Clinical Suppression of Refractory Ventricular Tachycardia with Oral Bretylium Not Predicted by Electrophysiologic Drug Testing*

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We report the findings in a patient in whom intravenous bretylium was the only effective agent to suppress refractory ventricular tachycardia and ventricular fibrillation. After attempts to switch the patient to amiodarone and bethanidine (an oral analogue of bretylium) caused proarrhythmic effects, he was successfully converted to oral therapy with bretylium. Electrophysiologic testing was not predictive of the clinical response from oral bretylium. To our knowledge, this is the first report of a proarrhythmic effect from bethanidine and it suggests a divergence in the actions of various class 3 antiarrhythmic agents.

Bretylium tosylate is a class 3 antiarrhythmic drug useful in the treatment of drug-resistant ventricular tachycardia (VT) and ventricular and fibrillation.1 We report the findings in a patient in whom bretylium was the only agent that suppressed refractory VT and ventricular fibrillation. Other class 3 antiarrhythmic agents, amiodarone and bethanidine, were proarrhythmic. Electrophysiologic testing on bretylium failed to predict the effects of long-term therapy with oral bretylium.

CASE REPORT

A 51-year-old healthy man suffered an acute extensive anterior myocardial infarction on July 5, 1986. His hospitalization was complicated by recurrent bouts of supraventricular tachycardia. Digoxin and quinidine suppressed supraventricular tachycardia, but the Holter study before discharge revealed frequent and complex ventricular ectopic complexes (including ventricular salvos of three to five complexes). The patient had palpitations after discharge and returned to the hospital on Aug 10, 1986 in sustained VT while receiving quinidine sulfate (200 mg by mouth four times daily) and digoxin (0.25 mg by mouth four times daily). Lidocaine (50 mg) was administered intravenously, and VT converted transiently to sinus rhythm, but episodes of nonsustained VT recurred despite intravenous administration of lidocaine at 2 mg/min. Procainamide (500 mg by mouth) was added to the infusion of lidocaine, but sustained VT recurred and required DC cardioversion for termination.

Intravenous bretylium was added to the regimen, and the patient was transferred to the Milton S. Hershey Medical Center, Hershey, PA, for further evaluation. On arrival, the patient was in incessant VT while receiving lidocaine, procainamide, and bretylium. Serum levels of the drugs obtained at the time of admission were as follows: quinidine, 2.6 mg/mL; procainamide, 8.8 mg/mL; NAPA, 9.8 mg/mL; lidocaine, 4.6 mg/mL; and digoxin, 1.0 mg/mL. The VT morphology was right bundle-branch block with right axis deviation at a rate of 220 beats per minute. All antiarrhythmic agents were discontinued and ventricular pacing at 120 beats per minute instituted; however, episodes of VT and subsequent ventricular fibrillation (VF) occurred, requiring repeated defibrillations. Cardiac catheterization revealed a totally occluded left anterior descending coronary artery and severely depressed systolic function, with an ejection fraction of 0.25 percent. A large anteroapical aneurysm was present. Due to the extensive size of the aneurysm and his poor left ventricular function, the patient was believed not to be a surgical candidate. High-dose therapy with lidocaine (6 mg/min, and serum levels of 16 µg/mL) may have decreased the episodes of VT, but caused seizures. Lidocaine was discontinued, and intravenous bretylium was reinstated with a 10-µg/kg bolus and a 3-µg/min infusion. Sustained VT was suppressed, but episodes of nonsustained VT continued. Amiodarone (1,800 mg daily) was started in combination with intravenous bretylium. After eight days, bretylium was discontinued, but sustained VT again returned; however, the VT was now polymorphous and quite rapid, with a cycle length of 210 ms (rate, 291 beats per minute). Multiple DC cardioversions were required for termination. Bretylium was restarted, and VT was suppressed. Amiodarone dosage was reduced to 800 mg/day. On the 18th day of this combination, polymorphic sustained VT and VF developed. Defibrillation was required. Amiodarone was discontinued. Bretylium alone was continued, and all VT was abated within 48 hours. Amiodarone (600 mg) was restarted but promptly caused recurrence of VT within 24 hours and was considered proarrhythmic. The patient was maintained on intravenous bretylium alone (3 mg/min).

