Brief report

Effects of oral arsenic trioxide therapy on QT intervals in patients with acute promyelocytic leukemia: implications for long-term cardiac safety

Chung-Wah Siu, Wing-Yan Au, Cindy Yung, Cyrus R. Kumana, Chu-Pak Lau, Yok-Lam Kwong, and Hung-Fat Tse

Introduction

Arsenic trioxide (As$_2$O$_3$) is efficacious in acute promyelocytic leukemia (APL). It blocks potassium currents $I_{K_{s}}$ and $I_{K_{r}}$, causing QT prolongation. Ventricular tachyarrhythmias were reported in about 30% of patients treated with intravenous As$_2$O$_3$. As$_2$O$_3$ may be effective in other neoplasms, making clinical trials of As$_2$O$_3$ in these diseases pressing. However, reliance on intravenous As$_2$O$_3$ hampers these efforts. Long-term intravenous As$_2$O$_3$ is resource-demanding. Moreover, a potentially fatal cardiac toxicity is worrisome, especially in clinical trials.

We have developed an oral formulation of As$_2$O$_3$. Details of the preparation and pharmacokinetics of oral As$_2$O$_3$ have been previously reported. Oral As$_2$O$_3$ gives a similar bioavailability, but lower peak plasma arsenic concentrations, as compared with intravenous As$_2$O$_3$. Oral As$_2$O$_3$ represents an advance in arsenic therapy. Patients take oral As$_2$O$_3$ at home, rendering long-term therapy feasible, thus facilitating clinical trials. Most importantly, in more than 600 patient weeks of oral As$_2$O$_3$ administered during 5 years, no ventricular tachyarrhythmias were observed.

Prolongation of QT or corrected QT (QTC) increases the risks of ventricular tachyarrhythmias. QT-interval dispersion measures regional nonhomogeneities of ventricular repolarization. Greater dispersions increase ventricular arrhythmias. Heart rate variability (HRV) measures the beat-to-beat heart rate variations, correlating with changes in autonomic tone. HRV changes increase cardiac arrhythmias.

To explain the favorable cardiac side-effect profile of oral As$_2$O$_3$, we studied a cohort of patients on long-term oral As$_2$O$_3$, to determine the cardiac safety and changes of QT intervals and HRV.

Study design

Patients

We studied 17 consecutive patients with relapsed APL (Table 1). All had normal left ventricular ejection fraction and blood biochemistry.

Study protocol

Patients received oral As$_2$O$_3$ (10 mg/d) for 2 weeks, followed by a drug-free period of 6 to 8 weeks before the next course. Patients took oral As$_2$O$_3$ at 14:00 every day to match the timing for electrocardiography (ECG) and Holter recording, and blood arsenic assay. Treatment protocol was approved by the institutional review board of Queen Mary Hospital, and all patients gave informed consent in accordance with the Declaration of Helsinki.

ECG and Holter measurement

Data were collected at day 10 of oral As$_2$O$_3$ (As$_2$O$_3$-ON) and 4 weeks after stopping oral As$_2$O$_3$ (As$_2$O$_3$-OFF). Resting 12-lead surface ECGs were recorded (paper-speed: 50 mm/second) for measuring QT intervals. QT intervals at each lead and the corresponding RR-interval at lead II were measured to calculate the QTC (Bazett formula: $QTC = QT/square-root of RR$ interval). QT dispersion was the difference between the maximum and minimal QT measured from each of 12 leads. During As$_2$O$_3$-ON and As$_2$O$_3$-OFF, 24-hour Holter monitoring (Zymed DigiTrak Plus; Zymed 1810, Philips, The Netherlands) was performed to assess circadian QT variations.

Data interpretation

Holter recordings were reviewed and edited manually. Recordings must exceed 20 hours and be of good quality to be analyzed. The time domain (standard
deviation of normal RR interval (SDNN) and frequency domain (ratio of low-frequency to high-frequency power [LF/HF]) of HVR was measured to assess parasympathetic and sympathetic activities, respectively.\textsuperscript{12,13} ECG and Holter were analyzed by a cardiologist blinded to patient treatment.

