


Acute liver failure after administration of amiodarone

Ostra niewydolność wątroby po podaniu amiodaronu

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Abstract

Amiodarone is an anti-arrhythmic medicine used in the treatment of heart arrhythmias. Due to its long half-life, lipophilic structure, and accumulation in the tissues of the thyroid, liver, lung, cornea and skin, it can cause many adverse effects. Acute liver failure is a rare complication following the administration of amiodarone. Several dozen cases of acute liver failure after administration of amiodarone have been described. Its mechanism is not yet clearly known. It has been suggested that emulsifier of the intravenous form of the drug (polysorbate 80) could be a reason for the disorder, but it also occurs after oral administration. The diagnosis can be established when amiodarone results in liver failure with encephalopathy and blood coagulation disorders, excluding other hepatotoxic factors. The recommendations for the management of this disease have not yet been established. However, the prognosis is serious because high mortality has been observed.

Key words: amiodarone, adverse effect, acute liver failure, drug-induced liver injury, polysorbate 80

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Introduction

Amiodarone is a class III anti-arrhythmic drug used to treat atrial fibrillation and ventricular arrhythmias [1]. It is an iodine derivative of benzofuran, and its molecule contains two iodine atoms. It is metabolised in the liver by cytochrome P450 isoenzymes, where the dealkylation process takes place and the active metabolite desetyloamiodarone is formed. This causes many interactions with other drugs metabolised by this enzyme, such as H₁ receptor antagonists, warfarin, acenocoumarol, statins, digitalis glycosides, antiarrhythmics (procainamide, disopyramide, phenytoin, and diltiazem), antidepressants (fluoxetine, paroxetine, bupropion), antibiotics from the group of macrolides and ketolides, isoniazid, as well as grapefruit juice and St. John's wort [2]. It is a lipophilic drug that accumulates in the liver,

lungs, thyroid, adipose tissue, skeletal and cardiac muscles, from where it is gradually released. This causes the possibility of side effects originating from various organs, which is associated with the slow elimination of the drug from the body. Its half-life ranges from 30 to 100 days [3].

Epidemiology

Skin reactions associated with hypersensitivity to light and disorders of the gastrointestinal tract are the most common side effects of the drug [3, 4]. About 90–100% of patients have amiodarone microsomes deposited in the cornea, which is usually asymptomatic. Ophthalmologic control is required only in a case of visual disturbance [4]. It can be a cause of optic neuritis on very rare occasions. Hypotension, bradycardia, atrioventricular block and prolongation

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of the QT interval have been observed during intravenous therapy [5]. Thyroid function may be abnormal (hypo- or hyperthyroidism with excess iodine) with long-term oral administration of the drug [4]. Inflammatory or fibrotic lesions in the lungs have also been observed as a side effect of amiodarone [4].

Gastrointestinal symptoms were observed in approximately 30% of patients using amiodarone [6]. These include nausea, vomiting, anorexia, and mainly asymptomatic liver damage, with moderate elevations in aminotransferases. The latter affects 15–50% of patients treated with this drug [6]. Treatment must be discontinued in the case of a two-fold or three-fold increase in the activity of these enzymes [2]. Acute hepatic failure is a rarely described consequence of using the drug, the prevalence of which is estimated to be 1–3% [6]. A case of a patient with acute liver injury after the use of amiodarone was described for the first time in 1986 [7]. Since then, dozens of such case reports have appeared.

Definitions and classifications

There are several definitions of acute hepatic failure (acute liver failure or acute liver injury), and their common feature is rapid, and even fulminant, course of liver dysfunction leading to the development of encephalopathy. This could be due to toxic agents, it could be drug-induced (most commonly paracetamol), but also it may have viral or autoimmune causes particularly in people without previously diagnosed liver dysfunction [8], whereas drug-induced liver injury (DILI) is biochemical liver damage after the use of drugs or herbs [9].

Liver damage can be divided into two main types [10]:

- intrinsic (predictable), usually after using the drug in high doses;
- idiosyncratic (unpredictable), when damage occurs in a small group of patients, regardless of the dose of the drug, and in a way not previously seen in scientific research.

Part of the unpredictable reactions are allergic reactions associated with acquired or congenital hypersensitivity, and the remaining ones are idiosyncratic [11].

Three liver damage types have been calculated according to the point scale (R-ratio) [12]:

$$R = \frac{\text{activity of ALT/ALT} - \text{ULN}}{\text{activity of ALP/ALP} - \text{ULN}}$$

where: ALT – alanine aminotransferase; ULN – upper limit of normal; ALP – alkaline phosphatase, and:

- $R \geq 5$ hepatocellular DILI;
- $R < 2$ cholestatic DILI;
- $2 < R < 5$ mixed DILI

Amiodarone can cause any type of liver damage [9].

