Amiodarone after unsuccessful direct-current cardioversion of persistent atrial fibrillation

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Abstract

Aim: To assess the safety and efficacy of amiodarone used after unsuccessful direct current (DC) cardioversion of persistent atrial fibrillation (AF).

Methods: The study group comprised 67 patients (F/M 26/41; mean age 61.3±11.2 years) after unsuccessful DC cardioversion (DCC) of persistent AF (mean arrhythmia duration 212.6±135.2 days) in whom another attempt of DCC was intended. Repeat DC cardioversion was performed after loading with oral amiodarone, for a period necessary to achieve a cumulative dose of up to 12.0-16.0g. Pretreatment was an outpatient procedure. After successful DC cardioversion all study subjects received a maintenance dose of amiodarone, 100-200 mg daily, aimed at preventing AF. The follow-up period was 12 months.

Results: Spontaneous conversion to sinus rhythm (SR) during amiodarone pretreatment was observed in 13 pts (19.2%). DCC was performed in 54 pts and SR was restored in 41 of the study pts (76%). Complications occurred in 3 pts, including 1 case of apparent hyperthyroidism and 2 cases of decreased TSH level, and required amiodarone withdrawal. After 12 months, 72.2% of pts maintained SR on low dose (179.2±42.1 mg/day) amiodarone. Spontaneous conversion to SR during amiodarone loading was significantly related to long-term SR maintenance after successful DC cardioversion (p<0.013; RR 2.01; 95% CI 1.34-3.03).

Conclusion: Pretreatment with amiodarone and repeat DC cardioversion results in sinus rhythm restoration in about 80.6% of pts with persistent AF after an initial unsuccessful attempt. Direct-current cardioversion can be performed safely taking standard precautions for patients receiving amiodarone. At 12 months after successful repeated DC cardioversion, more than 72.2% of pts on low-dose amiodarone maintain SR.

Key words: persistent atrial fibrillation, electrical cardioversion, amiodarone

Introduction

Direct-current cardioversion (DC cardioversion) of persistent atrial fibrillation (AF) is a first-line therapy in patients qualified to a rhythm control strategy including sinus rhythm (SR) restoration [1]. The rates of effective DC cardioversion in patients with persistent AF vary between 60% and 90% and its final effect depends on the amount of energy and the type of impulse used, as well as on the selection of patients [1-3]. In patients after unsuccessful cardioversion there is always an option to repeat the procedure. In order to increase the efficacy of the repeated DCC, it should be preceded by antiarrhythmic drug loading. Among numerous drugs with documented properties of DC cardioversion efficacy augmentation, amiodarone seems to be the most validated one [4, 5]. The aim of the study was to assess the safety and efficacy of a cumulative dose of amiodarone after unsuccessful DC cardioversion of persistent AF.
Methods

Patients

Patients with planned SR restoration, aged from 18 to 75 years, after an unsuccessful attempt of DCC to restore SR, were enrolled into the study. The duration of AF before the index cardioversion was shorter than two years. The etiology of AF included: ischaemic heart disease, hypertension, haemodynamic insignificant left-sided valve disease (excluding mitral valve stenosis), or no perceptible cause was found (idiopathic AF).

The following exclusion criteria were used: documented amiodarone ineffectiveness, contraindications or intolerance to the drug, thyroid gland pathology, pregnancy or lactation, acute myocarditis, advanced heart failure (NYHA IV), severe valve disease (excluding mitral valve stenosis) requiring surgery, refractory hypertension (diastolic blood pressure >115 mmHg), hypotension (blood pressure <90 mmHg), pulmonary hypertension (peak pressure gradient through the tricuspid valve >35 mmHg), markedly enlarged left atrium (transverse diameter >60 mm), patients with ventricular rate <90/min (without taking a heart-rate-lowering drug), liver, renal or central nervous system impairment, active malignancy, alcohol abuse, chronic obstructive lung disease or another severe condition, the presence of contraindications to anticoagulation, suspected patient non-adherence, as well as lack of written consent from the patient. The study was held in the First Department and Chair of Cardiology, University of Medical Sciences in Warsaw. The study protocol was approved by the Ethics Committee at the University of Medical Sciences in Warsaw. After informing patients about the aim of the study and proposed treatment, written consent was obtained from each patient. Additional written consent was obtained before each DC cardioversion procedure.

