A CLUSTER OF CASES OF SEVERE CARDIOTOXICITY AMONG KALA-AZAR PATIENTS TREATED WITH A HIGH-OSMOLARITY LOT OF SODIUM ANTIMONY GLUCONATE

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Abstract. In India, sodium antimony gluconate is the drug of choice for kala-azar. Due to increasing unresponsiveness to this drug in the current epidemic that began in the early 1970s, daily doses of 20 mg/kg/day for 30 days or more is recommended as opposed to the 10 mg/kg/day dose for 6–10 days used in the past. Of the 130–150 patients treated annually at our center with locally made sodium antimony gluconate, serious cardiotoxicity has occurred in less than 10%. During April 1995 at the University Hospital in Varanasi, we encountered life-threatening cardiotoxicity after 3–28 days of therapy in each of the eight patients being treated with a new lot of this drug made by a different manufacturer. Of the eight patients, six each developed congestive heart failure and/or prolongation of the corrected QT interval (QTc), and three died as a direct consequence of drug-induced toxicities. In three instances, the life-threatening complications occurred with a cumulative dose of less than 300 mg/kg. In patients with prolonged QTc, ventricular premature beats and ventricular tachycardia were recorded; in one patient, the ventricular tachycardia progressed to torsade de pointes, culminating in ventricular fibrillation and death. Since switching to different lots of this drug, we have not seen further clustering of dangerous cardiotoxicity. The antimony content of the implicated drug was comparable with that in lots from other manufacturers that did not show overt toxicity, but the osmolarity was approximately 300 mOsm/L higher. The simple technique of measuring of osmolarity may help identify inappropriately manufactured drug.

Pentavalent antimonials, which were first manufactured and used between 1935 and 1945,1 have been the mainstay in the treatment of kala-azar. In previous epidemics in India, sodium antimony gluconate (SbV) in doses of 10 mg/kg/day for 6–10 days was considered adequate for the treatment of kala-azar.2 However due to increasing unresponsiveness in the ongoing epidemic that started in the early 1970s, a much higher dose (20 mg/kg/day) for 30 days or more is currently recommended.3–5 Treatment with SbV often results in minor side effects such as arthralgia, myalgia, transient elevation of hepatocellular enzyme levels, and minor electrocardiographic (ECG) changes.6, 7 A decrease in the height of T waves and T-wave inversion is seen in about 50% of patients.7 Although serious cardiotoxicity is uncommon, occurring in less than 9% cases, death may result in these patients.7, 8–10 Features of dangerous cardiotoxicity include a concave ST segment and prolongation of the corrected QT interval (QTc), which is measured by dividing the QT interval by the square root of the preceding interval between the preceding two QRS complexes (RR interval).11 Normal QTc values are less than 0.37 sec and 0.44 sec for males and females, respectively, while an increase of 0.03 sec or an absolute value of greater than 0.50 sec are considered ominous.6, 7

Sodium antimony gluconate is manufactured by several companies in India, and has been used safely for more than two decades. Recently, however, when we began to use a new lot of the drug from a different manufacturer, we encountered a spate of serious cardiotoxicity in the first eight patients treated. Our analysis suggests improper formulation of the drug. This phenomenon did not recur once we switched to different lots of Sb’ from other manufacturers.

CASE REPORTS

In April 1995, we began using a lot of Sb’ from a different manufacturer (manufacturer A, lot 1) for the first time at Banaras Hindu University Hospital (Varanasi, India). Since these patients were receiving routine therapy, their consent was obtained to be treated in the hospital as per hospital practice. Diagnosis of kala-azar at our institution is always confirmed by splenic aspirate. Each of the first eight patients treated with this new lot of Sb’ received intravenous treatment using the conventional dose of 20 mg/kg/day.3–6 The drug was infused in the usual manner, undiluted over a period of 10 min. None of the patients had a prior history of cardiac disease, and pretreatment ECGs were unremarkable in all eight, with normal QTc. As per usual practice, ECG monitoring was done at 7–10-day interval and more frequently if needed. This study was reviewed and approved by the Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University (Varanasi, India).