Elemental arsenic levels
After venepuncture, EDTA-anticoagulated blood was immediately separated into plasma and cell fractions. Arsenic levels were measured by inductively coupled plasma mass spectrometry.\textsuperscript{17}

Statistical analysis
Continuous variables were expressed as mean plus or minus standard error of the mean. Comparisons were performed with the Student \( t \) test or Fisher exact test (SPSS software, version 10.0). \( P \) values less than .05 were considered significant.

Results and discussion

Patients and arsenic levels
Sixteen patients completed the study (one died of sepsis). Consistently, cellular arsenic levels were significantly higher than plasma arsenic (Figure 1A), similar to previous observations during long-term oral \( \text{As}_2\text{O}_3 \).\textsuperscript{13}

ECG and Holter findings
Both QT and QTc were significantly longer during \( \text{As}_2\text{O}_3-\text{ON} \) than in \( \text{As}_2\text{O}_3-\text{OFF} \) (Table 2, \( P < .01 \)). However, the QT and QTc dispersion were comparable during \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \) (Table 2, \( P > .05 \)). Holter monitoring showed similar circadian heart rate variations during \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \), but 24-hour heart rates were consistently higher during \( \text{As}_2\text{O}_3-\text{ON} \) than in \( \text{As}_2\text{O}_3-\text{OFF} \), being significantly different during late evening (21:00, 22:00, 23:00), early morning (02:00, 03:00, 04:00), and afternoon (12:00, 13:00, 14:00; \( P < .05 \); Figure 1B).

QT measurements
QT intervals over 24 hours showed marked variations, although the pattern and measurement at each hour were comparable between \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \) (Figure 1C). Circadian variations of mean QTc intervals (Figure 1D) were comparable between \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \), but measurements at each hour were significantly longer during \( \text{As}_2\text{O}_3-\text{ON} \) (\( P < .05 \), except at 06:00, 19:00, 23:00). The mean differences of QTc between \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \) are shown in Figure 1E. QTc prolongation of more than 30 milliseconds was observed at only one time point (16:00, 2 hours after oral \( \text{As}_2\text{O}_3 \)). No case had QTc prolongation of more than 50 milliseconds. This resulted in a QTc of more than 500 milliseconds in only 3 of 16 patients, all within 4 hours of oral \( \text{As}_2\text{O}_3 \). Although the SDNN was significantly lower during \( \text{As}_2\text{O}_3-\text{ON} \) than in \( \text{As}_2\text{O}_3-\text{OFF} \), there was no significantly difference in LF/HF between \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \) (Table 2).

Ventricular arrhythmias
Ventricular premature beats were comparably frequent between \( \text{As}_2\text{O}_3-\text{ON} \) and \( \text{As}_2\text{O}_3-\text{OFF} \) (0.03\% \pm 0.02\% versus 0.03\% \pm 0.03\%; \( P = .8 \)). No ventricular tachyarrhythmia was observed.

Conclusions and observations
Long-term oral \( \text{As}_2\text{O}_3 \) significantly increased the mean heart rate and QTc interval, and reduced SDNN. However, QT-interval, QT and QTc dispersions, and LF/HF were not changed. Furthermore, for indicators of proarrhythmic risks,\textsuperscript{12,13} significant QTc prolongation of more than 30 milliseconds was observed at only a single time point (2 hours after oral \( \text{As}_2\text{O}_3 \)). QTc prolongation never exceeded 50 milliseconds, and a QTc interval of more than 500 milliseconds was observed in only 3 patients within 4 hours of oral \( \text{As}_2\text{O}_3 \). Importantly, these observations translated into absent ventricular proarrhythmia in all patients. These results were superior to intravenous \( \text{As}_2\text{O}_3 \), where 26\% of patients had QT intervals more than or equal to 500 milliseconds, with QTc interval prolonged by more than 60 milliseconds in 35.4\% of treatment courses, and by more than 60 milliseconds in 35.4\% of patients, resulting in torsades de pointes in 1\% of cases.\textsuperscript{5}

The cardiac safety of oral \( \text{As}_2\text{O}_3 \) may be due to several reasons. First, in ventricular proarrhythmias during intravenous \( \text{As}_2\text{O}_3 \), \( \text{As}_2\text{O}_3 \) was infused over 1 to 3 hours.\textsuperscript{6-9} Pharmacokinetic studies

