International Journal of Advances in Medicine
Purnesh BV et al. Int J Adv Med. 2023 Jan;10(1):105-107
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20223411

Case Report

Isolated neutropenia: an unexplored side effect of amiodarone

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Received: 05 December 2022
Revised: 20 December 2022
Accepted: 21 December 2022

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ABSTRACT

Amiodarone has long been used to treat a variety of arrhythmias. It's a strong P450 inhibitor, which means it'll interact with many widely given medications. Unfortunately, it can also produce a wide spectrum of toxicities due to lengthy half-life, immunophilicity, and widespread tissue distribution. Neutropenia associated with mechanistic target of rapamycin (mTOR) inhibitors can be improved by avoiding other medications that cause cytopenias, including proton pump inhibitors (PPIs), H_2 blockers and the sulpha group of drugs. A 62-year-old presented in disoriented state and had one episode of involuntary jerky movements. The patient went into atrial fibrillation, was intubated and changed the drug to amiodarone. Before the initiation of amiodarone patient's blood work seemed to be normal. After 10 days of amiodarone, his hemodynamic status was deranged, and he recovered. Neutropenia is present constantly and reduced to normal only after discontinuation of amiodarone.

Keywords: Amiodarone, Neutropenia, Therapeutic level, Vonconazole, P450

INTRODUCTION

Amiodarone is the most effective antiarrhythmic medicine for atrial and ventricular arrhythmias. It is also the drug of choice for ventricular arrhythmias in unstable patients. Compared with rate-control drugs and placebo, amiodarone has been reported to have the most efficacy and reduce relapse rate.[1] Despite its efficiency, amiodarone has not been extensively embraced due to a high rate of side effects. More than thirty-five percent of people taking long-term amiodarone stop taking it because of side symptoms. Lung fibrosis, thyroid gland dysregulation and abrupt liver failure are some of the well-documented adverse effects of amiodarone. Photosensitivity, dermal discolouration, corneal deposition, and neuropathic alterations such as peripheral neuritis, ataxia, tremors, and sensory impairments are all possible side effects.[2] Although several review studies have recorded the side mentioned above events, few have detailed severe, perhaps deadly haematological consequences. Direct bone marrow poisoning generating granulomas and aplastic anaemia have been described in a case report. Anti-amiodarone antibodies, immune-mediated thrombocytopenia, lupus-like syndrome, Coombs-positive hemolytic anaemia (in dogs), and vasculitis are all immunological symptoms of amiodarone.[4] Many drugs have been identified as causes of neutropenia, but just one isolated neutropenia caused by amiodarone has been recorded. Severe isolated neutropenia associated with amiodarone therapy is discussed here.

CASE REPORT

A 62-year-old male came to the emergency department in a disoriented state and had one episode of involuntary jerky movements. The patient complained of melena and coffee-coloured vomitus, and his sugars were found to be 26 mg/dl. No similar complaints in the past, and the patient was under the influence of alcohol for the last two days. Vitals blood pressure (BP): 62/36 mmHg, pulse rate (PR):138 bpm, and respiratory rate (RR): 30/min.

Electrocardiography (ECG) was taken and showed non-ST segment myocardial infarction and atrial flutter. The patient is treated with supportive treatment - D50 of three bolus, antibiotics and beta blockers. Creatinine -10.45, blood urea nitrogen (BUN) -130, and hence dialysis was required for managing acute kidney injury (AKI). The next day cultures were taken, and growth of aspergillus and candida was present. Voriconazole is started for further management. A chest X-ray was taken and showed mild pleural effusion with left shift. The patient went into atrial fibrillation, was intubated and changed the drug to amiodarone. Before the initiation of amiodarone patient's blood work seemed to be normal. After 10 days of amiodarone, his hemodynamic status was deranged, and he recovered. Fever also occurred after initiation of amiodarone and got relieved with antipyretics. Neutropenia is present constantly and reduced to normal only after discontinuation of amiodarone. Other possible causes were ruled out, and amiodarone was finally determined as a cause. The serum amiodarone level was way too high for its therapeutic level at 4.57 µg/ml. Thus, amiodarone was stopped, and the patient was closely monitored.