Pathogenesis

The mechanism of amiodarone hepatotoxicity has not been explained. However, clinical observations show different pathways after oral and intravenous administration [11]. Damage after oral use is explained by drug deposition in tissues. Amiodarone accumulates in liposomes and causes damage to cellular mitochondria [11]. Acute liver failure after intravenous use of the drug is probably driven by another mechanism, as yet not fully understood. Initially, liver toxicity was not suggested for amiodarone alone, but in conjunction with polysorbate 80, which is used as an emulsifier in medicines, cosmetics and food [13]. It is part of the intravenous form of the drug, and its damaging effect on hepatocytes has been confirmed earlier in cases involving the so-called E-ferol-syndrome [14]. Liver damage with jaundice and renal failure was observed after the use of vitamin E preparations containing polysorbate 80 and polysorbate 20 in neonates [14]. However, cases of acute liver damage following intravenous administration of amiodarone containing no preservative have also been reported [15]. Beuer et al. [16] hypothesised that an autoimmune mechanism of post-amiodarone liver damage is possible. However, it was not the subject of further research. In 2011, Gluck et al. [17] questioned the occurrence of acute hepatic failure after administration of amiodarone. The authors hypothesised that the cause of liver damage in its use is hypoxia caused by hypotonia or shock (so-called ischaemic hepatitis) [17]. This mechanism is most often related to older people (> 70 years of age) and to haemodynamically unstable patients caused by arrhythmias.

It is therefore difficult to identify one mechanism responsible for the development of acute liver damage when using amiodarone.

According to a literature review by Nasser [18], the development of acute hepatic failure occurs most frequently over a period of several dozen hours (about 1–6 days) after the administration of a multiple of the standard daily doses of the drug (about 900 mg/day). The lowest dose after which liver damage has been observed was 200–600 mg per day [18].

Diagnosis

Diagnosis of post-amiodarone acute liver injury requires the finding of acute failure of this organ and the exclusion of other causes. An important role is played by the history and clinical symptoms [9].

Clinical presentation

The course of the disease is dominated by symptoms of liver damage, such as jaundice, nausea and vomiting, as

well as disturbances of consciousness typical of hepatic encephalopathy (from slowness of movement to hepatic coma) [18, 19]. There are also symptoms associated with enlargement of the liver in the course of its damage, or venous stasis caused by heart failure, with a typical hepatojugular reflux [18]. Due to the cause of the drug's administration, cardiac arrhythmias and symptoms of heart failure, pulmonary oedema, peripheral oedema as well as abnormal blood pressure values (mainly hypotonia) have been observed [17, 18]. Hepatic insufficiency is often accompanied by kidney damage with oliguria or anuria [19].

Diagnostic tests

Laboratory tests usually show increased activity of aminotransferases (alanine and aspartate), increases in bilirubin, ammonia and lactates, prolongation of prothrombin time with INR increase, thrombocytopenia, hypoproteinemia and hypoglycaemia, as well as kidney damage presenting as an increase in creatinine and urea [15–20]. In patients with the cholestatic mechanism of liver damage, an increase in gamma-glutamyltransferase and alkaline phosphatase activity is also observed. It is recommended to exclude viral infections (hepatitis A, B and C virus, Epstein-Barr virus, cytomegalovirus) and autoimmune diseases of the liver and lesions of the type of vasculitis [20]. It is recommended to perform toxicological and microbiological tests.

The serum concentration of amiodarone and its metabolite desethylamiodarone can be measured [21]. However, no correlation has been found between increased blood levels of the drug and organ damage, because it is related to the metabolism of the drug and its tissue deposition [22]. The subject of the analysis is the relationship between the concentration of drug and its metabolites in the blood and thyroid damage [21]. However, there is no data showing the link between liver damage and the concentration of the drug in the blood. It may be helpful to determine the concentration of the drug or its metabolite in tissues [23]. Tsuda et al. [22] reported a case in which, after discontinuation of amiodarone, a correlation was observed between the decrease in drug concentration and the decrease in transaminase activity, with a noticeable improvement in imaging and histopathological findings.

Imaging diagnostics

In cases of cytotoxic liver damage, the American College of Gastroenterology [9] recommends imaging examinations after laboratory tests for viral and autoimmune diseases. In cases of cholestatic mechanism, the diagnostic pathway should be started with imaging examinations [ultrasound, computed tomography (CT) or endoscopic retrograde cholangiopancreatography (ERCP)]. In the analysed cases of liver damage after administration of amiodarone,

commonly used liver Doppler ultrasound often does not reveal any abnormalities [7, 13, 16, 20]. The enlargement of the liver in the course of peripheral circulation arrest has been repeatedly reported [14, 18]. In the course of ischaemic hepatitis, there are no changes in the liver in the ultrasound images [18]. There are more and more reports showing a characteristic picture in computed tomography of changes in hepatic liver damage [22–24]. The dominant picture is diffuse elevated radiodensity of the liver parenchyma [22]. This is related to the accumulation of a drug containing iodine in the liver [2, 23]. In the studies, the discontinuation of the drug causes a noticeable gradual decrease in the densities [23, 24]. In cases of organ biopsy, a CT picture correlated with the histopathological evaluation [22]. In the literature, there is no case of magnetic resonance imaging, positron emission tomography with CT or ERCP being performed for liver injury after the administration of amiodarone.

