Amiodarone-induced Fatal Acute Liver Injury in COVID-19
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Abstract
Background: Amiodarone is a commonly used anti-arrhythmic drug. Acute liver damage after intravenous administration is rare but can be associated with dramatic rise in hepatic transaminases. We describe a patient with laboratory-confirmed COVID-19 disease who developed fatal acute liver damage with multiorgan dysfunction following intravenous amiodarone. Case Report: A 63-year-old diabetic male was admitted with symptomatic COVID-19 disease. He was stable upon admission. However, his condition worsened and needed respiratory support in intensive care. As a likely consequence of his illness, he developed atrial fibrillation with fast ventricular rate. He was given intravenous amiodarone (300 mg loading dose followed by 900 mg over 24 hours). This was associated with a sudden and dramatic rise in serum transaminases. The amiodarone infusion was stopped and he was given intravenous N-acetylcysteine. However, he developed multiorgan dysfunction and succumbed to the illness. Conclusion: Acute hepatic injury is a rare, potentially fatal, adverse effect of intravenous amiodarone. Physicians need to carefully monitor hepatic function during the amiodarone infusion.

Keywords: Acetylcysteine, Amiodarone, COVID-19, Critical Care, Liver Function Tests.

Introduction
Significant arrhythmias have been widely reported in COVID-19 disease. Amiodarone is a class III anti-arrhythmic agent that offers an effective treatment in atrial and ventricular arrhythmias [1]. Although highly effective, clinicians are often wary of serious adverse effects. Commonly reported adverse effects after oral administration include thyroid dysfunction, corneal microdeposits, hepatic dysfunction and lung fibrosis [2]. However intravenous amiodarone has been reported to cause injection site reactions, diaphoresis, flushing, bradycardia, atrioventricular blocks and hypotension [2]. Acute hepatotoxicity is rare and ranges from mild asymptomatic increase in transaminases to fulminant hepatic failure [3]. Hence, we report a rare case where intravenous amiodarone caused acute liver failure associated with multiorgan dysfunction that proved fatal.

Case Report
A 63-year-old male, known diabetic on insulin, was admitted to our center after he tested positive for SARS-COV-2 disease. He complained of shortness of breath, but no fever or cough. On admission, he was alert and conscious, but tachypneic, needing high flow oxygen to maintain oxygen saturations. He was afebrile, blood pressure 145/72 mmHg and pulse 83/minute, regular. He had bilateral lung crepitations with normal cardiac examination. Baseline laboratory tests showed hemoglobin 13.7 g/dL, white cell count 11.3×10^3/µL, platelet 197×10^3/µL, absolute lymphocyte 0.44×10^3/mL, INR (international normalized ratio) 1.1, D-dimer 12.2 mg/L, creatinine 106 µmol/L, potassium 4.6 mmol/L, bilirubin 6.9 µmol/L, alanine transaminase (ALT) 21 IU/L, aspartate transaminase (AST) 61 IU/L, alkaline phosphatase (ALP) 96 IU/L. Inflammatory markers showed
ferritin 1,456 µg/L, lactate dehydrogenase 587 IU/L, procalcitonin 0.05 µg/L, C-reactive protein 117.5 mg/L and interleukin-6 level 79.7 pg/mL. HIV and hepatitis B and C serology were negative. His chest radiography showed bilateral airspace consolidations. However, the same night of admission, he developed chest pains with new ECG changes of ST-segment depression in leads I and aVL. He was diagnosed as non-ST-elevation myocardial infarction. High-sensitivity troponin-I was raised at 29,000 ng/L. He was transferred to the intensive care unit and immediately commenced on anti-ischemic treatment. Echocardiography showed mildly impaired left ventricular wall motion with inferolateral and distal anteroseptal hypokinesia, left ventricular ejection fraction 50%.

His coronavirus disease-2019 (COVID-19) disease was managed by the intensive care physicians. However, his condition deteriorated and developed acute respiratory distress syndrome, and was subsequently intubated and ventilated on day 3. He also developed septic shock and commenced on intravenous norepinephrine infusion. He then remained relatively stable until day 13, when he suddenly deteriorated and developed atrial fibrillation with fast ventricular rate in the early hours of the morning. He was given intravenous amiodarone as an anti-arrhythmic agent. The infusion was prepared by mixing 300 mg of amiodarone in 100 ml of 5% dextrose and infused over 1 hour. This was followed by further continuous infusion of 900 mg amiodarone over 24 hours. Repeat laboratory tests done next morning (4 hours after starting intravenous amiodarone) showed a sudden rise in ALT (from 35 to 3,532 IU/L), AST (from 24 to 6,460 IU/L) and total bilirubin (from 8.8 to 27.6 µmol/L). The amiodarone was immediately discontinued. Associated findings included a rise in INR (from 1.2 to 2.9), D-dimers (from 1.8 to 6.9 mg/L), creatinine (from 91 to 143 mmol/L), ferritin (from 1,984 to 30,448 µg/L), procalcitonin (from 0.45 to 4.2 µg/L). Table 1 and Fig.1 show the trend of laboratory results in relation to the amiodarone administration.

