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Amiodarone-Induced Pulmonary Toxicity in the Elderly

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Abstract

Amiodarone is very commonly used as a preventive or curative treatment for ventricular and supraventricular rhythm disorders. Its spectrum of toxicity is wide: thyroid, heart, lung, eye, skin, liver, gastrointestinal, tract and central nervous system. All these effects result from the mitochondrial toxicity of the drug and its lipophilic character. This toxicity is not dose-related, and can occur even very early. The pulmonary toxicity of amiodarone has become increasingly rare with the use of lower doses (1.6-2%) but remains one of the main causes of discontinuation, can be fatal in 10% of cases, and lead to irreversible pulmonary fibrosis in 5-7% of cases. These injuries are more severe in the elderly because of physiological changes due to aging.

Its diagnosis and management can represent a really challenge for clinicians, particularly in elderly. The aim of this review is to clarify the different epidemiological, clinical, physiopathogenic, therapeutic, and evolutionary aspects of the pulmonary toxicity of amiodarone in the elderly.

Keywords : Amiodarone ; Amiodarone-Induced Pulmonary Toxicity ; Elderly ; Iatrogenesis ; Pulmonary Toxicity

Introduction

Despite the significant development of so-called «invasive rhythmology» and the emergence of new antiarrhythmics, amiodarone, which has been introduced into clinical practice since 1962 [1], remains very commonly used as a preventive or curative treatment for ventricular and supraventricular rhythm disorders, and as the most effective and recommended treatment by the American College of Chest Physicians (ACCP) to maintain and control sinus rhythm after cardioversion in patients with atrial fibrillation [1-3].With its unique pharmacokinetic characteristics, such as the minimal negative inotropic effect, amiodarone, an amphiphilic molecule, has a long half-life, a large volume of distribution, and substantial tissue accumulation, mainly at the adipose tissue. The molecule and its metabolites may then be responsible of toxicity in fat-rich organs such as the liver, lungs, skin and thyroid [4,5]. These injuries are more severe in the elderly because of physiological changes due to aging, such as reduced kidney function and changes in body composition (increased fatty tissue and decreased total body water), which affect the pharmacokinetics of both hydrophilic and lipophilic drugs [6]. Changing the clearance of drugs promotes the risk of adverse effects in general; the poly-medication with the increased risk of drug interactions, as well as the presence of multiple chronic underlying diseases, makes the elderly subject more fragile and more exposed to drug toxicity [7]. The current incidence of amiodarone-induced pulmonary toxicity is estimated to be 1.6-2% [8,9]. The most common presentation is acute or subacute pneumonia, while pleural involvement is exceptional [10,11] and is often described as an unusual manifestation of amiodarone-induced pneumonia [11,12]. We propose a review of amiodarone-induced pulmonary toxicity and its particularities in the elderly.

Generalities/Epidemiology

Amiodarone is a class III antiarrhythmic agent widely used for the treatment of ventricular and supraventricular arrhythmias [4,13]. Its spectrum of toxicity is wide: thyroid, heart, lung, eye, skin, liver, gastrointestinal tract and central nervous system [10]. All these effects result from the mitochondrial toxicity of the drug and its lipophilic character. This toxicity is not dose-related, it can occur even very early and in both sexes [14]. The pulmonary toxicity of amiodarone has become increasingly rare with the use of lower doses [11,13]. The review of the literature notes a particularly increased prevalence of amiodarone toxicity in elderly

subjects. In fact, the average age was 70 [2,6,7,15-21] (Table I).

Authors	Average age (year)
keng L-T et al. [2]	88
Bouomrani S et al. [6]	71
Diaz-Guzman et al. [7]	61
Nalos et al. [15]	58,5
Saussine et al. [16]	69
Morrow et al. [17]	61
Liverani et al. [18]	66
Kaushik et al. [19]	74
Kharabsheh et al. [20]	74
Boriani et al. [21]	77

Table I: The Average Age of Patients Treated with Amiodarone According to the Literature.

Sex is not a risk factor for amiodarone-induced pneumonia despite the male predominance reported by the majority of authors [1,14,15,22,23]. Some authors, however, reported a slight female predominance [6,24]. The comorbidities most commonly associated with this toxicity of amiodarone are diabetes mellitus and arterial hypertension [24-26] (Table II).

Authors (country/year)	HT(%)	Diabete(%)
Andrey JL et al. (Spain, 2011)[24]	45,9	33
Mark DB et al. (UK, 2008) [25]	55,1	28,7
Miles RH et al. (USA, 2011) [26]	8,3	36

Table II: Incidence of Hypertension (HT) and Diabetes in Patients Treated with Amiodarone According to Different Authors.

