. Our data suggest that patients with resistant tuberculosis unresponsive to conventional therapy may benefit from the addition of amoxicillin-clavulanic acid to their regimen.

Acknowledgements: We are indebted to Richard Wallace, M.D., for encouragement to proceed with the clinical trials, to Michael Cynamon, M.D., for testing of isolates, and to Cathleen Cuches and Joan Morris for manuscript preparation.

References

3 Abraham EE, Chain E, Fletcher CM, Gardner AD, Keatley NG, Jennings MA, et al. Further observations on penicillin. Lancet 1941; 2:177-88
5 Solty's MA. The effect of penicillin on mycobacteria in vitro and in vivo. Tubercle 1952; 33:190-25