Bethanidine, an oral congener of bretylium, was obtained from Marvin Bacaner, M.D., and the A. H. Robins Co. The investigational protocol required electrophysiologic testing after a single loading dose. The infusion of bretylium was discontinued, and oral bethanidine (1,500 mg) was started three hours later. Sustained VT was induced from the right ventricular outflow tract using triple ventricular extrastimuli during ventricular drive at a 500-ms cycle length (Fig 1A). Induced VT had a cycle length of 280 ms and had a left bundle-branch morphology with right axis deviation. A second dose of oral bethanidine (750 mg) was given four hours after the initial dose. The same sustained VT was induced from the right ventricular outflow tract during ventricular pacing at 500 ms with double ventricular extrastimuli. The patient received two more 500-mg oral doses of bethanidine at six-hour intervals, but sustained VT developed. Bretylium was restarted, and VT was again suppressed. Bethanidine was increased to 1,000 mg by mouth every six hours for eight doses, but VT recurred within eight hours of terminating the bretylium. Similar observations were noted with bethanidine (1,500 mg by mouth every six hours) but was very difficult to terminate with DC cardioversion. Bethanidine was discontinued, and the patient was again stabilized on intravenous bretylium. After a period of one week, a second trial of bethanidine was attempted, with identical results. Oral bretylium (Dupont Critical Care) was started at 1,000 mg by mouth every six hours but nonsustained VT occurred. At a dose of 1,600 mg by mouth every six hours, VT was suppressed, and nearly all ventricular ectopic complexes were eliminated. Electrophysiologic drug testing was performed after one week of therapy with oral bretylium. Sustained VT was induced during ventricular pacing at a 400-ms cycle length with triple extrastimuli to the right ventricular outflow tract (Fig 1B). The VT morphology was of left bundle-branch block with left axis deviation with a cycle length of 280 ms. Attempts to lower the oral dosage of bretylium resulted in reappearance of episodes of nonsustained VT. As a precaution, an automatic implantable cardioverter-defibrillator was implanted prior to discharge from the hospital. On oral therapy with bretylium, the patient has remained free of arrhythmias for nine months and has not required use of his defibrillator.

DISCUSSION

This case illustrates the beneficial effect of both intrave-
nous and oral bretylium as therapy for sustained VT. Two other Vaughan-Williams class 3 antiarrhythmic drugs, amiodarone and bethanidine, failed to suppress VT and demonstrated proarrhythmic effects. Upon removal of each of these agents, episodes of VT subsided, only to reappear on rechallenge. An average of 11 percent of ventricular arrhythmias are aggravated by antiarrhythmic agents. Aggravation of ventricular arrhythmias by bretylium is rare, and amiodarone has only a 2 to 6 percent incidence of proarrhythmic effects. Bethanidine is investigational but has not previously been shown to be proarrhythmic. In this case, failure of one class 3 agent did not predict the success of another, despite the fact that bethanidine is an oral congener of bretylium.

Although sustained VT was easily induced in the electrophysiology laboratory on therapy with both bethanidine and bretylium, bretylium successfully prevented any further episodes of VT. Further studies will be necessary to determine whether inducibility of VT on bretylium accurately predicts subsequent clinical recurrences.

**REFERENCES**

Fatal Aspergillosis Associated with Smoking Contaminated Marijuana, in A Marrow Transplant Recipient

Randa Hamadeh, M.D.; Abbas Ardehali, M.D.; Richard M. Locksley, M.D.; and Mary K. York, Ph.D.

A 34-year-old man presented with pulmonary aspergillosis on the 75th day after marrow transplant for chronic myelogenous leukemia. The patient had smoked marijuana heavily for several weeks prior to admission. Cultures of the marijuana revealed *Aspergillus fumigatus* with morphology and growth characteristics identical to the organism grown from open lung biopsy specimen. Despite aggressive antifungal therapy, the patient died with disseminated disease. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts.

