

Original Article

REASONS FOR UNJUSTIFIED ADMINISTRATION OF AMIODARONE IN CORONARY CARE UNIT

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Abstract. *Although clinical use of amiodarone is supposedly well-known since the drug has been in use for over fifty years, there have been some concerns that it is often used inappropriately. This paper aims to describe clinical and adverse events observed in patients treated in Coronary Care Unit and to check if the drug was being used in proper indication and dose. Also, the purpose of this survey was to determine whether the medical staff is familiar enough with adverse events and right indications of amiodarone administration. This qualitative study was based on three methods: interview with physicians operating in Coronary Care Unit, insight into patient files and observation of the amiodarone prescription. Five physicians operating in Coronary Care Unit were interviewed and patient files of seven patients have been observed. Amiodarone prescription was observed by making rounds together with physicians. Several problems regarding amiodarone administration have been established. Amiodarone was often diluted in physiological solution instead of 5% glucose solution and it was administered via peripheral vein, not the central one. Physicians are using amiodarone more often than they are supposed to, mainly due to lack of other antiarrhythmic agents. It was also noticed that medical staff do not strictly follow the guidelines for atrial fibrillation treatment, often using amiodarone as the first choice antiarrhythmic. Finally, physicians are not fully familiar with adverse events of amiodarone, especially with acute adverse events. It was concluded that inappropriate use is present in some cases. Thus, physicians should follow guidelines more carefully when prescribing the drug and additional education should be implemented.*

Key words: *antiarrhythmic, atrial fibrillation, inappropriate use, adverse event*

Introduction

Amiodarone is one of the most common drugs used to treat arrhythmias. According to Trappe, Brandts and Weismueller, typical arrhythmias in intensive care patients are atrial fibrillation (AF), atrial flutter, AV-nodal reentry tachycardia with rapid ventricular response, atrial ectopic tachycardia, and pre-excitation syndromes combined with atrial fibrillation or ventricular tachyarrhythmia. Immediate DC-cardioversion in all patients with unstable hemodynamics is indicated, while conversion to sinus rhythm is possible using antiarrhythmic drugs. In their opinion, short-term intravenous administration of amiodarone, as superior antiarrhythmic agent, is absolutely necessary in critically ill patients with recent onset atrial fibrillation [1]. Rhythm control and rate control management strategies are defined for treatment of atrial fibrillation and flutter as the most frequent arrhythmias in emergency department. Amiodarone may be used for both cardioversion and heart rate control [2].

Amiodarone has been developed in 1960s as a coronary vasodilator (with 13-year-long period of investigation [3]), which brings us to conclusion that amiodarone is a drug with long term usage. Amiodarone is currently used as antiarrhythmic agent for treatment of a variety of arrhythmias but there have always been concerns about its side effects. Mild adverse events are often seen in patients treated with amiodarone, but serious life-threatening adverse events are also possible. This is the reason why systematic interdisciplinary follow-up protocol for outpatients treated with amiodarone is necessary [4]. One of the most severe systemic side effects of amiodarone chronic use is pulmonary toxicity which may lead to death. This is the reason why administration of amiodarone in intensive care unit should not last more than 24/48h [5]. Extent and speed of onset of pulmonary damage is linked with severity of amiodarone-introduced pulmonary toxicity [6, 7]. Special care is needed when amiodarone is prescribed because its administration may increase the risk of acute pancreatitis [8]. Thyroid dysfunction, corneal micro deposits, gastrointestinal problems and photosensitivity are also linked with amiodarone use, but this is not relevant to acute intravenous administration in intensive care. If thyroid dysfunction is indicated, collaboration between cardiologist and endocrinologist is mandatory [9]. Due to

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Received December 14th, 2015 / Accepted February 1st, 2016

possibility of intracardiac thrombus formation, conversion of AF should not be attempted 48h after onset without anticoagulation or transesophageal echocardiography [10]. Amiodarone is well tolerated in patients with both normal and impaired left ventricular systolic function [11]. Drug-drug interactions are also observed where the most important are between digoxin and warfarin. When amiodarone is administered with other QT prolonging drugs, especially class IA antiarrhythmics or in the presence of hypokalemia, torsades de pointes mostly occurs [5].

