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Short Communications

Electrocardiogram Abnormalities Induced by Amsacrine

Raymond B. Weiss[1,2], Dorothy Moquin[1], Jonathan D. Adams[1], James D. Griffin[3], and Harvey Zimbler[4]

[1] Section of Medical Oncology, Walter Reed Army Medical Center, Washington, DC 20012
[2] Uniformed Services University of the Health Sciences, Bethesda, MD, 20814
[3] Sidney Farber Cancer Institute, Boston, MA, 02115
[4] Berkshire Medical Center, Pittsfield, MA 01201, USA

Introduction

Amsacrine (*m*-AMSA) is an investigational agent that has activity in the treatment of acute leukemia [10]. The dose-limiting toxicity is myelosuppression [10]. Recently, serious cardiac arrhythmias and congestive heart failure have been noted in some patients receiving this drug, and a few patients have died [1, 2, 5, 7, 9]. Most of these patients had received prior anthracycline therapy, but in two reports [1, 7] the patients had either no prior anthracycline treatment or only low total doses. The cardiac abnormalities were clearly related to the amsacrine therapy, but the pathogenesis is unknown.

We have observed electrocardiographic changes in three patients receiving infusions of amsacrine, in the form of prolongation of the QT interval. All three had normal ECGs just prior to the amsacrine treatment. Prolongation of the QT interval can be a precursor to serious ventricular arrhythmias [8]. We speculate that QT interval prolongation may be the initial manifestation of amsacrine effect on the heart and that in a few patients this abnormality initiates ventricular arrhythmias.

Case Reports

Patient No. 1. A 64-year-old woman with stage IV lymphocytic lymphoma was treated with a combination of cyclophosphamide, vincristine, and prednisone for 4 years and then the disease progressed. She was then treated with doxorubicin, bleomycin, and prednisone. The total doxorubicin dose was 455 mg/m^2. Subsequently amsacrine treatment was started with a monthly dose of 60 mg/m^2, later escalated to 160 mg/m^2, administered over 60–90 min. She has continued this treatment for 12 months with stabilization of her lymphoma. Serum potassium was determined before each amsacrine dose and was always normal. Cardiac monitoring with an oscilloscope was performed during earlier infusions, and no abnormalities were recognized.

Later, it was decided that paper tracings for a permanent record would be valuable. At this time prolongation of the QT interval was noted, beginning about 30 min after starting the infusion, whereas the ECG just before treatment was normal (Fig. 1). During each of three subsequent amsacrine infusions the same QT interval prolongation has occurred. The patient has had no other cardiac symptoms or abnormalities.

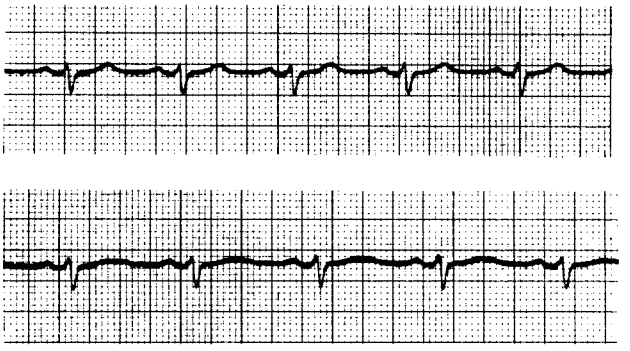

Fig. 1. Top: Lead II ECG for patient no. 1 before treatment. Bottom: Lead II ECG 40 min after 1 h infusion of amsacrine was begun, showing prolongation of QT interval

Patient No. 2. A 56-year-old man with stage III mixed lymphoma was treated with a combination of cyclophosphamide, vincristine, bleomycin, doxorubicin, and prednisone. The total doxorubicin dose was 340 mg/m^2. When he no longer responded to this regimen, amsacrine was administered at monthly intervals in a dose of 60 mg/m^2 initially, with later escalation to 160 mg/m^2. A partial tumor response was obtained, and the drug has been given for 10 months. Serum potassium levels determined before each dose were all normal. Oscilloscope monitoring was done during the first few amsacrine infusions, and no abnormalities were recognized. Later, paper tracings were obtained because of the observation made on the first patient, and this patient also had QT interval prolongation (0.38 s lengthening to 0.44 s; heart rate: 74) beginning after 30 min of the infusion. No cardiac symptoms or abnormalities have occurred at any time.

Patient No. 3. A 46-year-old woman with acute lymphoblastic leukemia was treated with cytarabine, teniposide, and intrathecal methotrexate. Maintenance therapy consisted of methotrexate, vincristine, 6-mercaptopurine, and prednisone. No anthracyclines were given. A year later amsacrine treatment was started, with a dose of 60 mg/m^2 TID (180 mg/m^2/day) for 5 days.