These data can be explained by the renal and/or hepatic functional alterations caused by these two diseases that potentiate those due to normal physiological aging. They may also reflect some correlation between these two pathologies and the frequency of rhythm disturbances, especially supraventricular ones [22]. The main indications for amiodarone are summarized in (table III). The three preferential indications of this molecule were in order of decreasing frequency: Atrial Fibrillation (AF), Ventricular Tachycardia (VT) and Premature Ventricular Complexes (PVC) [27,28] (Table III).

Authors (country/ year)	Number of patients	Indications (%)
Shukla R et al. (UK, 1994) [27]	109	AF (76) Flutter (7,5) Atrial Tachycardia (2) VT (13) VPC (1,5)
Conen D et al. (Switzerland, 2007) [28]	84	AF (57) Flutter (6) Atrial Tachycardia (1) VT (32) VPC (4)
AF: Atrial Fibrillation, VT: Ventricuar Tachycardia, VPC: Premature Ventricular Complexes.		

Table III: Therapeutic Indications of Amiodarone According to Different Studies.

Factors Favoring Amiodarone-Induced Pulmonary Toxicity in The Elderly

The majority of cases of amiodarone-induced pulmonary toxicity are reported in elderly subjects, typically over 60 years of age [2,6,7,15-21]. Indeed, age is one of the main factors favoring iatrogenic accidents in general and that of amiodarone in particular [17]. According to Teerakanok J et al, patients aged over 60 years have an increased risk of amiodarone toxicity after one month of treatment and this risk becomes greater after 6-12 months of treatment [1], and according to Paparis SA et al, the pulmonary toxicity of amiodarone increases 3-fold every 10 years in patients over 60 years of age compared to those under 60 years [4]. This particularly increased toxicity in the elderly is explained by the physiological variations in senescence which clearly influence the pharmacokinetics and pharmacodynamics of the drugs: indeed, in the elderly, there is a change in the volume of distribution of the drugs (with a decrease in muscle mass, decrease in total water and increase in fat mass) and a decrease in albumin levels of 20 to 40%. This leads to an overdose of water-soluble drugs and an accumulation of fat-soluble drugs such as amiodarone, and an increase in the free fraction of drugs [1,3,7]. Fatty mass (increased in the elderly) is a reservoir that stores the fat-soluble active substance and then releases it gradually, leading to an overdose and an increase in the half-life of the administered drug [7,17]. In terms of drug elimination, with age there is a reduction in hepatic mass, hepatic blood flow, microsomal oxidation due to decreased cytochrome P450 (CYP-450) concentrations, renal blood flow, glomerular filtration rate, and tubular excretion leading to an

increase in the active fractions of the drugs and thus increasing the toxic risk even at usual therapeutic doses [1,3,7,17]. Senile alterations of pulmonary function; with in particular the accelerated Decline of Diffusion Capacity of Carbon Monoxide (DLCO), contribute to the increased frequency of pulmonary complications of amiodarone in the elderly [4].

Amiodarone Toxicity: Pharmacokinetics and Physiopathology

Iatrogenic accidents secondary to amiodarone result mainly from the mitochondrial toxicity of this molecule and its lipophilic character [14]. The therapeutic margin of Amiodarone is poorly defined. Some authors placed it at 0.5-1.5mg/l, others at 1-2.5mg/l, whereas Delhotal B et al. recommended an optimal target residual plasma concentration at steady state of 0.5 to 2.5mg/l and established the toxic threshold of amiodarone at plasma concentrations greater than 2.5mg/l [29]. Chronic exposure to amiodarone induces formation of vacuoles and inclusions in leucocytes, corneal epithelial cells, skin cells, alveolar macrophages, liver cells and cardiomyocytes [17]. Amiodarone (AMD) is metabolized mainly in the liver by N-desethylation, deiodination and glucuro-conjugation reactions. The main metabolite is Desethylamiodarone (DAMD), which has AMD-like activity and is present in the plasma at concentrations close to those of the parent molecule. This metabolite is the product of N-desethylation, which is primarily catalyzed by CYP-450 by the following isoenzymes: CYP2C8, CYP3A4, and CYP1A1 [18]. DAMD is lower than AMD at the beginning of treatment (for a few days) and then, in the long term, becomes higher because of its greater elimination half-life [18]. CYP2C8 is considered the most involved isoenzyme in the N-desethylation of amiodarone. It constitutes approximately 5% of total hepatic CYP and plays an important role in the metabolism of a variety of endogenous and exogenous compounds. It is highly expressed in the liver, but is also found in extrahepatic tissues, such as the kidney, adrenal gland, brain and mammary gland [19]. The Plomp TA et al study showed average AMD and DAMD concentrations of 0.55 and 1.4 mg/l for a received therapeutic dose of 200mg/day. This study suggested a linear relationship between the plasma concentrations of the molecule and its metabolite and the therapeutic dose received [30]. On the other hand, the Kannan R et al study did not report any correlations between the plasma concentrations of AMD or DAMD and the dose received [31], thus explaining that the toxicity of amiodarone is not related to dose and can occur even very early and with lower doses [14]. In amiodarone-treated patients, with a charge dose or with a maintenance dose, there was remarkable variability in the plasma concentrations of AMD and DAMD from one patient to another [32]. This inter-individual variation seems to be related to the clinico-morphological properties of the patient interfering with the pharmacokinetic properties of the molecule as well as to drug interactions [22]. Amiodarone is a highly lipophilic, iodine-containing compound with a distribution volume of the order of 66 liters per kilogram of body weight.

