To the editor

Cardiac toxicity of arsenic trioxide

Unnikrishnan et al have reported the occurrence of torsades de pointes in 3 of 19 patients treated with arsenic trioxide.\(^1\) The propensity for arsenic to cause reversible Q-T interval prolongation is well known and has previously been characterized.\(^2\) To minimize the risk of long Q-T–related arrhythmias associated with arsenic therapy, Cell Therapeutics, makers of the FDA-approved Trisenox (arsenic trioxide), have issued very specific guidelines regarding therapy, recognizing that machine generated values may become unreliable in the presence of marked tachycardia and T-wave flattening. These values are likely machine generated and are probably incorrect in view of the marked tachycardia and T-wave flattening observed in these patients. In summary, arsenic trioxide prolongs the Q-T interval in a gradual and reversible fashion and is liable to cause torsade de pointes unless stringent precautions are taken. Aggressive electrolyte replacement is mandatory, and monitoring of the Q-T interval warranted, recognizing that machine generated values may become unreliable in the presence of marked tachycardia and T-wave flattening. Finally, if cardiac arrhythmias occur, distinguishing torsades de pointes (an adverse drug reaction until proven otherwise) from other arrhythmias has important therapeutic and public health implications.

Jean T. Barbey

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J.T.B. was a paid consultant for Cell Therapeutics but currently has no financial interest in that company or in any competing company.

References

To the editor:

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Unnikrishnan et al describe 3 patients out of 19 treated with arsenic trioxide who developed torsades de pointes (TDP) that proved fatal in 2. The source of the arsenic trioxide given these patients and its characterization and formulation are not stated in the article. But inasmuch as the article was submitted to Blood prior to FDA approval of Trisenox brand of arsenic trioxide for injection on September 25, 2000, and no Trisenox studies under the Cell Therapeutics investigational new drug application (IND) were performed at Our Lady of Mercy Cancer Center, we are sure that the arsenic trioxide formulation administered in that study was not manufactured by Cell Therapeutics, the only commercial source of this agent in the United States.

We believe this distinction is important because the safety experience reported for Trisenox has been very different from that reported in the Unnikrishnan et al article and that reported with another research product by Westervelt et al; a report cited in Unnikrishnan et al. As director of the Pharmacovigilance Committee at Cell Therapeutics, I would like to review our safety experience to date with Trisenox, particularly with reference to Q-T prolongation, TDP, and the FDA-approved guidelines for safe and effective use of Trisenox as described in the product label.

Trisenox for injection was approved for marketing in September 2000, for the treatment of relapsed and refractory acute promyelocytic leukemia (APL). In the multicenter pivotal study of Trisenox in relapsed or refractory APL, 70% of the patients achieved a complete remission, with 78% demonstrating a molecular remission. The median survival is greater than 18 months.

Our current pharmacovigilance database consists of more than 360 patients treated with Trisenox at doses ranging from 0.15 to 0.35 mg/kg/d. These data include patients treated on clinical investigations in a variety of malignancies conducted under our company-sponsored IND, in NCI-sponsored trials under a Cooperative Research and Development Agreement (CRADA), or on a compassionate-use program for patients with APL. In addition, postmarketing surveillance adverse-event reports on patients treated since product launch in October 2000 were evaluated. Q-T prolongation is well known and expected effect of arsenic trioxide treatment. To date, only 3 cases of Q-T prolongation above 500 millisecond (ms) have been reported. No deaths due to cardiac arrhythmias have been attributed to Trisenox.

In a detailed independent review of 1000 electrocardiograms from 99 patients on clinical trials, 26 cases of Q-Tc above 500 ms were identified, with 3 cases having an absolute Q-T above 500 ms. A single case of self-limited TDP occurred in a patient undergoing induction therapy for APL who was also receiving amphotericin B. The TDP resolved after electrolyte correction, and the patient went on to receive consolidation therapy uneventfully. Under the management guidelines included in the label, treatment emergent adverse events have decreased over time, are less common in consolidation and maintenance, and usually have not required stopping therapy.