Amiodarone loading and DC cardioversion procedure protocol

Patients willing to participate in the study remained in the Cardiac Intensive Care Unit (CICU) after unsuccessful DC cardioversion. Amiodarone was added to the therapy, initially as an intravenous 150 mg bolus, which was followed by continuous intravenous infusion. This procedure allowed a dose of 900 mg to be reached on the first day of the study. Oral amiodarone was also started at that time. A daily dose of 600 mg was maintained for three weeks, then the dose was lowered to 400 mg/day until the time of repeated DC cardioversion. The therapy was held on an outpatient basis. After achieving a cumulative dose of 12-16 g, usually within 3-4 weeks of the therapy, DC cardioversion was performed unless a spontaneous return of SR occurred. The procedure was performed in the CICU, in fasting patients, without taking morning medications (no food or drinking for at least 6 hours before the procedure). In the case of prolonged digoxin intake, the drug was discontinued for at least 48 hours before the planned procedure. In all patients, 12-24 hours before DCC, biochemical parameters including potassium level (should not be lower than 4 mEq/l) were assayed, and the INR was measured. In patients on chronic diuretics, the time from biochemistry sampling to DCC was shorter. Standard ECG recording, heart rate and blood pressure measurements were carried out just before the procedure.

After written consent was obtained from a patient, the procedure was performed under short-term general anaesthesia with iv. fentanyl (Fentanyl – Polfa; 0.05 mg, iv. bolus, i.e. 1 Amp for patients weighing less than 70 kg and 0.1 mg iv., i.e. ½ Amp for patients weighing more than 70 kg) as a premedication and followed by hypnomidate (Hynonomidate – Janssen; 0.1-0.3 mg/kg body weight in 2-3 minute infusion). As soon as loss of the eyelash reflex was observed, the DC cardioversion shock was delivered. Pads were placed in the precordial region: in the right subclavian area and in the apical area. A monophasic device with maximum output of 360 J was used (Servocard produced by Hellige or WR 50011 S reanimation set produced by Temed). The initial discharge was 2 J/kg body weight, followed, when ineffective, by discharges of doubled energy until SR restoration or a total dose of 1080 J was delivered.

Cardioversion was considered successful when SR was maintained for at least two hours after the procedure. After SR restoration, oral amiodarone 100-200 mg daily was continued. During hospitalisation the patients were instructed on how to self-recognize the AF palpating radial artery, before and after the planned cardioversion. The patients were informed about the possibility of taking additional doses of amiodarone: 3x200 mg at one hour intervals, in case of the recurrence of arrhythmia at home. They were also instructed that should AF last longer than 12 hours despite an additional dose of amiodarone, hospitalisation is recommended.

During amiodarone loading control visits were scheduled every seven days. Control visits following cardioversion were scheduled after seven days and then 1, 3, 6 and 12 months after the procedure. Before enrolling in the study, AF type (paroxysmal, persistent), duration of present arrhythmia and the presence of comorbidities were evaluated based on medical records and history.
Echocardiography

Transthoracic echocardiography was performed at the beginning of follow-up. The examination was performed using a Sonos 2500 Philips device with 2.5 MHz transducer. Dimensions of the heart chambers were measured from the M-mode parastral long-axis and short-axis views (third or fourth intercostal space) as well as from the two-dimensional apical four-chamber views. Dimensions of the heart chambers were measured according to the recommendations of the American Society of Echocardiography [6, 7]. The following echocardiographic parameters were analysed: left atrial area (LAar), left atrial diameter (longitudinal and transverse axis; LAlax, Lasax), end-diastolic and end-systolic left ventricular diameters (LVEDD, LVESD) – exclusively for shortening fraction (FS) calculations. Transthoracic echocardiography was performed at the beginning of the study and repeated at 2 and 12 months of follow-up. The end-diastolic and end-systolic left ventricular diameters were measured from the M-mode views. Each diameter final value was an average of five measurements recorded from five consecutive heart beats.