This property results in a delayed onset of action of 2 to 3 days, and a long elimination half-life of 50 to 70 days [2]. These pharmacokinetic characteristics justify the use of a charge dose to quickly obtain an effective plasma concentration and thereafter the therapeutic activity. On the other hand, the residual activity of the molecule must be taken into account during the ten days following the cessation of treatment [24]. AMD is also considered an inhibitor of CYP3A4. Therefore, amiodarone has the potential to interact with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4, such as certain calcium channel blockers, statins, beta-blockers (such as propanaolol which is an enzyme inhibitor of CYP3A4), or even some anticoagulants such as warfarin whose amiodarone potentiates the anticoagulant effect [1,20,22,33]. Data also suggest that accumulation of amiodarone in the privileged tissues (high in lipids) can be explained, in addition to the high lipophilicity of the product, by a phenomenon of trapping the molecule in the light of acid organelles after protonization of the amine function in the lateral group [16]. Thus, amiodarone and its active metabolite accumulate in high concentrations in the liver, lungs, skin, fat, thyroid, and skeletal muscles explaining the variability in the clinical presentations of iatrogenic accidents associated with this treatment [23].

Clinic of Amiodarone-Induced Pulmonary Toxicity

Although rarely observed, toxic pulmonary involvement caused by amiodarone is one of the main causes of discontinuation [11,13,34]. The chronic form of this pulmonary toxicity was first described in the United States in the 1980s by Rotmensch in the form of pneumonia. As for the acute form of amiodarone-related pulmonary toxicity, it was first described in 1985 in two patients who developed acute and febrile respiratory distress syndrome [2]. Classically estimated at 5-7% [4,35], amiodarone-induced pneumopathy appears to be clinically overestimated [8,9]. Indeed, in Sunderji R et al's large, double-blind, and controlled trial involving 3,439 patients receiving 400mg or less of amiodarone daily, pulmonary toxicity was observed in only 1.6% [8]. This pulmonary toxicity of amiodarone has been significantly reduced by the use of lower doses of the drug, but can occur at any dose [10]. Clinically, amiodarone-induced pneumopathy can manifest itself as: cough, chest discomfort, often progressive dyspnea, chest pain, and more rarely hemoptysis or acute respiratory failure in exceptional forms of intra-alveolar hemorrhage or acute respiratory distress syndrome [4,6,34,36]. However, it can remain totally infra-clinical (insidious) and will only be diagnosed by chance with pulmonary imaging [4,34,36]. Radiologically, this toxic pneumonitis can take the following forms: diffuse interstitial lung disease, acute or chronic pneumonia, eosinophilic pneumonia, single or multiple nodules or massive lesions, desquamative interstitial pneumonia

and diffuse alveolar haemorrhage [6,10,36,37].

These lesions can be rapidly progressive [4] with a risk of irreversible pulmonary fibrosis [4,34,37]. Pleural effusion remains exceptional in case of pulmonary amiodarone toxicity [6,10-12]. It is classically bilateral and exudative [12,38]. It is rarely isolated [11], most often associated with pulmonary parenchymal toxicity or other organ-toxicities [6,12,38], and may exceptionally be the first sign of this toxicity [12,38]. In patients receiving long-term amiodarone, the onset of a high-density change in the liver and lungs on computed tomography indicates the occurrence of pulmonary and hepatic toxicity [18]. Some criteria have been proposed to diagnose amiodarone-induced pulmonary toxicity: PaO2/FiO2 ratio = 200, bilateral pulmonary infiltrates, pulmonary arterial pressure below 18mmHg and the exclusion of cardiopulmonary and infectious diseases [39].

