Pharmacological Research 122 (2017) 118–126

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Perspective

Effectiveness of heart rate control on hemodynamics in critically ill patients with atrial tachyarrhythmias managed by amiodarone

Joe-Elie Salem[a,b,c,d,g,*], Pauline Dureau[a,b,c,d], Christian Funck-Brentano[a,b,c,d], Jean-Sébastien Hulot[a,b,c,d], Maria El-Aissaoui[e], Nadia Aissaoui[e], Saik Urien[f,1], Christophe Faisy[a,b,c,d,f,1]

[a] AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology and CIC-1421, F-75013 Paris, France
[b] INSERM, CIC-1421 and UMR ICAN 1166, F-75013 Paris, France
[c] Sorbonne Universités, UPMC Univ Paris 06, Faculty of Medicine, Department of Pharmacology and UMR ICAN 1166, F-75013 Paris, France
[d] Institute of Cardiometabolism and Nutrition (ICAN), France
[e] Critical Care Unit, Hôpital Européen Georges Pompidou, Assistance Publique – Hôpitaux de Paris, University Paris Descartes Sorbonne Paris Cité, Paris, France
[f] CIC-1419 INSERM, EAU-08 University Paris Descartes Sorbonne Paris Cité, Paris, France
[g] Cardiology - Rythmology Unit, Pitié-Salpêtrière Hospital, Assistance Publique – Hôpitaux de Paris, F-75013 Paris, France

ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 3 May 2017
Accepted 9 June 2017
Available online 10 June 2017

Keywords:
Amiodarone
Atrial tachyarrhythmia
Pharmacology
Shock
Heart rate

ABSTRACT

Atrial tachyarrhythmias (AT) are common in intensive care unit (ICU) patients and might contribute to hemodynamic instability if heart rate (HR) is persistently too rapid. We aimed to assess if HR control below 115 or 130 bpm with amiodarone improves hemodynamics in ICU patients with AT.

This observational study included 73 ICU patients with disabling AT receiving amiodarone for HR control. A total of 525 changes (mainly within 4–8 h) in mean arterial pressure (MAP) and 167 changes in plasma lactate in response to HR variations above 115 or 130 bpm were analyzed. Epinephrine, sedative drugs, fluid loading, use of diuretics, continuous renal replacement therapy and amiodarone dosing were among covariables assessed.

Univariable analysis showed that HR variations above 115 bpm were poorly correlated to change in MAP ($r = 0.11$, $p < 0.01$). Multivariable analysis showed that changes in MAP were still positively associated to HR variation ($p < 0.05$) and to initiation or termination of epinephrine ($p < 0.05$) or sedatives infusions ($p < 0.05$). Changes in plasma lactate did not correlate to HR variations above 115 bpm. When considering 130 bpm as a threshold, HR variations were not associated to changes in MAP or to changes in plasma lactate. Amiodarone dose was associated to HR decrease but not to MAP or plasma lactate increase.

In ICU patients with AT, strict HR control below 115 bpm or 130 bpm with amiodarone does not improve hemodynamics. A prospective randomized trial assessing strict versus lenient HR control in this setting is needed.

1. Introduction

Atrial tachyarrhythmias (AT) (atrial fibrillation, atrial flutter, atrial tachycardia or atrioventricular arrhythmias) are highly prevalent and are associated with a poor outcome in critically ill patients admitted in intensive care units (ICU) [1,2]. AT are often associated with a ventricular heart rate (HR) above 120–130 beats per minute (bpm) which contributes to baroreflex impairment [3], diastolic dysfunction and may lead to cardiac systolic dysfunction. Such induced ventricular tachycardiomyopathy is associated with hemodynamic instability and increased morbidity or mortality [2,4,5]. In severely ill patients with AT, a rate or rhythm control strategy with amiodarone is recommended for the treatment or prevention of ventricular tachycardiomyopathy [6,7]. Attempts to restore sinus rhythm are frequently unsuccessful in the setting of critically ill patients [8–10], particularly when using electrical cardioversion without antiarrhythmic pretreatment. HR control is thus the preferred strategy in this situation [10–12]. In non-ICU patients, guidelines recommend aiming at a HR control between 90

Abbreviations: AT, atrial tachyarrhythmias; bpm, beats per minute; CRRT, continuous renal replacement therapy; ECG, electrocardiogram; ECV, electrical cardioversion; HR, heart rate; ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; mg, milligram.

* Corresponding author at: Centre d'Investigation Clinique Paris-Est, Hôpital La Pitié-Salpêtrière, 47-83 Bld de l'hôpital, 75651, France.
E-mail address: joeelie.salem@gmail.com (J.-E. Salem).

[1] Saik Urien and Christophe Faisy contributed equally as last authors.

http://dx.doi.org/10.1016/j.phrs.2017.06.004
1043-6618/

and 115 bpm during stress situations [6,7,13]. There are no specific guidelines for patients in severely ill condition but it is commonly advocated that reaching a HR below 115 bpm or a maximum of 130 bpm is advisable [6,7,14]. Thus, it is unknown whether exceeding these HR cut-offs, even for short periods of time, is associated with alterations of hemodynamics, i.e. fall of mean arterial pressure (MAP) [15,16] or increase of plasma lactate levels [17].

In a former study [18], we modelled the relationship between amiodarone dose and heart rate variation but did not assess the influence of heart rate control on restoration of hemodynamics. The objective of this study was to determine if magnitude of HR variations above 115 or 130 bpm are associated to variations in MAP or plasma lactate. The analyses took into account variables such as paroxysmal vs persistent AT and others confounding factors relevant to ICU patients [19] such as epinephrine treatment, sedative or curare drugs infusion, fluid loading, amiodarone dose, use of diuretics or continuous renal replacement therapy (CRRT).

