Isolated Neutropenia: An Unexplored Side Effect of Amiodarone

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Abstract

Amiodarone has been widely used for the treatment of various arrhythmias. It is a potent P450 inhibitor leading to interaction with many commonly prescribed drugs. Also, due to its long half-life, lipophilicity, and broad tissue distribution, it can cause a wide range of toxicities. A 62-year-old male with the unknown past medical history presented to the emergency department following a grand mal seizure. The patient initially presented with atrial flutter, which was controlled with beta blockers but was switched to amiodarone after 2 weeks when he developed atrial fibrillation with the rapid ventricular response. Approximately 1 month into his hospital stay, the patient developed severe isolated neutropenia. After ruling out other etiologies, amiodarone was withdrawn. The patient's absolute neutrophil count recovered 3 days after discontinuation of amiodarone.

Keywords: Amiodarone; AFib; Isolated neutropenia; Supratherapeutic level; Voriconazole; P450

Introduction

Amiodarone is the most effective antiarrhythmic drug for atrial and ventricular arrhythmias and the drug of choice for ventricular arrhythmias in an unstable patient. Amiodarone has been found to have higher efficacy and lower relapse rates compared to placebo and rate-control medications [1]. Despite its proven effectiveness, amiodarone has not been adopted widely, owing to frequent adverse events. More than 35% of patients on long-term amiodarone discontinue the drug due to adverse effects [2]. Some of the well-documented side effects of amiodarone are thyroid gland dysregulation, pulmonary fibrosis, and acute liver failure [3]. Additional reactions include dermal discoloration, photosensitivity, corneal depositions, and neuropathic changes such as peripheral neuritis, ataxia, tremors, and senso-

ry deficits [4]. Though many review articles have documented the adverse events noted above, few have described severe, potentially fatal, hematological effects. Case reports have described direct bone marrow toxicity causing granulomas and aplastic anemia [5-11].

Furthermore, amiodarone can induce immunological manifestations such as anti-amiodarone antibodies, lupus-like syndrome, immune-mediated thrombocytopenia, Coombs-positive hemolytic anemia (in canines), and vasculitis [12-17]. Many medications have been implicated as causal agents of neutropenia, but only one case has been reported describing isolated neutropenia induced by amiodarone [18]. Herein, the second case of severe isolated neutropenia associated with the administration of amiodarone is discussed.

Case Report

A 62-year-old male with a history of alcohol dependence was brought to the emergency department (ED) after he was witnessed to have grand mal seizure. Before his presentation, he had been incarcerated for 2 days for "driving under the influence (DUI)". Responding medics found him to have an altered mental status, melena, coffee-ground emesis, and severe hypoglycemia with blood glucose of 24 mg/dL. In the ED, the patient was reported to have a temperature of 36 °C, respiratory rate 30/min, a pulse of 138/min, blood pressure (BP) of 62/36 mm Hg, severe acute kidney injury (AKI) with electrolyte derangement (creatinine (CRE):10.45 mg/dL, blood urea nitrogen (BUN): 130 mg/dL), liver injury (aspartate aminotransferase (AST): 173 IU/L, alanine aminotransferase (ALT): 71 IU/L), and thrombocytopenia (platelet (PLT): $10 \times 10^3/\mu L$). An electrocardiogram (EKG) showed a "non-ST segment myocardial infarction (NSTEMI)" and atrial flutter. He was started on a beta-blocker for arrhythmia, broad-spectrum antibiotics (piperacillin/tazobactam and vancomycin), three boluses of D50, and vasopressors to stabilize him. Dialysis was required to manage the AKI.

On day 2, the patient was found to have a mild pleural effusion on chest X-ray and leukocytosis with a left shift (white blood cell (WBC): $30.6 \times 10^3/\mu L$, absolute neutrophil count (ANC): $26 \times 10^3/\mu L$) despite being on antibiotics. Bronchoalveolar lavage was performed. Voriconazole was started after bronchial cultures grew Aspergillus and Candida (day 2: hemoglobin (Hb) 8.27 g/dL, PLT: $19 \times 10^3/\mu L$, AST: 146 IU/L, ALT: 78 IU/L, CRE: 2.96 mg/dL, BUN: 45 mg/dL).
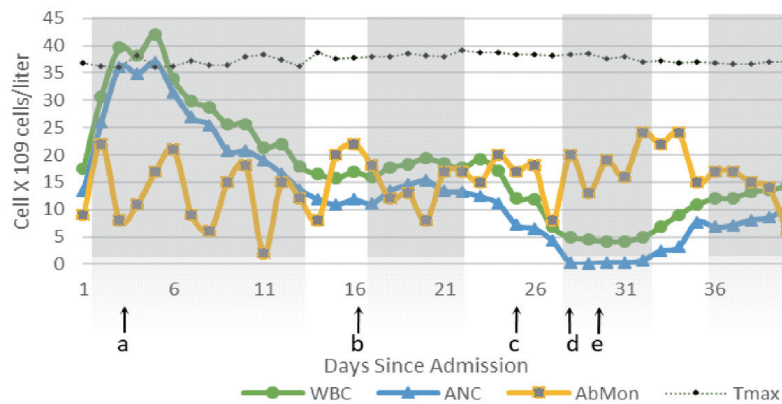
On the 15th day of his admission, the patient became un-