Statistical analysis

The results are presented in tables. Quantitative variables are given as the mean ± standard deviation (SD), categorical variables as the number and percent of patients with the analysed parameter. The analysis of freedom from AF recurrence was based on life expectancy curves. Successful SR restoration served as the starting point of follow-up. The end of follow-up was marked by the pre-specified study termination date, death, AF relapse, or patient’s withdrawal of consent. The results are presented as Kaplan-Meier curves. To analyse the effect of clinical and echocardiographic parameters on freedom from AF at one year, the generalised additive logistic regression method was used. The relationship between the analysed parameters and the probability of long-term freedom from AF is shown as graphic charts, with relative risks and confidence intervals depicted. For echocardiographic parameters their medians were considered the cut-off values.

A p value of <0.05 was considered statistically significant.

Results

Patient characteristics

The study group comprised 67 consecutive patients (female/male 26/41; mean age 61.3±11.2 years) with persistent AF, in whom the first DCC was unsuccessful. In all patients enrolled, additional therapy with loading doses of amiodarone was given. Simultaneously, anticoagulant therapy was administered and mean values of INR between 2.0 and 3.0 were maintained [8]. The mean duration of AF before the repeated DC cardioversion was 212.6±135.2 days. Clinical and echocardiographic characteristics of the analysed population are presented in Tables I and II.

Results of DC cardioversion

A cumulative dose of amiodarone of 12.0-16.0 g was achieved within 27.3±13.7 days. Spontaneous conversion to SR during amiodarone pretreatment occurred in 13 (19.4%) patients. At that time no side effects of the therapy and no signs of drug intolerance were observed. Repeated cardioversion was performed in 54 patients and SR was restored in 41 (76%) patients. The average amount of energy required to restore SR was 527.2±223.6 J and it was significantly lower than the average energy used during the first DC cardioversion (p <0.05, Table III). No complications were observed.
during repeated DC cardioversion. Pretreatment with amiodarone and subsequent DC cardioversion resulted in SR restoration in 54 (80.6%) patients in whom the previous DCC attempt failed. Results and detailed data on the repeated DC cardioversion preceded by loading with amiodarone are presented in Table III.

### Long-term sinus rhythm maintenance

All of the 54 patients in whom SR was restored with repeated DC cardioversion or during amiodarone pretreatment received amiodarone in a maintenance dose of 100-200 mg/day (mean dose 179.2±42.1/mg/day). In 6 (11%) patients β-blockers were added (atenolol, mean dose 32.1±12.5/mg/day). At one year sinus rhythm was present in 39 (72.2%) patients. At 1, 3 and 6 months, SR was recorded in 85.3%, 79.4% and 72.2% of patients, respectively. The percentage of patients who maintained SR after repeated DC cardioversion is shown in Figure 1. During 12-month follow-up, in 1 (1.5%) patient clinical and laboratory evidence of hyperthyroidism was observed, and in another 2 (3%) patients significant changes in TSH level were noted; in all these cases amiodarone was stopped.

#### Predictors of sinus rhythm maintenance

To identify the parameters significantly influencing SR maintenance in patients on amiodarone, the following factors were analysed: presence of comorbidities, duration of present AF, history of paroxysmal AF, heart failure (NYHA class) and echocardiographic parameters. The initial analysis evaluated the effect of gender and age on SR maintenance over 12 months. Based on logistic regression, the probability of maintaining SR was influenced only by gender and age of the patients. No significant relationship between other analysed parameters and the rate of successful DCC and 12-month freedom from AF relapse was found.