Arrigo, Bettex and Rudiger recommend treatment of AF in intensive care unit setting with substances with a low risk profile and short half-life, such as beta blockers, while amiodarone is indicated in cases of contraindications or inefficacy of the initial treatment. Compared to beta blockers and calcium channel blockers, amiodarone has less negative inotropic effects and is safer for patients with structural heart disease. Long half-life and potential severe side effects are limiting its usage in intensive care unit. It is up to clinician to decide which agent he will use in critically ill patient based on efficiency/risk ratio [12].

According to recent research where amiodarone, as preferential antiarrhythmic drug, was compared with non-amiodarone antiarrhythmic drugs, amiodarone was not supported as a drug of choice in patients with left ventricular hypertrophy [13]. According to Brendorp, Pedersen, Torp-Pedersen, Sahebzadah and Køber, beta-blockers are the first line therapy in patients at high risk of sudden death while amiodarone is favorable only in patients with heart failure [14]. Collected data from the research on adverse effects in randomized placebo-controlled trials has shown that treatment with amiodarone for the prophylaxis of sudden cardiac death has less favorable net clinical benefit. Treatment with amiodarone in this setting should be used only in selected cases [15].

The term unreasonable use of the drug means it is being used beyond the protocol and thus costs of treatment are increasing but without improvement of patient condition or shortening hospitalization period. According to Kosińska and Brandy, amiodarone was potentially inappropriately prescribed in 7.47% of geriatric patients in Poland [16]. Napolitano, Izzo, Di Giuseppe and Angelillo's survey has shown that amiodarone was potentially inappropriately prescribed in 19.1% of cases of elderly patients in Italy with 24.9% of potentially inappropriate doses [17].

Clinical trials with amiodarone have been conducted for many years and will likely continue in the future [18]. Obviously, doubts about administration of amiodarone are present. In this paper, we wanted to provide one more piece of evidence to reduce the dilemma. Research was done, including interviews with physicians from coronary care department and observation of patients. Scientific method was used to reach conclusions with general procedure consisting of six steps: 1- State the problem, 2- Formulate the hypothesis, 3- Design the experiment or survey, 4- Make observations, 5- Interpret the data and 6- Draw conclusions [19].

Material and Methods

This qualitative study was based on three methods: interview with physicians operating in Coronary Care Unit of Cardiology Department, University Hospital Center "Bezanijska Kosa" in Belgrade, Republic of Serbia, insight into patient files and observation of the amiodarone prescription.

Starting from January of 2015th five physicians operating in Coronary Care Unit were interviewed using semi-structured interview. Nineteen questions were asked and anticipated time for conversation was twenty minutes. Before the study, the Head of Cardiology Department and the Director of the Hospital were contacted personally to present the study protocol and to obtain their approval to conduct the survey. Also, the study design and the Head of Department's statement have been submitted to the Ethics and Scientific Committee of the Hospital and their approval was obtained. Interviews were held in person with doctors at beforehand agreed time. Questions were asked from the prepared paper form and answers were recorded by audio device. The paper form was signed by an examinee (*physician*) as consent that interview will be recorded.

Beside interviews with the above-mentioned staff, records of seven patients hospitalized in Coronary Care Unit and prescribed with amiodarone were used as a source of the data. For each patient being studied, the data included age, sex, ethnic affiliation, weight and height of the patient, followed by the history of disease with onset, type of arrhythmia, and other cardiac and non-cardiac illnesses. In addition to this, the patient records included concomitant medication, duration, dose and route of amiodarone administration, adverse reactions (if any) and how they have been solved (by which agent) as well as outcome of the therapy.

Finally, the third part of the study was observation of amiodarone prescription by making ward-rounds together with physicians. The main objective of the third part is to recognize why amiodarone is prescribed, particularly paying attention to indication, dose, route and duration of amiodarone administration.

