Original Research

CARDIOLOGY

Influence of concomitant medication on plasma concentration of amiodarone in patients with atrial fibrillation - a pilot study

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Abstract

Background. Although amiodarone is a drug with many side effects, it is one of the most commonly used drugs in the treatment and prophylaxis of supraventricular and ventricular arrhythmias.

Aim. The purpose of this pilot study was to evaluate plasma concentrations of amiodarone in patients with atrial fibrillation (AF) and to identify possible drug-drug interactions between amiodarone and concomitant medications.

Method. A prospective observational study was conducted in 27 consecutive patients treated with amiodarone from May to July 2017 in a Clinical University Hospital. The patients included met our inclusion criteria. HPLC-UV was the device used to determine the plasma concentration of amiodarone.

Results. Only 51.8% of the patients had amiodarone plasma concentration within therapeutic interval (500-2500 ng/ml). The drugs associated to amiodarone in the therapeutic plan were diuretics, beta blockers, statins, antiplatelets, fluoroquinolones, non-steroidal anti-inflammatory drugs. We observed a statistically significant difference between the plasmatic concentrations of amiodarone in patients treated with furosemide vs. patients concomitantly treated with other drugs. Interactions between other mentioned drugs and amiodarone were not registered. We can report an underuse of amiodarone for more than 50% of the patients. Also, we found a significant interaction between furosemide and amiodarone, most likely through the interaction with MDR.

Conclusion. Furosemide may influence the pharmacokinetics of P-gp-interfering drugs. However, the relevance of these findings needs to be confirmed and further research is needed to characterize the interaction between amiodarone and furosemide.

Keywords: amiodarone, plasma concentration, drug interaction, P-glycoprotein

Background and aims

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, both in the European Union and in the United States [1]. Although amiodarone is a drug with many side effects, it is one of the most commonly used drugs in the treatment and prophylaxis of supraventricular and ventricular arrhythmias [2]. This drug has the greatest ability to maintain sinus rhythm [1].

Amiodarone has a variable bioavailability (20-80%) after oral administration. The half-life (T1/2) is on average 52 days, but may sometimes exceed 100 days [3,4]. Metabolism of amiodarone occurs primarily in the liver, via CYP3A4 and CYP2C8. The result of this process is desethylamiodarone (DEA), an active metabolite. It is further metabolized by CYP3A4 [5]. Amiodarone and its major DEA metabolite are metabolized by CYP450 but, in turn, it can inhibit certain CYP450 subfamilies. Amiodarone has a weak inhibitor effect on CYP2C9, CYP2D6, and CYP3A4 while DEA has strong inhibitory effect on CYP2D6 and moderate inhibitory effect towards CYP1A1, CYP1A2, CYP2A6, CYP2B6, and CYP2C19 [6].

A high lipophilia characterizes both amiodarone and DEA. Due to this property, they are accumulated in multiple tissues [7].

DOI: 10.15386/mpr-1130

Manuscript received: 02.08.2018
Received in revised form: 12.12.2018
Accepted: 21.12.2018

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The absorption and elimination of amiodarone are mediated by P-glycoprotein (P-gp) [8]. P-gp is also known as MDR or ABCB1 because it belongs to ABCB (MDR) superfamily of ATP-binding cassette (ABC) transporters [9]. P-gp has a great pharmacological relevance being one of the most important transporters in humans. The P-gp efflux transporter protects the body against toxic compounds but, at the same time, interferes with the absorption and/or elimination of the drugs. As a consequence, P-gp has a significant pharmacokinetic importance [10,11].

More than 34% of patients treated with amiodarone have side effects [4]. Careful and continuous monitoring is essential during amiodarone therapy.

Sometimes, it is necessary to monitor the plasma concentration of the drug. Based on determined plasma concentrations, underdose or overdose of the drug could be identified and it is possible to initiate a correct management plan. Measures could be taken to individualize the therapy or identify drug-drug interactions [12]. Important clinical events may be the result of the interactions between concomitantly administered drugs.

The purpose of this pilot study was to evaluate the plasma concentrations of amiodarone in patients with AF and to identify possible drug-drug interactions between amiodarone and concomitant medications.

Ethics approval

The study was conducted according to the principles of Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989). The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. As provided in the study protocol, a written informed consent in compliance with the current revision of the Declaration of Helsinki has been obtained from each subject prior to enrolment, during which they were informed of their rights and obligations and other study details.

