ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 127 SECTIO D 2004

Ward of Pulmonary Diseases and Phthisiology
Independent Public Hospital named after John of God in Lublin
Department and Clinic of Internal Diseases, Skubiszewski Medical University of Lublin

ADAM PODSTAWKA, JERZY MOSIEWICZ, WOJCIECH MYŚLIŃSKI

Pulmonary complications in amiodarone treatment

Amiodarone is an antiarrhythmic drug which, according to Vaughan Williams' classification is included in class III. It is applied in treating supraventricular and ventricular arrhythmias. The mechanism of its antiarrythmic activity involves prolonging the duration of the action potential and of the effective refraction period in the myocardial cells. Amiodarone is especially useful in the treatment of arrhythmias reluctant to other drugs, as well as in the prophylaxis of paroxysmal atrial fibrillation, or flutter. It is also used in the treatment of ventricular fibrillation, ventricular tachycardia and Wolf–Parkinson–White syndrome. Amiodarone is an especially valuable antiarrhythmic drug in patients with impaired systolic function of the left ventricle and cardiomyopathy complicated with arrhythmia.

Its advantageous activity is proven by the results of ALIVE study, which revealed much higher effectiveness of amiodarone than lidocaine in the treatment of ventricular fibrillation not subsiding after electric defibrillation, as well as in prevention of ventricular fibrillation recurrences after cardiac arrest outside hospital (6). The European standards recommend applying amiodarone as the first line drug in patients with unstable ventricular tachycardia or ventricular fibrillation resistant to three first defibrillator discharges (14). The effectiveness of amiodarone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation is similar to the effectiveness of class IC antiarrhythmic drugs. However, amiodarone can be the drug of choice in patients with impaired ventricular function, or ischemic heart disease, unless an emergency cardioversion is necessary (4). Amiodarone can also be used as a prophylactic drug, protecting the patient from the recurrence of atrial fibrillation (18). Besides, contrary to other antiarrhythmic drugs, it reveals proarrhythmic or cardiodepressive activity less frequently.

Although it is a fact that amiodarone treatment is quite effective, yet its clinical administration may be restricted by numerous undesirable effects, such as: lesions of thyroid, liver and lungs, gastrointestinal and neurological disorders, as well as skin reactions. One of unfavourable side-effects of amiodarone is its pulmotoxicity. It was described for the first time by R o t m e n s c h in 1980. It occurs in 5–10% patients receiving amiodarone and can have lethal effects (8).

The toxic action of amiodarone is influenced by its chemical composition. This drug has got a non-polar ring and a hydrophilic cationic lateral chain. Its cationic-amphoteric structure influences the metabolism of lipids and lysosomal membranes, damaging cellular structures (11). Besides, the main metabolite of amiodarone – desethyloamiodarone – is deposited in tissues to an even greater extent and is more toxic (3). The long half-life of the drug (even up to 45 days) is also disadvantageous, because its potential toxic effect can last long after cessation of treatment (8).

It was revealed that the toxic effect of amiodarone, especially on the pulmonary tissue, depends on the dose of the drug, the period of administration and on additional risk factors, including old age, accompanying pulmonary tissue diseases, cardio- and thoracosurgical operations with intensive oxygen therapy, as well as administration of other cardiologic drugs. The undesired effects occur more frequently

when the daily dose exceeds 400 mg a day, and the treatment period exceeds two months. However, amiodarone used even in low, supporting doses, not exceeding 300 mg a day, may reveal unfavorable side-effects towards the respiratory system (8).

The frequency of undesired effects after amiodarone treatment depends on its concentration in the serum. It was found that the frequency of side-effects was lower at amiodarone concentration in the serum below 2.5 mg/l, which secured appropriate arrhythmia control. However, in sensitive patients pulmotoxicity may occur at small concentrations of amiodarone (< 2.5 mg/l). It was also noticed that patients with lowered ejection fraction of the left ventricle (< 25%) revealed lower concentrations of amiodarone in the serum, which resulted from the reduced bioavailability of the drug administered orally in patients with circulatory insufficiency, whereas higher serum concentrations of the drug make it possible to foresee the occurrence of certain side-effects (17).