Results

Interview was conducted with five medical doctors employed by the University Hospital Centre „Bezanijska Kosa“, Department of Coronary Unit, between 28th January and 9th of March 2015. Three participants were female and two were male. Physicians were interviewed by audio recording, using semi-structured interview. Based on the analysis of the interviews, seven categories have been created.

A The patients: Coronary Unit has eleven beds. The Unit treats around a hundred patients per month. One of the interviewed doctors has stressed out that patients with acute coronary syndrome are mostly hospitalized for three days in the Unit. Patients with more serious rhythm abnormalities, ischemic cardiomyopathy with,

for example, non-sustained VT or repeated ventricular tachycardia are hospitalized longer, up to five or six days. All the interviewed medical doctors have noticed that there is a correlation between the dynamic of admission and season, i.e. atmospheric conditions. In winter, the number of admitted patients increases, while in summer the number decreases. Also, in fall and spring, when atmospheric conditions (temperature, humidity ...) change significantly, the number of hospitalized patients is higher. In Coronary Unit the admission of patients is mainly based on the following diagnosis: acute coronary syndrome; patients with ST and non-ST elevated myocardial infarction; supraventricular arrhythmias type tachyarrhythmia absoluta and ventricular rhythm abnormality with heart decompensation symptoms; complications of coronary diseases, in terms of dilative ischemic cardiomyopathy followed by malignant rhythm disorder; lung edema, embolism, state of shock of various etiology. According to Journal of the American College of Cardiology (JACC) guidelines for the management of patients with atrial fibrillation, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated because of its potential toxicities.

B Drug preparation: Amiodarone is mainly diluted in 5% glucose 'even for diabetics, because it is noticed that prepared in such way it reacts protectively on veins due to its negative influence on venous system and development of thrombophlebitis. Very rarely, for diabetics with irregular diabetic condition and with significantly expressed hyperglycemia we are diluting amiodarone in physiological solution.'(4) According to guidelines and summary of drug characteristics, diluting amiodarone in physiological solution is not allowed because amiodarone and physiological solution are incompatible.

C Drug availability and price: All participants point out that the price of amiodarone is not a determining fact in administration especially emphasizing that 'we are using it because we have it.' (2) Also, they stress that 'the choice of antiarrhythmic drugs which you have is something that the management of the institution may afford you, so probably the price of antiarrhythmic drug is in these regards determining, but it is not a determining factor for doctor's selection, doctor will decide and select something which he sees as the best choice for his patient. "(3) However, participants are stressing that there is a problem of availability of other, alternative drugs. "We do not have any other serious antiarrhythmic drugs except amiodarone for parenteral use for such kind of arrhythmias." (5) "Shortage of the wider palette of antiarrhythmics leads us to use amiodarone very often... For supraventricular rhythm disorders, adenosine should absolutely be the first choice, and we use it, but it is limited."(4) "Adenosine we have, but it is very expensive. For supraventricular arrhythmia we are using mainly Isoptine®-verapamil, when we are not using amiodarone. And some drugs such are bretilium and some even better antiarrhythmics for malignant

rhythm disorders we don't have."(5) "Dronedaron we don't have. Or even some other drugs, maybe adenosine, which we should use in my opinion. These are drugs which are not used by routine, they are more expensive and simply we don't have them in Coronary Unit available for the reaction in particular moment." (3) One of the reasons why amiodarone is often used is that the doctors have experience working with it. "We have a lot of positive experience working with it" (3) and because it is comfortable for use. "The majority of the arrhythmias might be treated by amiodarone so its use is the most comfortable in Coronary Unit." (5) In accordance with the above mentioned, the lack of other antiarrhythmics may be a reason for more frequent although unjustified amiodarone administration.

