Respiratory Medicine (2014) 108, 638–646

Available online at www.sciencedirect.com

ScienceDirect

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

Initial characteristics and outcome of hospitalized patients with amiodarone pulmonary toxicity

J. Mankikian [a], O. Favelle [d], A. Guillon [b,c,e], L. Guilleminault [a,b,c], B. Cormier [f], A.P. Jonville-Béra [g], D. Perrotin [b,e], P. Diot [a,b,c], S. Marchand-Adam [a,b,c,*]

[a] CHRU Tours, Service de Pneumologie, Tours, France
[b] Université François Rabelais, UMR 1100, F-37032 Tours, France
[c] INSERM, Centre d'Etude des Pathologies Respiratoires, UMR 1100/EA6305, F-37032 Tours, France
[d] CHRU Tours, Service de Radiologie, Tours, France
[e] CHRU Tours, Service de Réanimation Médicale, Tours, France
[f] CHRU Tours, Service d'anatomopathologie, Tours, France
[g] CHRU Tours, Service de Pharmacologie Clinique Centre Régional de Pharmacovigilance, Tours, France

Received 19 September 2013; accepted 30 January 2014
Available online 10 February 2014

KEYWORDS
Amiodarone;
Amiodarone-induced pulmonary toxicity;
Drug toxicity;
High resolution computer tomography;
Pulmonary function tests

Summary
Amiodarone-induced pulmonary toxicity (APT) is a serious adverse event that can lead to death. The aims of our study are to determine factors associated with mortality and to describe outcome and sequelae of patients with APT.
Methods: Forty-six patients with APT were divided into two groups according to survival at day 90 for a clinical, functional, biological and radiological comparaison. We then evaluated the evolution of 15 survivors at a median of three months [1–6 months] and/or 12 months [8–36 months].
Results: Mortality of APT at day 90 was 37% (17 patients) and was linked to the speed of onset of symptoms and a high HRCT alveolar score. Angiotensin system antagonist treatment was prescribed significantly more in the survival group ($p = 0.042$, HR 0.34 (95% CI 0.12–0.96)). In surviving patients, dyspnea, vital capacity and HRCT alveolar score improved significantly while HRCT fibrosis score deteriorated gradually during the first six months. At the end of the study, all the surviving patients presented functional and/or radiological sequelae.

Abbreviations: APT, amiodarone-induced pulmonary toxicity; ARDS, Acute Respiratory Distress Syndrome; ASA, angiotensin system antagonist; BAL, bronchoalveolar lavage; BMI, body mass index; DEA, N-desethylamiodarone; HRCT, high resolution computer tomography; MMRC, Modified Medical Research Council; PFT, pulmonary function tests.

* Corresponding author. Service de Pneumologie et explorations fonctionnelles respiratoire, Hôpital Bretonneau, 2 boulevard Tonnellé, 37044 Tours Cedex, France. Tel.: +33 2 47473787; fax: +33 2 47473882.
E-mail addresses: karoun@orange.fr, s.marchandadam@univ-tours.fr (S. Marchand-Adam).

http://dx.doi.org/10.1016/j.rmed.2014.01.014

Conclusions: Severity of APT is linked to the extent and speed of onset of pulmonary damage. After the initial episode, the patients who survived improved slowly but with persistent sequelae.

Amiodarone is one of the most commonly prescribed antiarrhythmic drugs and is considered the most effective. Amiodarone-induced pulmonary toxicity (APT) occurs in 0.1—17% [1] of cases, with mortality ranging from 1 to 50% when Acute Respiratory Distress Syndrome (ARDS) develops [2—4]. Several mechanisms have been proposed to explain this toxicity [2,5—9]: direct drug-induced phospholipidosis secondary to lysosomal phospholipase inhibition and phospholipid accumulation due to the amphiphilic properties of amiodarone's metabolite, N-desethylamiodarone (DEA). DEA concentrates in organs with high lipid content, such as adipose tissue, the thyroid, liver and lungs. The clinical manifestation of phospholipidosis is the presence of foamy cells in bronchoalveolar lavage (BAL). However, foamy cells are not specific for amiodarone pulmonary toxicity and are currently considered merely to reflect the effect of a drug. An immunological hypothesis can also be put forward, based on the observation of T-cell infiltrates in some patients [7,10—12].