Soon after we started using this lot, we noticed significant cardiotoxicity developing in all eight patients. Although the same nursing staff and resident doctors had been taking care of patients in the kala-azar research ward for more than two years, a careful scrutiny was done to detect any accidental overdosing, including a comparison of the volume of Sb’ ordered with the volume infused. Since this lot was new and in use for the first time in our hospital, the number of used vials was matched with the expected consumption, and overdosing was ruled out. After all eight patients developed cardiotoxicity, this lot of drug was suspected to be the most probable cause of toxicity, and was not used by us again. An inquiry to the manufacturers regarding supply of the same lot to other Institutions and its possible toxicity did not evoke any response. Thus, it was impossible to know the use of this lot of Sb’ in other hospitals. Regulatory authorities were informed regarding this unprecedented toxicity. These case reports are being presented in order of decreasing severity of toxicity.
Case 1. A 50-year-old man developed palpitation and breathlessness of acute onset after only three doses of the drug. His jugular venous pressure was increased, there was tachycardia (heart rate = 140/min), crepitus in his lung bases, and pedal edema. Blood pressure was not measurable. He was treated with a dopamine infusion (10 μg/kg/min) and other supportive measures. The ECG showed prolongation of corrected QTc (0.61 sec). There was an initial improvement in his condition; however, a few hours later he had a cardiac arrest and could not be resuscitated.

Case 2. A 60-year-old man was responding well to treatment, and had became afebrile with the spleen regressing from 4 to 2.5 cm by day 14. However, on day 19 of treatment he complained of exertional dyspnea, pedal edema, and palpitation. He had increased jugular venous pressure, a pulse of 140/min, normal blood pressure, extensive crepitus in his lungs, and tender hepatomegaly. The ECG showed prolonged QTc (0.59 sec; Figure 1), and hepatic enzyme levels were increased to five times the upper limit of normal (alanine aminotransferase [ALT] = 156 IU and aspartate aminotransferase [AST] = 196 IU). He improved with diuretic therapy. Two days later his condition suddenly deteriorated and he died a few hours later due to cardiac arrest.

Case 3. A 20-year-old woman on the ninth day of therapy developed sudden onset severe breathlessness, palpitation and a painful abdomen. She had all the features of congestive heart failure, and the ECG showed flattening and inversion of T waves in limb leads, and deep inversion of T waves in chest leads. The QTc was prolonged (0.59 sec). She developed hypotension and tachycardia (pulse = 200/min), and was suspected to be having ventricular tachycardia (VT). She was immediately given a lidocaine bolus (50 mg) intravenously and shifted to the intensive care unit. Sinus rhythm was restored and a lidocaine infusion (2 mg/min) was continued; however, there was recurrence of VT the next day that was treated successfully with magnesium sulfate (1 g every 6 hr). Over the next several days, she had five such episodes of VT. She later developed torsade de pointes (Figure 2) and died after an episode of ventricular fibrillation, 10 days after the detection of Sb\(^{3+}\) toxicity.

Case 4. A 48-year-old woman developed severe nausea and vomiting on 25th day of her Sb\(^{3+}\) therapy. Her ECG showed a prolonged QTc (0.54 sec) and inversion of T waves. Holter monitoring revealed, in addition to the prolonged QTc, multiple ventricular ectopics and many episodes of ventricular tachycardia (Figure 3). Hepatic transaminase levels were also increased to four times the upper limit of normal (ALT = 156 IU, AST = 164 IU). On the same evening, she had an episode of cardiac arrest and was successfully resuscitated by thump-version and external cardiac massage. Thump-version is done by delivering a sharp, quick blow to the midpoint of the sternum during the first minute after the onset of cardiac arrest.\(^{12}\) The next day she had two similar episodes, and was fortunately resuscitated on these occasions as well. Within a few days, her electrocardiographic changes, as well as the hepatic enzyme levels, reverted to normal.