Figure 1. Changes in WBC, AbMon, ANC and temperature max (Tmax) (°C) during 40 days of hospitalization. Shaded gray areas indicate time during which patient was admitted to ICU for different reasons. a: Start of voriconazole; b: Amiodarone started; c: Vancomycin stopped; d: Onset of severe neutropenia; e: Amiodarone discontinued. Absolute monocytes (AbMon) value was multiplied by 10 to achieve a comparable value. Normal reference value of AbMon: 0.2 to 1×10^9 cells/L; adjusted reference AbMon value: 2 to 10×10^9 cells/L. WBC: white blood cell; ANC: absolute neutrophil count; ICU: intensive care unit.

stable and hypoxic (partial pressure of oxygen (PO_2): 59 mm Hg, oxygen saturation level (SaO_2): 89%, partial pressure of carbon dioxide (PCO_2): 37 mm Hg) after developing atrial fibrillation with a rapid ventricular response, he was intubated, and the beta-blocker was changed to amiodarone. Before initiating amiodarone, the patient's blood work was as follow: Hb: 7.7 g/dL, WBC: $17 \times 10^3/\mu L$, PLT: $470 \times 10^3/\mu L$, ANC: $13.9 \times 10^3/\mu L$, absolute lymphocytes (ALym): $0.9 \times 10^3/\mu L$, AST: 23 IU/L, ALT: 15 IU/L, CRE: 9.21 mg/dL, BUN: 70 mg/dL. The WBC count improved after 72 h. The patient was extubated and transferred to a regular floor bed (Fig. 1).

After starting amiodarone, the patient developed frequent unexplained fevers. Fevers lasted for a short period and resolved with antipyretics. Since the fevers were not continuous, lasted short periods with no obvious cause, they were attributed to be drug-induced fevers. On day 26th, 11 days after starting amiodarone, the patient again became hemodynamically unstable and was quickly stabilized. On day 29th, daily blood report revealed Hb: 7.4 g/dL, WBC: $5.6 \times 10^3/\mu L$, PLT: $378 \times 10^3/\mu L$, ANC: $0.1 \times 10^3/\mu L$, ALym: $2.5 \times 10^3/\mu L$, absolute eosinophil (AEos): $0.2 \times 10^3/\mu L$, absolute basophil (ABas): $0.6 \times 10^3/\mu L$, AST: 15 IU/L, ALT: 4 IU/L, BUN: 18 mg/dL, and CRE 6.66 mg/dL. Human immunodeficiency virus (HIV), hepatitis A, B and C, Epstein-Barr virus (EBV), influenza, parvovirus B19, and herpes simplex virus 6 (HSV6) were ruled out. Blood cultures for bacterial and fungal infections were negative. Malnutrition as a cause of neutropenia was not evident. Since the patient was receiving multiple medications, drug-induced neutropenia (DIN) was suspected. Piperacillin/tazobactam, vancomycin, and amiodarone were the only medications that had been started within 2 weeks of the onset of neutropenia. Piperacillin/tazobactam and vancomycin had been discontinued 2 days before the onset of presumptive acute DIN. Based on the literature review, amiodarone was determined as a cause. The serum amiodarone level was found to be a supratherapeutic level at 4.57 μg/mL. Thus, amiodarone was discontinued, and the patient was monitored closely. Within 1 week of discontinuation

of amiodarone, WBC and ANC had fully recovered to $12.3 \times 10^3/\mu L$ and $7.6 \times 10^3/\mu L$, respectively (Fig. 1).