Method

Subjects

Twenty-seven patients with permanent AF hospitalized in a Clinical University Hospital from May to July 2017, under treatment with amiodarone for at least 3 months, took part in the study. Patients with digestive, hepatic, lung or thyroid disorders were excluded. The medications concomitantly administered with amiodarone were recorded: beta blockers, statins, antiplatelets, anticoagulants, diuretics, non-steroidal anti-inflammatory drugs and antibiotics.

Two blood samples (5 ml) were collected 2 hours after drug administration. One was used to determine the renal parameters (urea and creatinine) and the other was centrifuged and plasma obtained was stored frozen (-20° C) until the plasma concentration was determined. Creatinine clearance was also determined using the Cockcroft-Gault Equation.

Sample preparation

The sample preparation was performed by adding 0.3 mL acetonitrile to 0.1 mL plasma in an Eppendorf tube. The tube was vortexed for 10 s, then centrifuged for 5 minutes at 10000 RPM, 9167g. The supernatant was transferred in an autosampler vial, and 25 µL were injected into the chromatographic system.

High-performance liquid chromatography assay

Amiodarone concentrations were determined using HPLC with UV detection (Agilent Technologies, USA). A 3 x 100 mm, 3.5 µm, Zorbax C18 chromatographic column (Agilent Technologies, USA) was used for separation. The mobile phase consisted of 70% acetonitrile and 30% formic acid 0.2%; the flow rate was 1 mL/min; the thermostat temperature was set at 35°C. The peaks were detected by using an Agilent 1100 series UV detector (wavelength 240 nm), the retention time of the analyte was at 1.84 min. The calibration curve was linear over the concentration range 50-1000 ng/mL for amiodarone.

Statistical analysis

Statistical analysis was carried out using the MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). The quantitative variables were characterized by mean and standard deviation (normal distribution), and qualitative variables with absolute and relative frequency. The comparison between groups was realized with t-test independent variables or chi-square. Pearson correlation was used for analyzing two quantitative variables. A p-value <0.05 was considered statistically significant.

Results

Of the total number of 27 patients, 44.4% were women and 55.6% were men. The mean age of the patients enrolled in the study was 65.6 ±11 years. The mean of values renal parameters are presented in the Table I. A significant correlation was observed between the plasma concentration of amiodarone and urea ($r = 0.126$; $p = 0.5$), serum creatinine ($r = 0.443$; $p = 0.02$) and creatinine clearance ($r = -0.453$; $p = 0.01$).

Concomitant medications with amiodarone were recorded (Table II).

Table I. The mean values of renal parameters.

Parameter	Mean value
Creatinine	1.35±0.56 mg/dl
Urea	61.4±33 mg/dl
Creatinine clearance	55.9±19.6 ml/min

Table II. Concomitant medications with amiodarone.

Class of drug/drug	No patients with treatment	No of patients without treatment
Beta blockers	18	9
Statins	16	11
Acenocumarol	27	0
Furosemide	18	9
Clopidogrel	7	20
Ciprofloxacin	5	22
Ibuprofen	6	21
Paracetamol	5	22

Table III. Plasma concentration of amiodarone and concomitant medications.

Class of drug/drug	Therapy = Amiodarone + Drug	Therapy = Amiodarone without Drug	p
	Mean plasma concentration of amiodarone (ng/ml)	Mean plasma concentration of amiodarone (ng/ml)	
Beta blockers	496.29±304.83	646.78±228.8	0.2
Statins	557.7±296.5	530±284.6	0.81
Furosemide	619.85±281.9	399.6±248.1	0.05
Clopidogrel	646.9±261.5	511.3±292.7	0.2
Ciprofloxacin	614.6±283.7	530.9±291.4	0.5
Ibuprofen	498.1±263.1	560.27±297.4	0.64
Paracetamol	484.25±196.7	560.59±305.1	0.6

Concomitant medications were administered for chronic disorders (heart failure, ischemic heart disease, and hypertension) or acute problems (headache, low urinary tract infection); 23 of the 27 patients had heart failure, but only 4 were treated with spironolactone in association with furosemide. All patients were treated with angiotensin converting enzyme inhibitors (ACEi) for a long time (at least 2 years) before being included in our study.

The mean plasma concentration of amiodarone was 554.07±302.52 ng/ml for the patients treated with 200 mg / day and 528.37±262.7 ng/ml for those who received 400 mg / day. The difference was not statistically significant (p=0.83).