D Administered dose: In Coronary Unit amiodarone is most often administered parenterally, first by bolus and afterwards by infusion. Peripheral vein is used for application, not the central one. "I think that in 90% of cases we are using peripheral vein. Central vein we use very rarely because patients don't require central vein puncture, that's the first reason, and the second is that our patients are very often decompensated, so it is very difficult to lay the patient on a flat, it is very difficult to punctuate the central vein." (5) Furthermore, they consider that "all of our patients simply don't have central vein." (1) Related to administered dose of drug all participants are stressing that "Mainly we are giving to the all patients same dose, minimal one." (1) "We are giving one bolus of hundred and fifty milligrams, which means one ampoule, after that we are applying infusion. We apply infusion beside per os therapy, achieving of the maximum dosage of one thousand and two hundred milligrams amiodarone daily." (4)

In extreme cases, a higher dose of amiodarone is administered "if the patient is extremely overweight and has huge body mass." (5) The duration of amiodarone administration is related to clinical outcome, "referring to ECG." (2) All participants are intended to use amiodarone as shortly as possible, until achieving the desired effects and in order to reduce adverse effects caused by usage of amiodarone. "I rarely keep patient on the therapy with amiodarone in some longer period of time." (5) According to the summary of drug characteristics, amiodarone must be administered through a central vein, except in cases of cardiopulmonary resuscitation in the event of cardiac arrest caused by ventricular fibrillation resistant to external electric shock, when due to inaccessibility of the central vein, peripheral veins can be used.

E Systemic side effects: Participants have pointed out systemic side effects which they have noticed in the Coronary Unit, as well as procedure during the occurring such side effects. The most often side effects are: thyroid malfunction, cornea deposits, extension of QT interval, hepatotoxic effect, photosensitivity with skin changes. Literature data mention lung fibrosis as one of the possible side effects in acute amiodarone administration although none of the doctors came upon this side effect. Amiodarone effects on thyroid, regarding hypo- or

hyperthyreosis, are often seen. "I have to say that almost 50% of patients who I'm treating with heart insufficiency and with dilative cardiomyopathy in some period used to have either hypo- or hyperthyreosis. Since they had malignant ventricular rhythm disorder and since the majority of those patients are having defibrillator, in consultation with endocrinologist, we have never, or rarely, in 10% of patients, we have excluded amiodarone when they had thyrotoxicosis. We have reduced the dose of amiodarone to one hundred milligrams per day, five days a week, and we have tried to resolve a problem with thyroid by application of thyro-suppressive therapy or by substitutional therapy". (4) In a case of cornea deposits "ophthalmologist assesses are the deposits significant and is it necessary to exclude amiodarone from the therapy. But if the treatment without amiodarone is impossible, we are just temporarily ceasing with amiodarone. And we are trying to proceed with some other antiarrhythmic." (2) In case of QT interval extension "over 500 milliseconds, or if significant bradycardia or conductivity disorder on a level of AV node, such as second or third degree AV block, occurs we are absolutely excluding amiodarone. This is ultimate indication to stop the therapy with amiodarone." (4) "Photosensitivity with skin hyperpigmentation is noticed only in amiodarone long term usage, not in acute administration." (4) Hepatotoxicity is very difficult to determine because "we are not certain that if patient has ischemic liver or it is a consequence of amiodarone use or some synergistic reaction with some other drugs, so we cannot give the precise answer. We are seeing such patients, but we don't know the real reason for this. Very often we have patients with increased AST and ALT markers of liver necrosis. Even if significant numbers of patients have liver ischemia we cannot say for sure is it ischemic hepatitis or side effect of amiodarone. Those patients are in very bad condition and they are admitted to Coronary Unit critically ill." (5) Since the majority of patients in Coronary Unit are in critical condition tests related to condition of the thyroid, liver, lungs are not performed immediately but upon improvement of the patient condition. "I mandatorily advise to perform AST and ALT tests, as well as lung's X-ray." (2) In case of side effects and cessation of amiodarone application, the most common choice is beta blocker or Dilacor®.