A dose-dependent effect was initially described, and high cumulative dose, high daily dosage (>400 mg/d) and duration of therapy (>12 months) are commonly recognized risk factors for pulmonary toxicity. However, some recent publications have reported toxicity with lower amiodarone doses or after only a few weeks of amiodarone therapy [13—16]. Many other risk factors have been described for amiodarone lung toxicity, notably age, but also male gender, pre-existing lung disease, renal disease, surgery, and high concentrations of inspired oxygen [3,17—24]. Clinical practice suggests that the outcome of APT after the initial episode is favorable after discontinuation of amiodarone, with or without corticosteroids [25].

To our knowledge, no study has evaluated the factors associated with mortality and pulmonary sequelae of APT. The aims of our retrospective study in patients with APT were to determine factors associated with mortality and to describe the medium- and long-term clinical, physiological and radiological pulmonary outcomes.

Methods

Patients

Our study was retrospectively conducted in the respiratory medicine department and intensive care unit of the university hospital of Tours, France. We reviewed 101 cases of drug-induced pulmonary toxicity among patients hospitalized between January 2000 and August 2011 (Fig. 1). Fifty-five patients were excluded, 43 because they had not received amiodarone during the previous month and 12 because of insufficient data to establish the diagnosis of APT.

French legislation does not require the agreement of an ethics committee, nor the informed consent of patients, for the retrospective collection of data that conform to current practice. However, the study protocol was evaluated and approved by the Institutional review board of the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*) (CEPRO 2011-031). The database was anonymous and complied with the restrictive requirements of the *Commission Nationale de l'Informatique et des Libertés*, the organization that ensures the application of data privacy laws in France.

Forty-six patients were diagnosed as having APT based on intrinsic and extrinsic pharmacological imputability criteria. The diagnosis criteria of APT were: a/amiodarone treatment at the time of diagnosis, b/new or worsening respiratory symptoms, c/new pulmonary infiltrates on chest radiography or high-resolution computed tomography (HRCT), d/exclusion of differential alternatives (cardiogenic edema, sepsis, other drug-induced pulmonary diseases), and e/improvement shown by surviving patients after amiodarone withdrawal, with or without corticosteroids.

Initial investigations

We collected the following data from the medical file of each patient: age, sex, body mass index (BMI), duration of

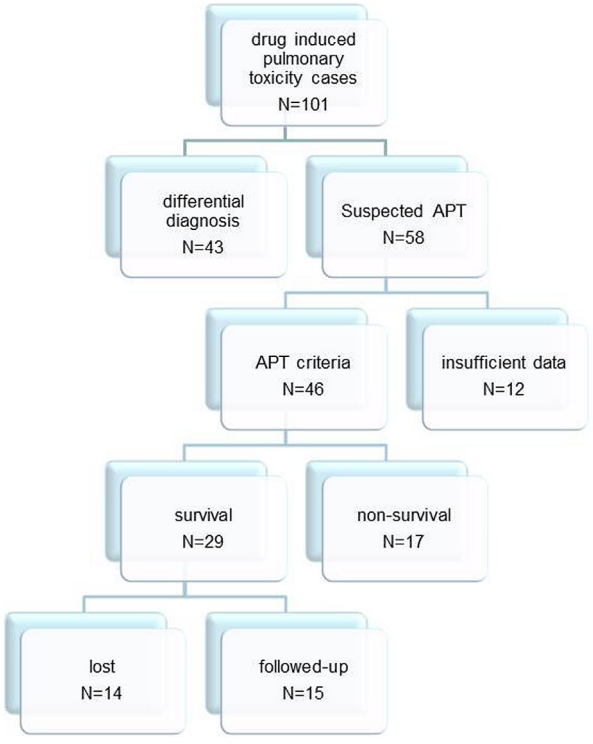

Figure 1 Patient flow-chart.