2. Material and methods

2.1. Patients and study design

This observational, cohort study was performed from January 2007 to April 2012 in the 18-bed medical ICU of a tertiary teaching hospital. In accordance with the French legislation on observational studies, approval by an investigational review board was not required. The use of confidential electronically processed patient data was approved by the French National for Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*; reference: 1922081). Data were extracted from the files of 73 consecutive critically ill patients who had received at least one dose of amiodarone (Mylan laboratory, Saint-Priest, FRANCE) to treat a disabling AT during their ICU stay (Fig. 1). HR and MAP data (average of at least 3 measures over 5 min) were collected at the time of the first amiodarone administration in intensive care unit (ICU) and then 4–6 times daily over 6 days or until death or ICU discharge. MAP values were obtained through an arterial catheter attached to a fluid-filled pressure transducer system incorporating a flush system, which continuously infused a solution under pressure to maintain patency of the catheter. An attached transducer senses arterial pressure and converted the pressure signal to a waveform on a Phillips® bedside monitor. The waveform reflected pressure generated by the left ventricle during systole. The monitor also displayed automatically numerical MAP values. HR were also displayed on the monitor and computed by automatic QRS detection from continuous acquisition of a digital electrocardiographic signal. Plasma lactate levels were drawn at the discretion of the treating physician without any predefined protocol and were determined by an arterial blood gas analyser (ABL 825, Radiometer, Copenhagen, Denmark). Details concerning modalities of amiodarone administration in this cohort and estimation of pharmacodynamically active amiodarone dose at each time point were estimated as previously described in detail [18]. Briefly, amiodarone could be administered either intravenously (IV) as amiodarone hydrochloride 150 mg/3 mL or orally as 200 mg tablet(s). Route, frequency of administrations and doses were left at the discretion of the treating physician. Other treatments were administered according to standard guidelines [14].

2.2. Variables collection

The following covariables were recorded at the time of first HR and MAP collection: age, gender, body weight, severity score at ICU admission, diabetes, hypertension, AT history, bilirubinemia, previous amiodarone treatment and type of AT. Paroxysmal and persistent AT were defined as an arrhythmia occurring less or more than one week before the first amiodarone administration in ICU, respectively. Prior chronic and sub-acute amiodarone treatment before ICU were defined as continuous amiodarone treatment since more than one month or a cumulated amiodarone dose of less than 4 g in the last month, respectively.

Time-dependent covariables potentially interacting with hemodynamic conditions were recorded at the time of each HR, MAP, and plasma lactate collection. These were: body temperature, arterial pH or PaO_2, hemoglobin, electrical cardioversion, fluid loading, pharmacodynamically active amiodarone dose or use of other antiarrhythmic drugs, loop diuretics, catecholamine, curare or sedative drugs and need for CRRT. Fluid loading was defined as administration of more than 0.5 L of saline solution in 30 min. Electrocardiographic acquisition allowing for accurate evaluation of type of rhythm was left at the discretion of the treating physician.

As previously reported [18], pharmacodynamically active amiodarone dose for each subject was determined at the time of each HR, MAP, and plasma lactate collection. In brief, amiodarone pharmacokinetics was ascribed to a virtual compartment model including zero or first order input rates. This virtual compartment, A(t), represents the biophase in which amiodarone amount is in equilibrium with the observed effect on heart rate. Pharmacodynamic half-life (KDE) was determined to be 3.33 days. G(t) represents the amiodarone amount in the gut at a given time and ka, the first-order absorption rate, which was fixed to 8. Amiodarone bioavailability (F) was fixed to 0.33.

$$dA(t)/dt = \text{input} - KDE \times A(t) \quad (1)$$

$$\text{input} = ka \times G(t) \times \text{Fifadministeredorally} \quad (2)$$

2.3. Statistics

Results are expressed as numbers (%), means ± standard deviation, or medians (interquartile ranges) as appropriate. Normality was assessed by the D'Agostino-Pearson omnibus normality test. Comparison of continuous variables were analyzed by Mann-Whitney test for non-paired and non-parametric distribution. Comparison of categorical variables were analyzed by Chi-2 test. The correlation (r) between linear variables was assessed by calculating Pearson's for parametric distribution or Spearman's coefficient for non-parametric distribution (Prism 6, GraphPad software®, San Diego, USA). Of note, we had a power of at least 80% to detect a modest correlation ($r > 0.27$) between variation of HR and variation of hemodynamic surrogates (MAP and plasma lactate). Multivariable analysis was performed by using linear mixed effect modeling that takes into account repeated measures (package nlme, Linear and Nonlinear Mixed Effects Models, R statistical software, https://www.r-project.org). The general equation is:

$$Y = \text{intercept} + \beta_1 * X_1 + \beta_2 * X_2 + \ldots + \beta_n * X_n + \eta \quad (3)$$

Where Y is the dependent variable, X1,. . ., Xn and β1,. . ., βn stand for the explanatory variables and the corresponding regression coefficient respectively. η denotes the random effect (it models the differences between the patients)

Estimation of pharmacodynamically active amiodarone doses [18] at each time-point were derived using R statistical software (https://www.r-project.org). Statistical significance was accepted for $P < 0.05$.

3. Results

3.1. Study population and time-dependent observations

Seventy three consecutive patients admitted to ICU received at least one amiodarone dose for AT HR control and were eligible for