F Local side effects: All participants mentioned local adverse events. "I have to say that almost thirty percent of patients in Coronary Unit suffer from some kind of thrombophlebitis." (4) The reason for this may be found in infusion of amiodarone as well as application and infusion preparation. The problem caused by amiodarone itself is "amiodarone, followed by high concentrated glucoses, is very aggressive agent and probably damages veins", (1) or happens "due to quick application of infusion." (2) One physician pointed out that the problem may be "not sufficient monitoring by medical nurses in Coronary Unit." (3) Injection itself may be a problem, especially if the patient is older with weak blood vessel and if infusion takes too long. The participants

pointed out that this local adverse reaction may be avoided by using the central vein for infusion instead of peripheral, which is mainly used at the moment. In case of obvious local side effects the most often response is "we are replacing cannula, in fact we are changing the position of cannula." (2) "We are changing place of injection or if possible we are shifting to per os use." (5) Concerning thrombophlebitis, no therapy is applied except for placing of compresses.

G Inappropriate use: Four out of five participants consider that inappropriate use is very rare. "The fact is that we don't have huge choice of antiarrhythmics and whenever we are applying amiodarone, we are applying that due to obvious reasons." (4) One out of five participants thinks that it is very often used inappropriately. "Very often amiodarone is used as the first antiarrhythmic, even if it is not necessary. Primarily, I think on supraventricular arrhythmia where we may practically use calcium antagonist, so I think that inappropriate application in Coronary Unit is present. I have experienced that in supraventricular arrhythmias, which may be simply treated by other antiarrhythmic, which has less complications and side effects." (5) All participants have emphasized that amiodarone is generally used inappropriately when it is not necessary to convert the patient into sinus rhythm, but only to calm down heart rate, and a lot of physicians are already using this approach. The participants also gave their recommendations for reducing inappropriate use of amiodarone. They state that guidelines should be followed more carefully, and more frequent educations/trainings should be held. "Education of the doctors has to be focused on not to be scared of arrhythmias. Amiodarone is in fact a good medicine if it is applied in proper indications." (4)

Participants: 1-male, 42 years old; 2-female, 40 years old; 3-female, 43 years old; 4-female, 52 years old; 5-male, 43 years old

Besides interview with physicians operating in Coronary Care Unit, medical records of seven patients treated by amiodarone have been observed. Of the total number of patients, six were male and one was female, age range from 25 to 82. Six out of seven patients have been treated with amiodarone parenterally and one patient received amiodarone per os. Diagnoses on admission were: Tachyarrhythmia absoluta; Tachyarrhythmia absoluta with decompensation of newfound dilated cardiomyopathy; Fibrillation Atriorum paroxysmal (Myopericarditis virosa suspecta); ST elevation myocardial infarction infer posterior, upon admission to the Coronary Unit the patient developed primary ventricular fibrillation; decompensating of chronic dilated valvular cardiomyopathy and terminal condition of heart failure. Retention period in Coronary Care Unit was up to five days. Two cases ended fatally, while others were converted into sinus rhythm within 48 hours. Amiodarone was indeed applied as a bolus followed by infusion, at the dose of two plus four ampoules. It was noted that amiodarone is often dissolved in physiological solution instead of 5% glucose solution, which is mandatory according to Summary of Product

Characteristics (SPC). It was observed that even with the same patient amiodarone was occasionally diluted in a glucose solution and occasionally in physiological solution. When asked to explain this discrepancy, physicians could not give an appropriate answer. In some cases amiodarone was combined with Dilacor[®], usually accompanied by anticoagulation therapy and IV diuretics. One patient's lab results have showed elevated values of thyroid hormones, forcing amiodarone exclusion from the therapy. In consultation with the endocrinologist, thyroid suppressive therapy was introduced. Other adverse events were not observed.

Finally, the third part of the study was visiting hospitalized patients together with physicians. Patients' therapy is prescribed exclusively by doctors employed in the Coronary Care Unit Department. Twenty four hours a day the attending physician is present in order to react immediately when it comes to hospitalization. Six out of eleven beds in Coronary Care Unit were occupied. All patients were on 24-hour ECG monitoring. Three out of six patients had visible thrombophlebitis caused by amiodarone infusion.