Her ECG was normal before treatment. After the first of the 3/day doses the QT interval lengthened from 0.38 s to 0.44 s (heart rate: 80). The QT interval remained prolonged throughout the 5 days of treatment, varying from 0.43 to 0.46 with a heart rate of 80–85 . Serum calcium and potassium were measured daily and remained normal. She failed to achieve remission, and no further amsacrine was given.

Reprint requests should be addressed to R. B. Weiss

Discussion

All three patients developed QT interval prolongation while amsacrine was infusing. All had normal serum potassium determined just prior to an amsacrine dose. None received any phenothiazines. Two had received prior doxorubicin treatment. None had any other cardiac abnormalities. The temporal relationship of the ECG abnormality to the drug infusion while serum electrolytes were normal provides clear evidence that amsacrine is the cause of the ECG change.

Prolongation of the QT interval may be idiopathic and familial or be caused by hypokalemia, hypocalcemia, or hypomagnesemia [8]. Quinidine can cause prolonged QT interval, and some patients with such quinidine-induced changes have developed ventricular fibrillation [4]. Procainamide also prolongs the QT interval, but to a lesser degree than quinidine [3]. These drugs decrease the rate of depolarization, prolong the cardiac action potential, and delay repolarization.

It appears that amascrine has a cardiac effect similar to quinidine. The mechanism is unknown, but it may be like that of quinidine. Although others have noted ST-T wave changes in some patients receiving amsacrine [6], this QT phenomenon has not been previously reported, perhaps because ECGs are not routinely done during drug infusion. We initially monitored our patients at Walter Reed Hospital with an oscilloscope and overlooked the abnormality. Only when frequent paper tracings were obtained was the QT prolongation seen.

Although the incidence is unknown, QT prolongation may occur in most patients receiving this drug, and this electrical phenomenon may have been the precursor to the ventricular arrhythmias previously reported [1, 2, 5, 7, 9]. The fact that only a few patients have been reported to develop ventricular arrhythmias is possibly explained by the need for a second cardiac insult to be present to compound the problem. Two of the patients who had fibrillation [2, 9] also had hypokalemia, another cause of QT prolongation. The summation of cardiac effect from both hypokalemia and amsacrine may have precipitated ventricular arrhythmia. It is possible that our three patients had no such arrhythmia because they did not have hypokalemia.

The role of prior anthracycline therapy in the pathogenesis of this ECG change is uncertain. Two of our patients received doxorubicin, but one did not and neither did two of the reported patients with arrhythmias [1]. Thus, ECG abnormalities can occur from amsacrine in the absence of prior anthracycline therapy.

Since QT interval prolongation from amsacrine may trigger a potentially fatal arrhythmia in a hypokalemic patient, we suggest that the serum potassium be measured before an amsacrine dose is administered. During infusion of amsacrine one must be cognizant of the possibility of drug-induced arrhythmia and be prepared to deal with it.

References

1. Falkson G (1980) Multiple ventricular extrasystoles following administration of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA). Cancer Treat Rep 64: 358
2. Foldes JA, Yagil Y, Kornberg A (1982) Ventricular fibrillation, hypokalemia, and AMSA therapy. Ann Intern Med 96: 121–122
3. Hoffman BF, Rosen MR, Wit AL (1975) Electrophysiology and pharmacology of cardiac arrhythmias. VII. Cardiac effects of quinidine and procaine amide. B. Am Heart J 90: 117–122
4. Koster RW, Wellens HJJ (1976) Quinidine-induced ventricular flutter and fibrillation without digitalis therapy. Am J Cardiol 38: 519–523
5. Legha SS, Latreille J, McCredie KB, Bodey GP (1979) Neurologic and cardiac rhythm abnormalities associated with 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) therapy. Cancer Treat Rep 3: 2001–2003
6. Steinherz L, Mangiacasale D, Steinherz P, Tan C, Miller D (1980) Echocardiographic and ECG abnormalities in pediatric patients receiving 4′-(9-acridinylamino)-methane sulfon-*m*-anisidide. Proc Am Assoc Cancer Res 21: 143
7. Steinherz LJ, Steinherz PG, Mangiacasale D, Tan C, Miller DR (1982) Cardiac abnormalities after AMSA administration. Cancer Treat Rep 66: 483–488
8. Vincent GM, Abildskov JA, Burgess MJ (1974) Q-T interval syndromes. Prog Cardiovasc Dis 16: 523–530
9. Von Hoff DD, Elson D, Polk G, Coltman C (1980) Acute ventricular fibrillation and death during infusion of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (AMSA). Cancer Treat Rep 64: 356–357
10. Weiss RB, Charles LM, Macdonald JS (1980) M-AMSA: an exciting new drug in the National Cancer Institute Drug Development Program. Cancer Clin Trials 3: 203–209

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