

## CASE REPORT

### Arsenic trioxide-induced QT interval prolongation: A case report

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#### ABSTRACT

QT prolongation refers to the prolonged QT interval in electrocardiography (ECG) which can even lead to life-threatening events such as ventricular arrhythmias, torsades de pointes, etc., several drugs can cause QT prolongation which includes sotalol, quinidine, arsenic, disopyramide, procainamide, amiodarone, haloperidol, etc., Arsenic trioxide (ATO) is used as an effective treatment option in promyelocytic leukemia (PML). Acute myeloid leukemia (AML) is a cancer that affects the blood and bone marrow. Acute promyelocytic leukemia (APL) is the M3 subtype of AML that affects mainly the white blood cells. In APL, immature granulocytes accumulate abnormally to form promyelocytes. ATO helps in the apoptosis of these cancerous promyelocytic cells. In patients on arsenic therapy, ECGs must be monitored to ensure QT prolongation as it a major side effect of the drug. Here is the case of a 58-year-old female patient and was newly diagnosed with APL. She developed QT prolongation with arsenic therapy. Other confounding factors such as electrolytes and presence of other QT-prolonging drugs were also corrected.

**KEY WORDS:** Acute Promyelocytic Leukemia; Promyelocytes; QT Prolongation; Torsades De Pointes; Arsenic Trioxide

#### INTRODUCTION

Arsenic trioxide (ATO) comes under the class of medications known as antineoplastics. It is shown to be very efficacious in treating both relapsed patients and newly diagnosed patients with APL. Even though, it is a single agent therapy, it induces complete remissions and causes few adverse effects and only minimal myelosuppression.<sup>[1]</sup> Another effect of arsenic is that it can cause QT interval prolongation and can even result in life-threatening ventricular arrhythmia, torsades de pointes, which is can even lead to cardiac death.


ATO slows and stops the growth of cancerous cells. It is available in the form of solution (liquid) that is to be injected into the vein by a medical practitioner (doctor) or nurse in a medical setup or clinic. The infusion is usually given over 1-2 h, but it can be given as long as 4 h if any side effects occur during infusion. It is usually injected once daily for a specific period.

#### Induction Treatment Schedule

Intravenously administer 0.15 mg/kg daily till bone marrow remission. Treatment should not exceed total induction doses, i.e., 60 doses. Administer ATO intravenously over 1-2 h. If vasomotor reactions are observed during infusion, the infusion can be even extended up to 4 h.

#### Consolidation Treatment Schedule

Begin consolidation treatment after 3-6 weeks of completion of induction phase. Administer ATO intravenously at

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0.15 mg/kg/dose daily for 25 doses over a period up to 5 weeks.

The mechanism in which ATO acts on cancerous cells is not well understood. ATO mainly acts on signal transduction pathways and leads to wide range of alterations causing cell death or apoptosis. Hydrogen peroxide and intracellular glutathione are the key mediators of sensitivity to ATO-induced apoptosis. Another major step in ATO-mediated apoptosis is the inner mitochondrial membrane potential loss. Mechanism of ATO-induced cell differentiation in APL cells is most likely by the degradation of promyelocytic leukemia (PML)-retinoic acid receptor alpha, which is a fusion protein. Degradation of this fusion protein allows to overcome the maturation block of cancerous promyelocytes.<sup>[2]</sup>

In addition to therapeutic role, patients must be closely monitored to prevent the occurrence of any side effects. More than 10 in every 100 people have one or more of the side effects. Stomach pain, muscle and bone pain, fever, headaches, tachycardia, edema, prolonged Q-T interval on electrocardiography (ECG), chest pain, hypotension, fatigue, headache, insomnia, rigors, paresthesia, anxiety, dizziness, depression, pain, dermatitis, pruritus, xeroderma, diaphoresis, erythema, hypokalemia, hyperglycemia, nausea, sore throat, hypomagnesemia, hyperkalemia, weight gain, abdominal pain, vomiting, diarrhea, anorexia, constipation, and decreased appetite.

## CASE REPORT

A 58-year-old female, came with history of facial puffiness, pitting edema for 1 week. The patient also had a history of fall and evaluated in local hospital. After that she developed fever with no chills and rigors. Laboratory investigations showed pancytopenia (*hemoglobin* [Hb]: 8.2 g/dl, total count [TC]: 4300 K/uL, platelet [PLT]: 22,000 K/uL) and peripheral smear revealed acute myeloid leukemia. For further evaluation, bone marrow aspiration was done which suggestive of acute promyelocytic leukemia (APL) (FAB M3). Biopsy showed mononuclear cell infiltrate. Flow cytometric analysis revealed approximately 82% of cells in blast region expressing dim CD13, heterogeneous CD117, moderate CD38, dim CD34, MPO positive, dim CD19, and negative for human leukocyte antigen - antigen D-related. The scatter parameters and antigen expression profile of the sample as studied by flow cytometry was suggestive of APL. On clinical examination, the patient was conscious and oriented with no pedal edema, afebrile, and the vitals were also stable. It was decided to start chemotherapy with ATO (injection ATO 10 mg I.V in 500 ml NS >4 h). The patient received 42 cycles of chemotherapy.

During hospital stay, the patient developed fever with cough and expectoration. Sample for blood and sputum

culture was sent. Sputum culture showed moderate growth of *Klebsiella pneumoniae* and *Aspergillus fumigatus*. The patient was treated with injection Amikacin 700 mg IV OD and tablet voriconazole 200 mg BD as per sensitivity report. Repeat sputum cultures showed clearing of *Klebsiella*. Chest X-ray also showed bilateral fluffy infiltrates. Pulmonology consultation was sought for optimization of antibiotics and their advice was followed. Following which her fever spikes settled and improved symptomatically. Chest X-ray showed marginal improvement. However, repeat sputum cultures also showed *Aspergillus* so advised to continue tablet voriconazole.