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Table 1. Characteristics and baseline laboratory data of 17 patients with relapsed acute promyelocytic leukemia treated with oral \( \text{As}_2\text{O}_3 \)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age, y</th>
<th>LVEF, %</th>
<th>Previous treatment</th>
<th>Creatinine level, ( \mu \text{M} )</th>
<th>Na level, mM</th>
<th>K level, mM</th>
<th>Ca level, mM</th>
<th>Status*</th>
<th>Outcome†</th>
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<tr>
<td>1</td>
<td>F/40</td>
<td>55</td>
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<td>81</td>
<td>141</td>
<td>3.7</td>
<td>2.41</td>
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<td>2</td>
<td>F/49</td>
<td>78</td>
<td>ATRA, Dauno, VP-16, Ara-C, IDA</td>
<td>85</td>
<td>142</td>
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<td>139</td>
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<td>141</td>
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<td>2.46</td>
<td>CR</td>
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<td>2.39</td>
<td>CR</td>
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<td>2.48</td>
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<td>144</td>
<td>3.5</td>
<td>2.25</td>
<td>CR</td>
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<td>146</td>
<td>4.1</td>
<td>2.43</td>
<td>CR</td>
<td>CR, 22 mo</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; F, female; ATRA, all-trans retinoic acid; Dauno, daunorubicin; CR, complete remission; Ara-C, cytosine arabinoside; VP-16, etoposide; IDA, idarubicin; M, male; R3, third relapse; TB, tuberculosis.

*Status after completion of the first course of oral \( \text{As}_2\text{O}_3 \).
†Status at latest follow-up, with maintenance therapy comprising oral \( \text{As}_2\text{O}_3 \) (10 mg/d) and ATRA (45 mg/m\text{2}/d), given for 2 weeks every 2 months for a planned 2 years.
showed that peak plasma arsenic levels after intravenous As$_2$O$_3$ reached 0.34 $\mu$M to 2.0 $\mu$M. However, after oral As$_2$O$_3$, peak arsenic levels were much lower at 0.25 $\mu$M to 0.55 $\mu$M (although gradual intestinal absorption led to a total area-under-the-curve comparable to intravenous As$_2$O$_3$). Because of lower peak arsenic levels, QTc prolongations after oral As$_2$O$_3$ were transient and lasted only 4 hours.

Second, arsenic shows a concentration-dependent blockade of $I_{Ks}$ and $I_{Kr}$ currents (IC$_{50}$, $I_{Ks}$: 0.14 $\mu$M ± 0.01 $\mu$M; $I_{Kr}$: 1.13 $\mu$M ± 0.06 $\mu$M). Hence, peak plasma arsenic concentrations reached after intravenous As$_2$O$_3$, but not oral As$_2$O$_3$, are high enough to block $I_{Ks}$ and $I_{Kr}$, thereby severely compromising repolarization and increasing susceptibility to ventricular proarrhythmia.

Finally, heart rates were significantly increased during oral As$_2$O$_3$. HVR analysis demonstrated significant decreases in parasympathetic activity without changes in sympathetic activity. The change in sympathetic/parasympathetic balance increases the heart rate, alleviating risks of ventricular tachyarrhythmias during QT prolongation. Hence, despite significant increases in QTc interval, overall QT intervals were unchanged during oral As$_2$O$_3$.

A limitation of this study is absence of an intravenous As$_2$O$_3$ control group. Since formulation of oral As$_2$O$_3$ in 2000, we have not used intravenous As$_2$O$_3$, making it difficult to include an intravenous As$_2$O$_3$ group just for this study. Previous reports of intravenous As$_2$O$_3$ have not measured QT dispersion, HRV, and circadian QT and HR variations, so how they relate to arrhythmias during intravenous As$_2$O$_3$ is difficult to judge. Finally, a 1% frequency of torsades de pointes in intravenous As$_2$O$_3$ might not have been detected in our study size.

Our results provide insights into how an oral formulation improves the cardiac safety of As$_2$O$_3$. Oral As$_2$O$_3$ is convenient and safe for outpatients, and may be the preferred formulation for prolonged arsenic treatment.

Acknowledgment

The authors thank the S. K. Yee Medical Foundation for provision of free oral arsenic trioxide to patients.

References


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