The high frequency and severity of complex arrhythmias or deaths reported by Unnikrishnan et al and Westervelt et al, 2 sites using investigational arsenic trioxide, appear to be different from the relatively lower frequency of events that have been reported with Trisenox. Why these experiences differ so markedly from that reported by Unnikrishnan et al or Westervelt et al is uncertain. It should be noted that patients 1 and 2 in the Unnikrishnan et al study received 20 mg of arsenic trioxide per day, potentially a higher than recommended dose of 0.15 mg/kg/d, although the patient weights were not given. Both patients had marked hypomagnesemia, hypokalemia, and pulmonary failure at the time they developed TDP. The “black box” warning in the Trisenox label recommends that the potassium and magnesium values be maintained at midnormal levels when administering Trisenox (at least 4 mEq/L for potassium and 1.8 mg/dL for magnesium). The third patient received 10 mg/dl of arsenic trioxide, which was stopped after 7 days for prolongation of the Q-Tc. TDP developed after the drug had been discontinued for 5 days and the Q-T interval was normalizing. As this patient also had respiratory failure and was on a ventilator, factors other than arsenic trioxide may have contributed to his refractory arrhythmia.

Based on the available data on more than 360 patients, the safety administration of Trisenox can be optimized with appropriate monitoring and management of electrocardiogram abnormalities as described in the product label.

Jack W. Singer

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J.W.S. is Executive Vice President of Cell Therapeutics and holds more than $10,000 worth of stock in that company.

References


Response:

Monitoring of cardiac toxicity with arsenic trioxide

We thank you for the opportunity to comment on the letters by Barbey and by Singer, regarding our brief report on the occurrence of torsades de pointes in 3 patients with relapsed/refractory acute myelogenous leukemia treated with arsenic trioxide. First, in response to Dr Barbey, the arrhythmias observed in all 3 patients were preceded by the long-short initiation sequence. We did not have room to present electrocardiograms (ECGs) from all 3 patients. In 2 of the patients, this rhythm was not symptomatic initially but did recur. It was not the cause of death in these 2 patients. In discussion of the electrolytes, “widely fluctuating” is a bit of an overstatement. Nevertheless, it is clear that the variation in the values presented in the manuscript are consistent with observations obtained in seriously ill, hospitalized patients with acute leukemia, who require daily monitoring of blood values, including electrolytes, and who require frequent replacement of electrolytes. These patients are not simple to manage, in that they require multiple antibiotics and blood products, in addition to daily arsenic, and intravenous intake frequently exceeds 3 liters per day in such patients. Additionally, the fluid retention syndrome noted with the use of arsenic trioxide makes fluid and electrolyte balance even
To the editor:

Meta-analysis of the association between low-affinity Fcγ receptor gene polymorphisms and hematologic and autoimmune diseases

Genetic polymorphisms of the low-affinity receptors of the Fc domain of IgG (FcγR) have been proposed to be associated with an array of hematologic, autoimmune, and other diseases. Most studies have addressed the R/H131 polymorphism of the FcγRIIa isoform and the V/F158 polymorphism of the FcγRIIIa isoform. For the majority of the associations, only single studies have been performed. But for conditions such as heparin-induced thrombocytopenia, systemic lupus erythematosus (SLE) and SLE-related nephritis, and idiopathic thrombocytopenic purpura, data have been generated from multiple teams of investigators. Information from different teams has often been controversial or even conflicting. We believe that there is a need to standardize and synthesize the accumulating data across these various studies.

Lehrnbecher et al made an effort to accumulate in a systematic fashion the epidemiologic data on genetic associations involving low-affinity FcγR receptor polymorphisms. Unfortunately, the synthesis of the data was problematic. Typically, when there was more than one study addressing the same association, the number of subjects in the patient and control arms were summed for the various genotypes and statistical tests were performed in the resulting contingency tables with the summed data. This approach is methodologically inappropriate. The synthesis of data across diverse studies needs to take into account the within study variance, which has been performed for conditions such as heparin-induced thrombocytopenia, systemic lupus erythematosus (SLE) and SLE-related nephritis, and idiopathic thrombocytopenic purpura, data have been generated from multiple teams of investigators. Information from different teams has often been controversial or even conflicting. We believe that there is a need to standardize and synthesize the accumulating data across these various studies.

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