During hospital stay, patient had hypokalemia which was corrected with KCL infusion. Serum electrolyte levels were maintained at normal levels (K = 4 mmol/L; Mg = 2.2 mg/dl). She was treated with ATO, IV-intravenous, antifungals, steroids, KCL infusion, and other supportive measures. During treatment with ATO, monitoring revealed prolongation of QT interval in ECG; hence, the treatment was administered only on days with QTc <500 ms. Since patient had a very high rise of QT interval, further doses were withheld as her blood parameters suggested an excellent response to the therapy (PLT: 592000 K/uL, TC: 7600 K/uL, Hb: 10.9 g/dl). Induction phase was completed. She was better and the fever subsided, counts improved and was discharged in a stable condition.

## ECG Monitoring Recommendations and Precautions

Before the arsenic therapy, 12 lead ECG must be performed and electrolytes (calcium, potassium, and magnesium) and creatinine must be checked. Pre-existing electrolyte abnormalities must be corrected and other factors (other drugs) contributing to QT prolongation should also be checked and if present should be discontinued also. Clinicians should be very careful and they should evaluate patients for pre-existing heart disease and a continuous cardiac monitoring is required in such cases. Potassium and magnesium levels must be kept above 4 mEq/L and 1.8 mg/dl, respectively. Patients who reached an absolute QT interval value > 500 ms should be assessed again, and concomitant risk factors, if any, must be immediately corrected, mean time risk/benefit of continuing versus removing arsenic therapy should also be analyzed. If the patient develops rapid/irregular or syncope, patient should be closely monitored and serum electrolyte levels must be assessed. The ATO therapy should be suspended temporarily till QTc level reaches below 460 ms.

## DISCUSSION

A retrospective study was conducted by Barbey et al to determine the extent of QT prolongation in patients on ATO therapy. 99 patients who were diagnosed with advanced malignancies were selected for the study. Routine ECGs and clinical data of patients who received 170 doses of ATO in

either phase I or phase II investigational study were analysed. QT prolongation was noted in 38 patients. Female patients and hypokalemic patients showed higher degree of QT interval prolongation.<sup>[3]</sup> Unnikrishnan et al described cases of 3 patients in whom arrhythmia developed while on treatment with arsenic trioxide.<sup>[4]</sup> Ohnishi et al conducted a study among 8 patients with relapsed acute PML. The study objective was to determine cardiac toxicities due to ATO therapy in patients diagnosed with refractory or relapsed APL. Out of 8, 5 patients (63%) gained complete remission from Promyelocytic Leukemia. All patients showed QT prolongation during induction phase of arsenic therapy. 8 out of 12 courses of therapy showed ventricular premature contractions.<sup>[5]</sup> Because of non sustained ventricular tachycardia<sup>[6]</sup>, treatment with antiarrhythmic agents was given for 4 patients. Lengfelder et al described arsenic trioxide as very potent and first line agent in treatment of APL.<sup>[7]</sup> Chiang et al studied the action of ATO on guinea pig papillary muscle and the study concluded that dose dependent IV infusion of ATO prolonged QT interval and action potential duration (APD).<sup>[8]</sup> The study suggested that Arsenic trioxide has direct effect on cardiac repolarisation and the drug must be administered with strict ECG monitoring.

## CONCLUSION

Arsenic trioxide is a very active and primary agent in treatment of PML and AML.<sup>[9]</sup> ATO can prolong QT interval. However, with ECG monitoring.<sup>[10]</sup> and management of co-medications and serum electrolytes on routine basis, arsenic trioxide can be administered safely in APL patients.

## REFERENCES

1. Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S. Mechanisms of action of arsenic trioxide. *Cancer Res.* 2002;62(14):3893-903.
2. Miller WH Jr. Molecular targets of arsenic trioxide in malignant cells. *Oncologist.* 2002;7 Suppl 1:14-9.
3. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol.* 2003;21(19):3609-15.
4. Unnikrishnan D, Dutcher JP, Varshneya N, Lucariello R, Api M, Garl S, et al. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood.* 2001;97(5):1514-6.
5. Ohnishi K, Yoshida H, Shigeno K, Nakamura S, Fujisawa S, Naito K, et al. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med.* 2000;133(11):881-5.
6. Prabhu MA, Srinivas BV, Thajudeen A, Namboodiri N. Bundle branch reentry: A rare mechanism of ventricular tachycardia in endomyocardial fibrosis, without ventricular dilation. *Indian Heart J.* 2016;68920:S198-201.
7. Lengfelder E, Hofmann WK, Nowak D. Impact of arsenic trioxide in the treatment of acute promyelocytic leukemia. *Leukemia.* 2012;26(3):433-42.
8. Chiang CE, Luk HN, Wang TM, Ding PY. Prolongation of cardiac repolarization by arsenic trioxide. *Blood.* 2002;100(6):2249-52.
9. Chandran PA, Gupta NA, Retnakumari AP, Malarvizhi GL, Keechilat PB, Nair SA, et al. Simultaneous inhibition of aberrant cancer kinome using rationally designed polymer-protein core-shell nanomedicine. *Nanomedicine.* 2013;9(8):1317-27.
10. Manikandan MS, Soman KP. A novel method for detecting R-peaks in electrocardiogram (ECG) signal. *Biomed Signal Process Control* 2012;7(2):118-28.

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