In order to estimate the association between the presence of the analysed clinical parameters and the probability of SR restoration and maintenance, a series of models were created including gender, age, and the index clinical parameter, i.e. AF duration, paroxysmal AF preceding persistent arrhythmia, and spontaneous SR return during amiodarone pretreatment. Among these only SR restoration during amiodarone pretreatment significantly correlated with SR maintenance at 12 months (p <0.013). Patients with a spontaneous SR return had double the chance of maintaining SR (RR 2.01; 95% CI 1.34-3.03). No significant correlations between SR maintenance at 12 months and the initial echocardiographic parameters were found. Data on the effect of particular echocardiographic parameters on the SR restoration success rate and long-term maintenance are presented in Figure 2.
Figure 2. Echocardiographic and clinical data correlations with sinus rhythm restoration and maintenance probability in the studied population.
Discussion

Direct-current cardioversion is an efficient and safe procedure of SR restoration in patients with AF [9-12]. Because of the low efficacy of antiarrhythmic drugs used to restore SR in patients with AF lasting for more than 48 hours, DC cardioversion is a first-line therapy in such cases. The success rate of DC cardioversion varies between 60% and 90%. A significant divergence of the reported results is caused by the lack of a clear definition of early success of the procedure [2, 3]. According to arbitrary accepted criteria, successful cardioversion is defined as both spontaneous restoration of SR during pretreatment and the presence of SR at least 24 hours after the last DC cardioversion shock [13]. The result of DC cardioversion also depends on the type of population investigated [2, 3]. The following factors are believed to effect the final result of the procedure, regardless of the success criteria accepted: duration of arrhythmia, age of patients and left atrial diameter [12, 14, 15].

According to the protocol of the study, repeated DC cardioversion was attempted after the initial failure. It was preceded by amiodarone loading. The efficacy and safety of such a strategy have been confirmed in many clinical studies. It has been validated in patients with chronic AF who qualified for rhythm control treatment and underwent unsuccessful DC cardioversion [16-18]. Sagrista-Sauleda et al. demonstrated a high efficacy of DC cardioversion in patients with AF or atrial flutter who received amiodarone before the procedure [16]. An additional advantage of such an approach is a chance of SR restoration during amiodarone pretreatment, and thus avoidance of DC cardioversion. In previous studies 16-48% of patients were reported to have converted to SR during amiodarone loading [16, 17, 19, 20]. In our study 20.8% of patients converted to SR during amiodarone pretreatment, consistently with previously published data.

Crijns et al. concluded that amiodarone administration resulted in the termination of AF in 12% of patients with persistent AF before planned DC cardioversion [21]. Gossellink et al. observed SR restoration in 16% of AF patients during amiodarone loading, and in 88% of patients requiring repeated DC cardioversion [22]. Giving amiodarone after unsuccessful DC cardioversion, Opolski et al. observed SR restoration in 18% of patients before the repeated procedure. The efficacy of repeated DC cardioversion was 59%, so the total success rate was 65% [23]. In the PIAF study, Hohnloser et al., who administered amiodarone before DC cardioversion in patients with persistent AF without any previous attempts of SR restoration, reported a 23% success rate in patients receiving pharmacotherapy alone [24]. Cappucci et al. reported that 25% of patients converted to SR during amiodarone pretreatment, while in patients on diltiazem the SR restoration rate was lower than 3% [25].

Some authors recommend pretreatment with amiodarone lasting no less than 4-6 weeks. Over that time higher doses of the drug may be delivered, increasing the chance of success of the following DCC [26]. The use of higher amiodarone doses in order to achieve and maintain the therapeutic plasma level of the drug and its active metabolites is based on studies on ventricular arrhythmias. It has to be stressed that aggressive amiodarone treatment may be associated with intolerance and the risk of potentially dangerous side effects [16, 25, 27]. In the case of supraventricular arrhythmias such as AF and atrial flutter, lower doses of amiodarone are acceptable [27].