Table 1: Trend of laboratory tests during admission related to intravenous amiodarone administration.

| Test                 | D1    | D2    | D3    | D4    | D5    | D6    | D7    | D8    | D9    | D10   | D11   | D12   | D13   | D14   |
|----------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| ALT (16-63 IU/L)     | 21    | 44    | 53    | 61    | 72    | 68    | 57    | 48    | 59    | 39    | 41    | 35    | 3532  | 3933  |
| AST (15-37 IU/L)     | 61    | 146   | 87    | 49    | 35    | 35    | 29    | 27    | 23    | 24    | 25    | 24    | 6460  | 7450  |
| ALP (46-116 IU/L)    | 96    | 135   | 215   | 275   | 200   | 195   | 179   | 177   | 234   | 192   | 242   | 215   | 399   | 411   |
| Total bilirubin (3-19 µmol/L) | 6.9 | 6.8  | 5.6   | 9.1   | 4.9   | 7.9   | 6.4   | 4.2   | 4.4   | 3.7   | 9.9   | 8.8   | 27.6  | 32.7  |
| INR (0.8-1.29)       | 1.1   | 1.2   | 1.2   | 1.2   | 1.2   | 1.2   | 1.2   | 1.2   | 1.1   | 1.1   | 1.1   | 1.2   | 2.9   | 3.1   |
| PT (9.8-12.1 sec)    | 12.8  | 13.3  | 13.5  | 13.5  | 13.5  | 13.3  | 13.2  | 13.3  | 12.7  | 13.1  | 12.9  | 13.7  | 13.9  | 32.1  |
| PTT (26.4-37.5 sec)  | 36.1  | 36.5  | 36.5  | 43.5  | 43    | 35.7  | 37.7  | 41.5  | 43.9  | 41.1  | 43    |       |       |       |
| Creatinine (71-115 µmol/L) | 106 | 104  | 93    | 113   | 115   | 123   | 115   | 96    | 98    | 75    | 64    | 91    | 143   | 248   |
| D-dimer (<0.55 mg/L) | 12.2  | 3.4   | 3.9   | 3.9   | 2     | 1.6   | 1.3   | 1.5   | 1.7   | 1.2   | 1.7   | 2.2   | 1.8   | 6.9   |
| Ferritin (26-388 µg/L) | 1456 | 1349  | 873   | 912   | 993   | 1475  | 650   | 661   | 771   | 668   | 905   | 1984  | 30448 | 32450 |
| CRP (0-3 mg/L)       | 117.5 | 94    | 59    | 188   | 158   | 89    | 44    | 38    | 140   | 140   | 267   | 373   | 306   | 310   |

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Considering the likely diagnosis of amiodarone-induced acute liver injury, in addition to stopping the amiodarone infusion, intravenous N-acetylcysteine (NAC) was given (5 gm in 200 ml normal saline). Regarding the atrial fibrillation, electrical cardioversion with 100 joule shock was attempted that was unsuccessful. Hemodialysis was started due to acute renal failure. However, the patient developed multiorgan failure and had cardiac arrest 12 hours later and succumbed.

Discussion

Acute organ toxicity after intravenous amiodarone use is rarely reported, where the majority of literature reports acute liver injury. We report a rare case where a patient with critical COVID-19 disease developed sudden and dramatic rise in serum transaminases after intravenous amiodarone that was accompanied by sudden rise in coagulation and inflammatory markers, and decline in renal functions, that proved fatal. Intravenous amiodarone has low aqueous solubility and hence needs to be dissolved in a solvent [4]. The solvent contains polysorbate 80 and benzyl alcohol. Although the exact mechanism of hepatic injury with intravenous amiodarone is unclear, polysorbate 80 in the solvent of the intravenous preparation is proposed to cause hepatic injury. This observation was first reported by Rhodes et al. [5] and suggested a change in the solvent.

Hashmi et al. [6] studied 1510 patients who received intravenous amiodarone and identified elevated transaminases and its relation to all-cause 30-day mortality. 5% developed high liver enzymes, while 15% had >1000 IU/L elevation in transaminases with a 30-day mortality of 9%. Huang et al. [7] reported hepatotoxicity in 13% out of 802 patients receiving amiodarone; only 1% had severe transaminitis. Our patient, who was initially admitted due to symptomatic COVID-19 disease, had normal laboratory parameters until day 13 of the illness when he had atrial fibrillation and commenced on intravenous amiodarone [Fig.1]. The amiodarone not only caused sudden rise in transaminases, but also led to raised coagulation parameters as hepatic function worsened. This was associated with sudden elevation in serum ferritin, procalcitonin and C-reactive protein, indicating a worsening of the COVID-19 illness and severe renal impairment. Treatment is mainly supportive after discontinuing amiodarone. However, a recent study has shown benefit of using N-acetylcysteine (NAC) [8]. We treated this patient with NAC but patient did not improve and succumbed to the illness.

Our case is unique as the overall clinical picture raises speculations regarding the role of intravenous amiodarone in organ toxicity in an already sick patient with critical COVID-19 illness. Hence, the case highlights the need to closely monitor liver enzymes after commencing intravenous amiodarone in critical COVID-19 disease.

Conclusion

Acute hepatic injury is a rare, potentially fatal, adverse effect of intravenous amiodarone. Physicians need to carefully monitor hepatic function during the amiodarone infusion.

Contributors: KBN: study design, data analysis, initial draft preparation; MH: study design; KA: data collection and initial draft preparation; MA: data collection, data analysis; AAQ, AAB, OE: data collection and critical inputs into the manuscript. KBN will act as a study guarantor. All authors approved the final version of the manuscript and are responsible for all aspects of the study.

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