Invasive aspergillosis has become a significant cause of death in immunosuppressed patients. Patients with acute leukemia and lymphoma are particularly susceptible. Postulated risk factors include granulocytopenia, and treatment with corticosteroids, antibiotics and cytotoxic chemotherapy. Qualitative disorders of granulocyte function described in acute leukemia may also increase the risk of Aspergillus infection. Because Aspergillus species are found in soil, air, and vegetable matter (including tobacco), inadvertent exposure is likely. We report a case of disseminated *Aspergillus fumigatus* infection in a bone marrow transplant recipient associated with the use of contaminated marijuana.

**CASE REPORT**

A 34-year-old man with Philadelphia chromosome-positive chronic myelogenous leukemia was admitted to the hospital for an allogeneic bone marrow transplant (BMT) following chemotherapy and splenectomy. He was pretreated with cyclophosphamide, total body irradiation and intrathelial methotrexate and maintained on cyclosporin and corticosteroid prophylactic therapy. His course was complicated by acute graft-vs-host disease (GVHD) that resolved on high-dose steroid therapy. He was discharged in good condition on the 39th day after BMT. His drug regimen included cyclosporin, prednison (30 mg twice daily), ketoconazole (200 mg daily), and gamma globulin (32 g intravenously every two weeks).

The patient remained transfusion-independent and clinically well until day 75 post-BMT when he had two generalized tonic-clonic seizures. Lumbar puncture yielded normal CSF. Brain CT scan was unremarkable. Magnetic resonance imaging of the brain showed two parietal nodules. Chest roentgenogram revealed multiple nodules, several of which were cavitory. Bronchoalveolar lavage was not diagnostic by Gram-stain, KOH wet mount or bacterial culture. The patient was empirically started on intravenous amphotericin-B therapy. Open lung biopsy was performed, which revealed septate hyphae in the direct KOH wet mount of the tissue.

Fungal cultures of the lung tissue and bronchial lavage fluid subsequently grew *Aspergillus fumigatus*; viral cultures yielded cytomegalovirus. Further history revealed that the patient had been smoking marijuana daily for several weeks prior to admission. Culture of his marijuana yielded *Aspergillus fumigatus*. Pathologic examination of the submitted lung tissue revealed both fungal and cytomegaloviral pneumonitis.

Despite aggressive therapy with amphotericin B and the experimental drug DHFG (9-[1,3 dihydroxy-2 propoxymethyl] guanine), the patient developed a progressive interstitial pneumonia that required intubation and ventilatory support. He continued to deteriorate with worsening of his pulmonary status, development of cholestatic jaundice and renal insufficiency. The addition of high-dose steroid treatment did not improve his condition. He expired 110 days after bone marrow transplantation. Autopsy revealed disseminated aspergillosis involving the lung, endocardium and brain, together with cytomegaloviral pneumonitis.

**DISCUSSION**

Aspergillus spores are ubiquitous and are the most frequently found fungus in the environment. Increased concentrations of spores have been noted in winter months. Pathogenicity of the *Aspergillus* species has to do with properties of the spores; namely their light weight, thick walls, and small size, which allow for their growth in terminal bronchioles. Host predisposing factors are most often related to the presence of underlying pulmonary disease such as asthma, possibly cystic fibrosis, old tuberculous cavitary disease, and/or to alterations in immune function such as chronic granulomatous disease or neoplasia. In acute leukemia, invasive pulmonary aspergillosis classically occurs in the setting of prolonged granulocytopenia and often presents with unrelenting fever and development of pulmonary infiltrates in the face of antibiotic therapy. Diagnosis of aspergillosis is often difficult to establish without lung biopsy. Blood culture and Aspergillus precipitins are not helpful. Sputum culture is positive in about 30 percent of patients, but may be useful in the diagnosis of invasive disease in selected patient subgroups. Nasal cultures have been reported to help identify patients at risk for aspergillosis. Recently, detection of Aspergillus antigen has been described and seems to offer some advantage over the methods mentioned above. Our patient's presentation was atypical in that he developed invasive aspergillosis two months after BMT and weeks after recovery of his neutrophil count.

We evaluated the possible role that marijuana had served as a source of exposure to Aspergillus organisms. A sample of the patient's marijuana grew two morphotypes of *Aspergillus fumigatus*, one blue-green and one white colony type. Final identification was based on microscopic characteristics of vegetative growth. Both produced thin-walled, smooth conidiophores with flask-shaped vesicles. Conidia were columnar and phialides were uniseriated. Each colonial...