Histopathology

In the majority of reported post-amiodarone liver damage cases, no liver biopsy was performed. Histopathological examinations carried out after the death of the patient caused by acute hepatic injury revealed hepatonecrosis, indicating a toxic or ischaemic process [7, 19, 25]. Among patients after intravenous administration of the drug, even small doses, and a history of fast-developing jaundice, hepatonecrosis and fibrosis of the organ were observed in post-mortem liver samples [25]. Two very characteristic histopathological images of liver damage are steatosis [25] and phospholipidosis [26]. The characteristics of steatosis are comparable to the changes observed in alcohol abuse with Mallory bodies and neutrophilic infiltration [25]. Occasionally liver cirrhosis with regenerative nodules and developed fibrosis have been observed [22]. In phospholipidosis, lysosomal fat accumulation has been observed in the electron microscope due to the accumulation of amiodarone in hepatocytes lysosomes, and due to the blockage of enzymes that should remove lysosomal lipids [22, 26].

Treatment

There are no treatment guidelines because of the low prevalence. The base of the treatment is amiodarone discontinuation, patient monitoring in conditions of intensive supervision or intensive care, fluids, intestinal or parenteral feeding, and the prophylactic use of proton-pump inhibitors and pressure amines if necessary [15, 19, 27, 28]. In patients with acute renal failure, renal replacement therapy has been successfully used [28]. It is also recommended to correct the coagulation disorder using vitamin K or the transfusion of fresh frozen plasma [27]. Recently, the beneficial effects of N-acetylcysteine

administration has been reported [15, 29]. The drug was used in the scheme recommended for the treatment of poisoning with paracetamol, *i.e.* 300 mg/kg in divided doses over 24 hours [30].

The continuity of anti-arrhythmic therapy is an important issue. In most of the described patients, amiodarone was not re-applied, rather a switch was made to other antiarrhythmic drugs, most commonly beta-blockers, digoxin and non-dihydropyridine calcium channel antagonists [31, 32]. For the primary prevention of sudden cardiac death in the course of ventricular arrhythmia, an implantable cardioverter-defibrillator or percutaneous ablation should be considered [22].

Attempts have been made to reintroduce the drug after normalisation of liver function (so-called re-challenge test). Even after switching to the oral form of the drug, a renewed increase in aminotransferases has been observed [18]. There have also been reports of cases in which liver damage following intravenous amiodarone treatment has not been followed by worsening of liver function after oral treatment [13, 31, 32]. This supports the hypothesis that liver failure is influenced by factors other than amiodarone, *e.g.* polysorbate 80.

Prognosis

High mortality in the course of acute hepatic failure resulting from the use of amiodarone is well-documented in the literature [15, 18, 19]. However, it is impossible to precisely define mortality, as many cases remain unrecognised. A poor prognosis has been observed in cases where liver cell necrosis and organ fibrosis have occurred [25].

Despite the description of cases of acute hepatic failure after oral administration of the drug, it is a safe treatment with adequate control [12]. Diab et al. [33] attempted to determine the risk factors for acute hepatic injury after amiodarone administration. They showed the importance of previous liver damage, circulatory failure, high doses of the drug, hypotension in the course of arrhythmia, and the administration of amiodarone in the postoperative period after surgery including coronary artery bypass grafting. The influence of many other factors studied, such as male gender, hypoalbuminaemia, hyperglycemia, cardiopulmonary resuscitation, and the occurrence of hepatitis has not yet been confirmed [33].

Due to the high mortality, the importance of early diagnosis and the discontinuation of amiodarone must be underlined.

Streszczenie

Amiodaron jest lekiem antyarytmicznym powszechnie stosowanym w terapii zaburzeń rytmu serca. Ze względu na bardzo długi okres półtrwania, lipofilną budowę i gromadzenie w tarczycy, wątrobie, płucach, rogówce i skórze amiodaron może powodować wiele działań niepożądanych. Ostra niewydolność wątroby jest rzadkim powikłaniem po jego podaniu. Opisano zaledwie kilkadziesiąt takich przypadków. Mechanizm uszkodzenia wątroby nie jest jeszcze dobrze poznany. Sugerowano szkodliwy wpływ polisorbatu 80 (konserwantu dożylną formy leku), ale do ostrego zaburzenia funkcji wątroby dochodzi również po doustnym stosowaniu leku. Rozpoznanie jest ustalane, gdy po podaniu amiodaronu rozwija się ostra niewydolność wątroby z encefalopatią i zaburzeniami krzepnięcia krwi, po wykluczeniu udziału innych czynników hepatotoksycznych. Nie opracowano jeszcze zaleceń postępowania w tych przypadkach. Rokowanie jest jednak poważne, gdyż obserwowano wysoką śmiertelność.

Słowa kluczowe: amiodaron, działania niepożądane, ostra niewydolność wątroby, polekowe uszkodzenie wątroby, polisorbate 80

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