Prognosis and Treatment of Amiodarone-Induced Pulmonary Toxicity

The overall mortality associated with chronic amiodarone-induced pulmonary toxicity is estimated at 10%, but can be as high as 36% in severe acute forms and fragile patients [1,4,10-12,14,25,39]. Otherwise, this pneumopathy can progress to irreversible fibrosis in 5-7% of cases [40]. Treatment is based on discontinuation of the culprit drug and, in severe cases, systemic corticosteroids for 4 to 12 months; the initial dose is 40 to 60mg/day, followed by a progressive decrease [10]. Corticosteroid therapy allows rapid improvement of pulmonary gas exchange and reversibility of radiological abnormalities [35]. Relapse after discontinuation of corticosteroid treatment has been reported mainly in obese subjects. More severe forms of amiodarone toxicity with simultaneous multi-organ involvement have been reported: simultaneous parenchymal pulmonary, pleural, and hepatic involvement [6], and simultaneous thyroid, pulmonary, and ocular involvement [41]. These multi-organ forms can occur early and even with low doses of amiodarone [41,42].

Prevention of Amiodarone Toxicity in the Elderly

The rules of good medical prescription to be respected in the elderly to avoid these iatrogenic accidents are as follows:

- Before the prescription: to know all the pathologies of the patient and his medical and surgical history, to know all the medicines taken by the patient, to prioritize the pathologies and to fix the objectives of the treatment according to the quality of the aging (normal, pathological, successful) and the quality of life sought, to know the weight, the renal and liver functions, the state of hydration and the nutritional state of the patient, to make sure that the treatment which one envisages would have a satisfactory rendered medical service, and to know the principal pharmacokinetic parameters of the various prescribed drugs (possible interactions?),

- During the prescription: write a legible prescription, ensure that the treatment is well understood, that its use is possible and that it can be taken, take into account the other necessary care, note the prescriptions on the health record for that other stakeholders know, and set the expected duration of treatment,

- After the prescription: regularly evaluate the treatment, schedule a suitable clinical and para-clinical surveillance and know how to stop the medication when necessary.

For amiodarone, there are several guidelines for monitoring patients who are taking this drug in the long term. The most used are those of the North American Society of Pacing and Electrophysiology published in 2000 [43] and updated in 2007 [44] (Table IV).

Tests	Baseline	During treatment	If clinical signs suggestive
ECG	+	Yearly	When clinically relevant
Pulmonary function tests (including DLCO) and High-resolution CT Scan	+		Unexplained cough or dyspnea, especially in patients with underlying lung disease, if there are suggestive x-ray film abnormalities, and if there is a clinical suspicion of pulmonary toxicity
Chest X-ray	+	Yearly	+
Thyroid function tests	+	Every 6 months	
Liver function tests	+	Every 6 months	
Ophthalmologic evaluation	+		if visual impairment or for symptoms

Table IV: Tests and Cadence of the Surveillance of the Patients Under Amiodarone According to The Guidelines of North American Society of Stimulation and Electrophysiology.

Good clinical, biological and radiological surveillance in accordance with the recommendations allows the early detection of adverse effects related to amiodarone treatment and thus their rapid and appropriate management to improve the prognosis, potentially fatal in the elderly.

Alternatives

AMD's cardiac and extracardiac adverse effects have prompted the pharmaceutical industry to develop several other therapeutic approaches for treating arrhythmias such as dronedarone. Since obtaining its Marketing Authorization in 2009 and marketing it in France in October 2010 under the name Multaq®, this medicine has a prominent place in the treatment of patients with atrial fibrillation [45]. Dronedarone is a benzofuran derivative that is structurally related to amiodarone but, unlike it, does not have an iodine atom and has a sulfonamide group responsible for its lower lipophilicity. These two differences explain the much lower risk of adverse effects classically observed with amiodarone.

Conclusion

Amiodarone is a widely prescribed antiarrhythmic agent, particularly in the elderly because of the frequency of supraventricular rhythm disorders in geriatrics. Among the toxicities associated with this drug, amiodarone-induced pulmonary toxicity is one of the most serious, and may be life-threatening in the elderly.

A preliminary screening of the pulmonary functions (clinical, radiological and eventually functional) to the prescription of this molecule is currently indicated as well as regular clinico-radiological monitoring. The early detection of this iatrogenic accident makes it possible to provide appropriate care avoiding severe forms of this pulmonary toxicity such as acute respiratory distress syndrome as well as the subsequent progression to irreversible pulmonary fibrosis. The most used guidelines for monitoring patients under amiodarone in long term are those of the North American Society of Pacing and Electrophysiology published in 2000 and updated in 2007.

Pharmacogenetics (identification of specific HLA haplotypes predisposing to this toxicity) as well as the development of similar molecules of new generations with a lower toxic profile represent the two main future paths in this field.

Conflicts of interest : None

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