Conclusions

Pretreatment with amiodarone and repeat DC cardioversion results in sinus rhythm restoration in about 80.6% of pts with persistent AF after an initial unsuccessful attempt. Direct-current cardioversion can be performed safely taking standard precautions in patients receiving amiodarone. At 12 months after successful repeated DC cardioversion, more than 72.2% of pts on low-dose amiodarone maintain SR.

References

Amiodaron po nieskutecznej kardioversji przetrwałego migotania przedsionków

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Streszczenie

Wstęp: U chorych z przetrwałą migotaniem przedsionków (AF), u których kardioversja elektryczna (KE) była nieskuteczna, podanie leków antyarytmicznych może poprawić skuteczność kolejnej ICE.

Cel: Ocena skuteczności i bezpieczeństwa stosowania nasycających dawek amiodaronu przed kolejnym zabiegiem u chorych po nieskutecznej KE przetrwałego AF.

Metodyka: Grupę badaną stanowiło 67 chorych (K/M 26/41; wiek œr. 61.3±11.2 lat) z przetrawałym AF (czas trwania arytmii 212.6±135.2 dnia) po nieskutecznej KE, których zakwalifikowano do kolejnego zabiegu podjęciem podawania wysysających dawek 12,0-16,0 g amiodaronu drogą doustną. Leczenie prowadzone było w warunkach ambulatoryjnych. Po przywróceniu rytmu zatokowego (RZ) pacjenci otrzymywali przewlekle amiodaron w dawkach podtrzymujących 100–250 mg/dzień przewlekle celem profilaktyki nawrotu AF. Czas obserwacji wynosił 12 miesięcy.

Wyniki: Podczas wysysania amiodaronu powrót RZ obserwowany był u 13 (19,4%) chorych. U pozostałych 54 chorych wykonano planowy zabieg KE przywracając RZ u kolejnych 41 (76%) chorych. Podanie wysysających dawek amiodaronu oraz wykonanie po-wtórnego KE pozwoliło na przywrócenie RZ u kolejnych 54 (80,6%) chorych po nieskutecznej KE przetrwałego AF. Nie stwierdzano działań ubocznych, lub nietolerancji leku. W części zabiegu KE nie obserwowano żadnych działań ubocznych zabiegu. Po roku od kardioversji RZ utrzymywało się 39 (72,2%) chorych otrzymujących przewlekle amiodaron w średniej dawce podtrzymującej 179,2±42,1 mg/d. Spośród ocenianych wyjściowych parametrów klinicznych tylko fakt powrotu RZ podczas podawania wysysających dawek amiodaronu w sposób istotny korelował z utrzymywaniem się RZ po 12 miesiącach obserwacji (p<0,013). Pacjenci, u których doszło do spontanicznego ustąpienia arytmii mieli dwukrotnie większe szanse na odległe utrzymanie RZ (RR 2,01; 95% CI 1,34-3,03). Podczas przewlekkiego leczenia amiodaronem u 1 (1,5%) chorego stwierdzano kliniczne i laboratoryjne objawy nadczynności tarczycy, u 2 (3%) chorych obserwowano niepewną dynamikę zmian wartości TSH; wszyscy wspomnieni chorzy wymagali odstawienia leku.

Wnioski: Powtórna KE, poprzedzona podaniem amiodaronu pozwala na przywrócenie RZ u 80,6% chorych z przetrwałym AF po nieskutecznej pierwszej kardioversji. Dalsze stosowanie podtrzymujących dawek amiodaronu pozwala na utrzymanie RZ u 72,2% chorych w czasie 12-miesięcznej obserwacji.

Słowa kluczowe: przetrwałe migotanie przedsionków, kardioversja elektryczna, amiodaron

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