A possible correlation between concomitant medications and plasma concentrations of amiodarone has been considered (Table III).

Discussion

The therapeutic range of amiodarone plasma concentration is 500-2000 ng/ml [13]. Of the patients enrolled in our study 14 (51.8%) had the amiodarone concentration within the therapeutic range and 13 (48.2%) had a lower concentration than the therapeutic one.

The prevalence of AF in Europe varies with gender (male / female = 1.2: 1) and age (0.12-0.16% of those younger than 49 years and 3.7-4.2% in patients between the ages of 60 and 70) [14]. Similar values can be seen in our study; 55.6% of enrolled patients were males and 44.4% were women. Their average age was 65.6±11 years. No statistically significant correlation between amiodarone plasma concentration and age or gender was observed.

Theoretically, the daily dose of amiodarone is directly proportional to its plasma concentration. The patients in our study took 200 mg (70.4%) or 400 mg (29.4%) amiodarone / day but the difference in plasma concentrations of amiodarone was not statistically significant between the two groups. This may be a consequence of pharmacokinetic modification (absorption, distribution, metabolism or elimination), of pharmaceutical interactions or other factors [15]. Moreover, amiodarone is a drug with high interindividual variability [16]. Also, in one study, Lafuente et al. have demonstrated that there is no direct correlation between the concentration of amiodarone in adipose tissue and the daily dose used [8].

A statistically significant correlation was found between plasma concentration of amiodarone and renal parameters (creatinine, urea and creatinine clearance). Increases in creatinine, urea and decrease of creatinine clearance were observed in the patients with high plasma concentrations of amiodarone. Pollak et al. reported similar results in a study [17]. Amiodarone is a potent inhibitor of organic cationic transport 2 (OCT2) [18]. It is also known that creatinine is a substrate for the cation transport pathway comprising OCT2 [19]. This may explain the relationship between plasma concentration of amiodarone and renal parameters. However, the renal side effects of amiodarone are not very commonly reported.

ACEi and angiotensin II receptor antagonists (ARB)

are commonly used in patients with early CKD. ACEi/ARBs have demonstrated a cardio-protective effect in the non-CKD population. Because our patients have used ACEi for a long time (years) before including amiodarone treatment and repeated tests (urea, creatinine) were normal, we did not insist on these classes of medication. Also, they cannot influence the pharmacokinetics of amiodarone [20].

In our results, there was a significant difference in the plasma concentration of amiodarone between the two groups with and without furosemide. In patients treated with furosemide the plasma concentration of amiodarone was 55% higher than in those without this drug in the treatment plan. No other study reported this interaction.

An explanation could be the effect of furosemide on MDR expression. It is known that there is a link between MDR and the decrease in intracellular concentrations of drugs [21]. Furosemide inhibits the Na+K+2Cl- co-transporter pump in the ascending limb of loop of Henle, and the primary effect is the inhibition of sodium reabsorption. It may have a similar effect on the P-gp pump [22,23]. An in vitro study has shown that furosemide reverses MDR status in the bladder cancer cell line [23]. But, P-gp is also expressed in normal human tissues such as intestinal mucosa or hepatocytes [24]. These are tissues with great importance for the pharmacokinetics of amiodarone. Thus, furosemide may decrease MDR status and P-gp expression. In this way, it may influence the pharmacokinetics of P-gp-interfering drugs.

Concerning the other drugs administered concomitantly with amiodarone in patients with AF, we did not find significant differences in plasma amiodarone concentration. However, the concentration of amiodarone in patients treated with beta-blockers was 30% lower than in patients without these. In subsequent studies, it would also be interesting to determine the beta-blocker concentrations. Amiodarone is an inhibitor of CYP2D6 [25]. This family of enzymes is involved in the hepatic elimination of many beta blockers (metoprolol, carvedilol, nebivolol) [26,27]. As a consequence, it is possible to increase beta-blocker plasma concentrations and may need to decrease their dose in some situations.

Possible limitations of our study are represented by the small number of patients enrolled, measurements were performed only once in each patient, therefore intraindividual variability in time could not be assessed.

Conclusions

The data found in this prospective pilot study suggest that furosemide might have influence plasma concentration of amiodarone in patients with AF, most likely through the interaction with MDR. However, the relevance of these findings need to be confirmed and further research is needed to characterize the interaction between amiodarone and furosemide.

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