Discussion

Acute DIN is a reduction in absolute neutrophil count due to drugs. DIN is caused by decreased production or increased destruction of neutrophils. The American Academy of Allergy, Asthma, and Immunology defines neutropenia as mild (ANC: 1,500 to 1,000/μL), moderate (ANC: 1,000 to 500/μL), and severe (ANC: < 500/μL). The prevalence of DIN is 8.9 and 7.2 cases per million every year in the USA and Europe, respectively [19-21]. Even though mortality rates have decreased from 10-16% 25 years ago to less than 5%, in the current era, severe neutropenia can lead to significant morbidity and death. Despite improvements in the management of agranulocytosis, protracted neutropenia still carries a risk of mortality of 9.3% and significant morbidity of > 21.4% [22-24]. Economically, each episode of neutropenia can lead to an average hospital stay of 10 days, costing upwards of $19,000 per episode and yearly more than $1.09 billion overall in the USA alone [22]. Keeping these statistics in mind, early detection, and intervention to patients with DIN become essential goals.

Neutropenia can also be categorized according to chronological features: acute (transient) and chronic. An ANC of < 1,500/μL for more than 3 months is considered chronic neutropenia. Nutritional deficiency of vitamin B12, folate, thiamine, and copper can lead to chronic neutropenia or agranulocytosis [25, 26]. Though a decrease in ANC due to a nutritional deficiency is chronic in nature, considering the patient's extensive history of alcohol abuse, malnutrition was ruled out by monitoring levels of vitamins, proteins, and essential metals. Additionally, the patient was adequately nourished throughout his 28-day stay at the hospital before the onset of neutropenia.

Infections and drugs are leading causes of acute onset of neutropenia. Microorganisms such as viruses (hepatitis A, B, C; HIV, EBV, HSV6, cytomegalovirus (CMV), *Pneumocystis*

carinii pneumonia (PCP)), bacteria (typhoid fever, Shigella enteritis, brucellosis, tularemia, rickettsia, tuberculosis), and parasites (*Leishmania donovani* and malaria) can cause neutropenia in susceptible individuals [27-31]. At the time of onset of neutropenia, the patient was also being treated for pulmonary *Aspergillus*, and his chest X-ray was also improving. A detailed viral panel did not reveal any pathogens in the patient. Additionally, multiple blood samples were cultured during the severe neutropenia period, and no bacterial or fungal growth was observed.

After ruling out ongoing infectious causes, possible DIN was considered. Though many drugs can lead to neutropenia, among administered medications to the patient, piperacillin/tazobactam, vancomycin, and amiodarone were suspects. However, piperacillin/tazobactam and vancomycin had been discontinued 2 days before the onset of neutropenia. Furthermore, piperacillin/tazobactam was restarted 72 h after discontinuation as prophylaxis for neutropenia and was continued during the ANC recovery period (day 28 - 35).

Even though amiodarone can lead to autoimmune events, the time of onset, the serum concentration, and a quick recovery from neutropenia suggested more direct mechanisms at work [13, 17]. In addition, studies have shown how amiodarone utilizes various mechanisms to cause direct cytotoxic effects in multiple tissues [32-35].

Amiodarone has a unique structure that allows it to form free radicals in a high oxidative environment [36-39]. Radical formation potentially explains why amiodarone most commonly damages highly oxidative environments such as lung, liver, and thyroid [40]. Neutrophils have an abundant reservoir of myeloperoxidase (MPO), which can nonspecifically oxidize amiodarone to produce aryl radicals [41]. Free radicals cause deoxyribonucleic acid (DNA) breakage, mitochondrial damage, and lipidosis giving rise to multilamellar lysosomal inclusions, which can lead to changes in morphology and function of neutrophils [36, 42]. Due to its amphiphilic structure, amiodarone and its metabolites have wide tissue distribution. In a short period, amiodarone can reach 150 times higher concentrations in leukocytes than in plasma [43]. Additionally, our patient was concurrently receiving voriconazole, which inhibits cytochrome P450, decreases clearance, and raises the systemic concentration of amiodarone and its metabolites, further enhancing toxicity [44]. This interaction leads to an increase of amiodarone serum concentration, which was twice the upper limit of normal.

Conclusions

During his 35-day stay, even though the patient was intubated twice, resuscitated multiple times, required vasopressors frequently, and had numerous comorbidities, pieces of evidence point towards amiodarone as the cause of neutropenia. Besides isolated neutropenia, amiodarone can cause various life-threatening hematologic conditions. Furthermore, amiodarone treatment guidelines focus primarily on monitoring lung, liver, and thyroid function. Individuals such as those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, polypharmacy, malnourishment, or chronic alcoholism, who are especially susceptible to oxidative damages, may be more prone to amiodarone toxicity. Thus, monitoring hematologic changes becomes an essential component of at-risk patients' care.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Informed Consent

Not applicable.

Author Contributions

HP gathered and organized the data related to the case study. HP and DP wrote and edited the manuscript.

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