Case 5. A 30-year-old man was in his fourth day of treatment when he developed sudden hypotension from which he was successfully resuscitated over the next three days. His
Since other patients treated with the same lot of Sb his knee, elbow, and shoulder joints bilaterally on day 20.

ECG showed ST depression and T wave inversion. The QTc interval was 0.46 sec. He recovered completely and the ECG changes reverted to normal two weeks later.

**Case 6.** A 40-year-old man developed dyspnea on ninth day of therapy. He had increased jugular venous pressure, pedal edema, and basal crepitus. He also had QTc prolongation (0.64 sec). With cessation of Sb therapy and management of his congestive heart failure, he recovered without any serious complications.

**Case 7.** A 25-year-old man developed severe arthralgia in his knee, elbow, and shoulder joints bilaterally on day 20. Since other patients treated with the same lot of Sb had developed cardiotoxicity, an electrocardiogram was conducted, which showed QTc prolongation (0.54 sec) and T wave flattening. The drug therapy was stopped and patient had an uneventful recovery.

**Case 8.** A 35-year-old woman was started on Sb and was being followed every 10 days as an outpatient. She was doing well until the 28th day when she complained of palpitation. There were no remarkable findings, except a heart rate of 100/min. Her ECG revealed flattening or inversion of T waves in chest leads, with deep inversions in the lateral chest leads. The drug therapy was stopped immediately and she made an uneventful recovery.

Of the five surviving patients, only two (nos. 5 and 6) required further treatment for leishmaniasis. After they had recovered from the cardiotoxicity, as indicated by absence of cardiac signs and symptoms and normal ECGs, Sb from another manufacturer was used and both patients completed full 30 days of treatment without any complications. In all patients for whom serum transaminases, amylase, creatinine, urea, and electrolytes were measured, no abnormalities were observed, except in two patients (nos. 2 and 4) in whom hepatic enzyme levels were increased. None of the patients showed any electrocardiographic features of acute myocardial infarction or of any other disease to account for the arrhythmias that were recorded. Autopsies were not permitted in any of the deceased.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Lot</th>
<th>Total Sb, mg/ml (mean ± SE, n = 4)</th>
<th>Osmolality, mOsm/L (mean ± SE, n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>121.3 ± 1.5</td>
<td>1,375 ± 27</td>
</tr>
<tr>
<td>A</td>
<td>2</td>
<td>121.5 ± 1.7</td>
<td>1,290 ± 12</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>120.3 ± 1.1</td>
<td>1,053 ± 12</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>114.8 ± 0.9</td>
<td>996 ± 13</td>
</tr>
</tbody>
</table>

**RESULTS**

Analysis was done on sealed vials from this particular lot (A1) and three other lots of Sb, including one made by the same manufacturer (A2), but not used by us, and two lots (B1 and C1) from other manufacturers that were used by us safely. Antimony content was determined by electrothermal atomic absorption spectroscopy. Osmolality measurements were performed by freezing point depression on a One-Ten Osmometer (Fiske Associates, Needham, MA). Specimens were diluted 11-fold with water to achieve a sufficiently dilute solution to allow reproducible measurements, and osmolality was measured within 6 min of dilution. Because dilutions were made volumetrically, adjustment for the dilution factor gave final results in mOsm/L, or osmolality. Overall imprecision, expressed as the coefficient of variation, was 3.0%; within-day imprecision was 2.8%. As shown in Table 1, all lots had antimony contents that were higher than the nominal value of 100 mg/ml, but were comparable across manufacturers. However, both lots from the one manufacturer (A) had high osmolality. Serum antimony levels were not measured.