Discussion

From our results, we noticed that amiodarone is often inappropriately used for supraventricular rhythm disturbances. It is used for frequency correction. If a patient suffers from atrial fibrillation and we do not expect sinus rhythm to be reached, and there is a rapid chamber activity, usually another reason is present (worsening of heart function, heart failure) due to which the patient is in absolutes. In such cases, correction is achieved by solving heart failure problem, not by amiodarone administration. When the probability of converting a patient into sinus is minimum, amiodarone should not be administered, but this was not always the case. Such patients are usually on long-term amiodarone administration which is practically contraindicated and many of adverse events may occur. The Journal of the American College of Cardiology (JACC) in its guidelines for the management of patients with atrial fibrillation, states that amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated because of its potential toxicities [20]. According to data collected during interviews, this was not always the case. Amiodarone was sometimes administered as first line antiarrhythmic, not considering a less toxic solution. Also, the participants were not aware of the fact that amiodarone is incompatible with physiological solution. Insight into patient files shows that even with the same patient, amiodarone was sometimes diluted in physiological solution and other times it was diluted in in 5% glucose. Analysis of patient medical files has showed that amiodarone was not prescribed inappropriately; it was prescribed in proper indication and in proper dose. As excuse for unjustified administration, the interviewed doctors said that amiodarone does not have too many significant adverse

effects and it is useful and provides safety and comfort. Besides, Coronary Unit does not have wide range of antiarrhythmics available and which may be a better solution than amiodarone in patient treatment. The reason for unjustified administration of amiodarone may be found in lack of knowledge and awareness of medical staff about indications for use and adverse events. Thus, training of medical staff has to be implemented more frequently in order to overcome this problem. However, according to some data, amiodarone is being used inappropriately in other countries as well. For example, amiodarone is approved by the US Food and Drug Administration only for refractory ventricular arrhythmias but it is one of the most frequently prescribed antiarrhythmic medications in the United States [21]. Research conducted in Poland has shown that amiodarone was potentially inappropriately prescribed in 7.47% of cases in geriatric patients [16] and a survey taken in Italy has shown that amiodarone was potentially inappropriately prescribed in 19.1% cases in elderly patients with 24.9% of potentially inappropriate doses [17].

Discussion about obtained results was based on two facts. First, the research was carried out in the University Hospital Centre "Bezanijska Kosa" which is a tertiary health institution. We could expect less inappropriate use than in other health care institutions because medical staff has higher expertise. Considering the fact that the drug was developed in 1961 and there are precise guidelines for its use as well as numerous scientific papers which are publishing unjustified administration and adverse events [22], inappropriate use should be minimum. Secondly, all interviewed doctors said that they have experience with amiodarone administration.

Unjustified administration of amiodarone in Coronary Care Unit is rare, as considered by the majority of the interviewed doctors. Some of the interviewed doctors indicated that one of the reasons of unjustified administration is lack of other antiarrhythmics. However, the rational application of the drug would reduce costs and thus procurement of other medicines would be possible. Some studies have confirmed that costs increase by unjustified application of the drugs [23].

Conclusion

Research conducted at Coronary Care Unit of University Hospital Centre "Bezanijska Kosa" pointed to existence of inappropriate use of amiodarone in some cases. There are two reasons for this occurrence. The first one is due to objective reasons. The Coronary Unit has a sufficient number of antiarrhythmics available and amiodarone is always accessible. How often amiodarone was prescribed due to lack of other agents could not be determined. The nature of the second reason is subjective. Doctors opt for amiodarone because it is secure and convenient. This problem may be alleviated by strictly applying the scheduled treatment protocol.

Finally, we may conclude that besides the lack of other antiarrhythmics available, amiodarone was mostly inappropriately prescribed due to the lack of familiarity with its side effects. Also, physicians were not aware that amiodarone is incompatible with physiological

solution and they were often administering it as a first line antiarrhythmic, not considering another, less toxic solution. Thus, physicians should follow guidelines when prescribing the drug and additional education should be implemented.

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