DISCUSSION

Acute DIN is a drug-induced decrease in absolute neutrophil count. DIN is due to a decrease in neutrophil production or an increase in neutrophil destruction. Neutropenia is classified as mild (ANC: 1,500 to 1,000/ul), moderate (ANC: 1,000 to 500/ul), or severe (ANC: 500/ul) by the American Academy of Allergy, Asthma, and Immunology. DIN is found in 7.2 and 8.9 instances per million in the United States and Europe, respectively.[5] Even though the mortality rate has been reduced from ten to sixteen percent to less than 5% in the last twenty-five years, severe neutropenia can still cause huge morbidity and death today. Despite advances in the treatment of agranulocytosis, persistent neutropenia still has a 9.3% death rate and a substantial morbidity rate of more than 21.4%.[6] From a financial standpoint, every episode of neutropenia will lead to an average hospital stay of ten days. With all these figures in mind, early response and interventions for DIN patients become critical aims. Neutropenia is divided into two types based on its duration: acute (transient) and chronic.

Chronic neutropenia is an ANC of 1,500/ul for more than 3 months. Vitamin B12, folate, thiamine, and copper deficiency can cause persistent or agranulocytosis or neutropenia. Malnutrition can be ruled by watching levels of vitamins, protein, and essential metals, despite a decrease in ANC because nutritional deficiency is chronic. Given the patient's history of alcohol abuse, malnutrition as a cause was ruled out by checking levels of vitamins, proteins, and essential metals. Additionally, before the beginning of neutropenia, the patient was well-nourished throughout his twenty-eight-day stay in the hospital.[7] The most common causes of acute neutropenia include infections and medications. Viruses, hepatitis all types, *Pneumocystis carinii* pneumonia, bacteria like (typhoid, *Shigella enteritis*, brucellosis, tularemia, rickettsia, tuberculosis), and parasites (*Leishmania Donovan* and malaria) can all produce neutropenia. The patient has been a treatment for pulmonary aspergillus with an improving chest X-ray. A comprehensive viral test revealed no infections in the patient. Many blood samples were cultured during the severe neutropenia stage, but no fungal or bacterial growth was found. After excluding the possibility of persistent infectious causes, DIN has been examined.[8] Though several drugs can cause neutropenia, piperacillin, tazobactam, vancomycin, and amiodarone were suspected among the medication given to the patients. Piperacillin tazobactam and vancomycin, on the other hand, had been stopped two days before the development of neutropenia. In addition, piperacillin-tazobactam was reintroduced seventy-two hours after stoppage as neutropenia prophylaxis and was continued in the ANC recovery phase for twenty-eight to thirty-five days.[4] Despite the fact that amiodarone can cause autoimmune reactions, the onset time, serum concentration, and fast improvement from neutropenia showed that more direct mechanisms were at work.

Furthermore, research has demonstrated that amiodarone uses various methods to generate cytotoxic effects in a variety of tissue. Amiodarone has a different structure which permits an oxidative environment to produce free radicals. Amiodarone's ability to harm highly oxidative areas such as the lungs, liver, and thyroid could be explained by radical generation.[5] Myeloperoxidase (MPO) is prevalent in neutrophils and can nonspecifically oxidize to create aryl radicals. Free radicals may cause breakage of DNA, and damage mitochondria and lipidosis, resulting in multilamellar lysosomal inclusion, which can alter neutrophil shape and function. Amiodarone and its metabolite have broad tissue distribution due to its amphiphilic nature. Amiodarone can achieve fifty times the high concentration in leukocytes than in plasma in a short period.[6] In addition, our patient was taking voriconazole, which inhibits cytochrome P450, reduces the clearance and raises the systemic level of amiodarone and its metabolite, resulting in increased toxicity. An amiodarone serum concentration is twice the upper limit due to this interaction.

CONCLUSION

Although the patient has been intubated twice, revived by many cycles, had repeated vasopressor, and had numerous comorbidities throughout his 35-day stay, evidence points to amiodarone only cause of neutropenia. However, amiodarone can produce a range of potentially catastrophic hematologic problems in addition to isolated neutropenia. In addition, amiodarone therapy guidelines strongly emphasize monitoring liver, lung, and thyroid function. Individuals with glucose-6-phosphate dehydrogenase impairment, malnutrition, or persistent drunkenness seem more sensitive to amiodarone toxicity.

As a result, looking for haematological change has become crucial in at-risk patients' therapy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Purnesh BV, Periyasamy M, Vinatha MC, Alex J. Isolated neutropenia: an unexplored side effect of amiodarone. Int J Adv Med 2023;10:105-7.