**DISCUSSION**

The reported incidence of Sb-induced serious cardiotoxicity is typically 9–10% of treated patients. Our experience had been similar, and the incidence of Sb cardiotoxicity among our patients using the Sb from manufacturers B and C was 8%, with 4% mortality. However, the experience with drug from manufacturer A was unique, since each of the first eight patients treated had serious and/or fatal cardiac toxicity occurring between day 3 and 28 of Sb therapy. Six patients had the symptoms of congestive heart failure and QTc prolongation, and three patients died as a direct consequence of toxicity.

The Sb manufactured in India has been used for more than two decades. The drug has been found to be safe and of acceptable toxicity, although occasional cardiac toxicity, arthralgia, and elevation of hepatic enzyme levels have been seen. We began using the drug made by manufacturer A for the first time after it was provided to us by the State Government. When the first patient died, we attributed it to the uncommon but recognized cardiotoxicity of Sb. Subsequent clinical events, however, led us to implicate the drug as excessively toxic. Although a cumulative dose of more than 600 mg/kg of Sb has been associated with prolongation of QTc in other studies, our patients developed cardiotoxicity within 30 days and before a cumulative dose of 600 mg/kg of the drug had been given. Specifically, three patients (nos. 1, 3, and 6) developed QTc prolongation, and

![Figure 3. Holter records of patient no. 4 showing episodes of ventricular tachycardia, ventricular premature beats, and prolonged QTc. bpm = beats/min.](image-url)
one (no. 5) developed severe hypotension and shock before a cumulative dose of even 300 mg/kg had been given.

A common explanation for untoward clinical results is that the drug is reanalyzed and found to have an incorrect chemical structure due to manufacturing errors for that lot. The difficulty in using this approach with pentavalent antimonials is that their structures are unknown. Sodium antimony gluconate in the form of sodium stibogluconate appears to be a mixture of structures with molecular masses of 100–4,000. Nevertheless, determination of drug osmolarity may distinguish correct drug lots from incorrect ones. For both sodium stibogluconate and meglumine antimonate, lots with ineffective antileishmanial activity had higher osmolarities than clinically effective ones. For sodium stibogluconate, while effective lots had osmolarities between 723 and 857 mOsm/L, an ineffective lot had an osmolarity of 2,988 mOsm/L. However, antimonic acid (hydrated antimonic acid, and gluconate would theoretically have an osmolarity of 2,988 mOsm/L. However, antimonic acid (hydrated antimonic acid, sodium, and gluconate would theoretically have an osmolarity of 842 mOsm/L and an ineffective lot had an osmolarity of 1,241 mOsm/L. In the present report, documented toxicity of a clinical antimonial was associated with a relatively high osmolarity. The Al lot, when administered at the customary recommended dosage in India, resulted in severe cardiotoxicity and/or death in each of eight patients, and had an osmolarity more than 300 mOsm/L higher than lots without excessive toxicity. Elevated osmolarity reflects an increased concentration of particles, and thus will reflect both the concentration of the drug and its state of aggregation. The osmolarity of the drug lots with expected performance was somewhat higher than values observed previously for clinically effective lots, but this may be explained by a higher antimony content. While the implicated lots in this study had higher osmolarity than the effective lots, they had comparable antimony contents, implying some other cause for the increase in their osmolarity.

The antimony content of lot Al drug is equivalent to 996 mmol/L of antimony. Since properly formulated sodium stibogluconate has a 1:1 ratio of antimony to sodium gluconate, a completely dissociated mixture of hydrated Sb, sodium, and gluconate would theoretically have an osmolarity of 2,988 mOsm/L. However, antimonionic acid (hydrated antimony pentoxide) has very limited solubility and would precipitate almost completely if it were not solubilized by complex formation with the gluconic acid. A completely dissociated mixture of sodium and stibogluconate ions would still result in a much higher osmolarity than has been observed in any preparation, requiring that there be some aggregation of these particles. Such an aggregation is also necessary to account for the high molecular mass species observed in sodium stibogluconate.

Recent structural studies of meglumine antimonate suggest that it is a mixture of relatively short chains of alternating N-methylglucamine and antimonic acid moieties, with each antimony atom coordinated with four N-methylglucamine hydroxyl groups (Roberts WL, McMurray WJ, Rainey PM, unpublished data). Sodium stibogluconate may contain similar oligomers. Higher osmolarity would then correspond to lower amounts of polymerization and increased amounts of monomer (Sb linked to a single gluconate). The role that the state of polymerization may play in the effects of the drug is not clear. In vitro, the various forms of sodium stibogluconate have equal potency for a given antimony content. However, the state of polymerization may modify the effects on humans by changing the distribution and disposition of Sb .

For both meglumine antimonate and sodium stibogluconate, the extent of polymerization appears to be in a labile equilibrium, decreasing as drug concentration decreases, possibly through simple mass action effects (Roberts WL and others, unpublished data). This provides a basis for the recommendation that pentavalent antimonials be administered undiluted. It also implies that the extent of polymerization and thus osmolality will be reproducibly determined by antimony concentration in consistently prepared lots. Higher than expected osmolarity may serve as a nonspecific indicator of a problem in formulation (e.g., incorrect antimony to gluconate ratio).

The presence of trivalent antimony in a preparation could also result in increased osmolarity, since gluconate can form fewer linkages with trivalent than pentavalent antimony. Trivalent antimony is considerably more toxic than pentavalent; indeed, pentavalent antimonials were developed to reduce the toxicity associated with trivalent antimony parasiticides. It has been reported that pentavalent antimonials frequently include some trivalent antimony. Unfortunately, selective measurement of trivalent antimony in the presence of pentavalent antimony is extremely difficult.

Whatever the basis, it appears that the simple technique of measuring the osmolarity may identify inappropriately manufactured pentavalent antimonials. This possibility should be verified by analysis of other clinically unacceptable lots, when they are encountered. There has been speculation on the mechanism of fatal Sb cardiotoxicity. In our patients, we recorded electrophysiologic events occurring after QTc prolongation that resulted in cardiac arrest or death. In one patient (no. 3), prolonged QTc predisposed her to multiple ventricular ectopics with torsade de pointes that culminated in ventricular tachycardia and fibrillation. The latter event could not be recorded, but was observed on the monitor. In another patient (no. 4) who had prolonged QTc and had three episodes of cardiac arrest and ventricular fibrillation, Holter monitoring revealed multiple ventricular ectopics and intermittent ventricular tachycardia, confirming the likely sequence of events of Sb cardiotoxicity. The first dangerous sign was prolonged QTc, leading to multiple ventricular ectopics, then ventricular tachycardia, torsade de pointes, ventricular fibrillation, and potentially death. There is also a danger of these events occurring several days after the offending drug has been withdrawn, as was seen in some of our patients. Although cardiotoxicity in our patients resulted from an apparent bad lot of drug, sporadic occurrences of Sb cardiotoxicity might also involve a similar progression of electrophysiologic events.

Lot-to-lot variations are known to occur with the manufacture of Sb preparations, and manufacturers should monitor various physical and chemical parameters, as well as clinical experience indicating efficacy and toxicity. One should be careful regarding the use of Sb , since cardiotoxicity is always possible, even with good batches of drug. It is advisable to obtain the drug from manufacturers with which one has accumulated considerable experience, particularly if it is likely to be used in situations where medical
facilities are minimal and basic equipment such as an electrocardiogram may not be available.

Editor's comment: The Journal is aware that the identity of the three manufacturers of the sodium antimony gluconate used in this study has not been revealed. For further information, please contact the senior author (Shyam Sundar): Phone # 011-91-542-310-895, Fax # 011-91-542-310-092, e-mail: shyam/varanasi@dartmail.dartnet.com.

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