The mechanism of amiodarone toxic effect is not ultimately recognized. Besides the phenomena of hypersensitivity features and inflammatory processes related to them, a certain role (maybe greater than the immunological mechanism) may be played by immediate, cytotoxic lesion of the pulmonary tissue, causing the inflow of inflammatory effector cells into the lungs. This is confirmed by ultrastructural examinations, in which immunoglobulin deposits and complement components were not found, whereas the accumulation of granular and membranous structures was revealed inside the distended lysosomes of macrophages, type II pneumocytes, insterstitial and endothelial cells (11). This accumulation of multilamellar bodies in the cytoplasm of various cells is caused by the decrease of phospholipid degradation, because amiodarone is a strong inhibitor of A_1 and A_2 lysosomal phospholipase. Amiodarone disturbs the distribution of lysosomal enzymes and causes their release, which initiates lesion of the pulmonary tissue. Besides, it suppresses pulmonary degradation of the surfactant, changes the physical properties of cell membranes, influences mitochondrial metabolical changes, causes the increase of toxic free oxygen radicals and induces cellular apoptosis. It can also activate pulmonary "natural killer" cells and change the profile of the secreted cytokines by alveolar macrophages (1). The common histological features of inflammatory alterations resulting from amiodarone administration are: the accumulation of foamy macrophages inside the alveoli, thickening of interalveolar connective tissue walls, as well as the proliferation of type II pneumocytes (11). In the bronchoalveolar lavage one can observe the increase of the number of: CD (suppressors) lymphocytes, cytotoxic T-cell, poly-morphonuclear cells, and foamy macrophages (8). Pulmonary tissue lesion and the subsequent inflammatory changes lead to fibrosis which is a permanent and irreversible process.

Certain papers suggest that the concentration of reverse triiodothyronine (reverse-T_3) may correlate with the frequency of side-effects, also from the respiratory system (17). Amiodarone inhibits the peripheral thyroxine (T_4) conversion to triiodothyronine (T_3) by inhibiting the activity of type I 5'-deiodinase. Therefore, most patients receiving amiodarone for a longer period of time, reveal the increase of T_4, correct or decreased level of T_3 and the increase of reverse-T_3 level (12). Amiodarone–induced hyperthyroidism may cause arrhythmia intensification and deterioration of heart efficiency, which, in turn, may lead to hemodynamic disorders, increasing the risk of the occurrence of pulmonary complications.

Clinical manifestations of amiodarone side-effects in relation to pulmonary tissue may take acute (pneumonia, respiratory insufficiency syndrome) or chronic forms (interstitial pneumonia with fibrosis). The symptoms of pulmonary toxicity of amiodarone may be: exertional dyspnea, nonproductive cough, body weight loss, fever, respiration-related chest pain, and even respiratory failure (2, 8). In these cases physical examination usually reveals bibasilar rales, decreased breath sounds, less frequently described, pleural friction (2). Laboratory tests, though unspecific, reveal increased erythrocyte sedimentation rate, leucocytosis, hypoxemia and the increase of lactate dehydrogenase (LDH) level (8, 11).

Radiological alterations may vary. They include reticular and patchy acinar infiltrates; less often – thickenings or pleural effusion, focal consolidation, diffuse acinar infiltrates, and nodular lesions

(2). Diffuse interstitial and patchy peripheral alveolar infiltrates frequently involving the upper lobes and requiring differentiation from active pulmonary tuberculosis were also described (11).

In the case of the development of adult respiratory distress syndrome (ARDS) the radiological image resembles bilateral diffuse interstitial pneumonia indicating infiltration of alveoli and interstitium. The occurrence of ARDS after treatment with amiodarone is especially furthered by surgical procedures related to exposition to high oxygen concentrations. Amiodarone is believed to increase the susceptibility of pulmonary tissue to the toxic influence of oxygen (10).

Multiple, nodular alterations, situated peripherally in inferior pulmonary lobes were also described. They suggested metastatic alterations in the lungs, histologically revealing the features of obliterative bronchiolitis with organizing pneumonia (Bronchitis Obliterans Organizing Pneumonia – BOOP). BOOP is a pulmonary tissue disease in which the lesion of small airways results from distorted repair processes, performed by proliferating fibroblasts and myofibroblasts. A microscopic feature of this kind of alterations is the existence of fibrous intraluminal plugs in the terminal bronchioles, often appearing as evenly spaced, rounded balls of myxomatosus connective tissue extending distally into alveolar ducts and alveoli. The clinical symptoms of BOOP may be: dyspnea, cough, expectoration, fever, body weight loss and hemoptysis (13). The occurrence of alveolitis was also reported. It was radiologically characterized by extensive bilateral fluffy opacification in the chest x-ray film suggesting pulmonary edema. The most probable cause of such kind of changes is the hypersensitivity response to amiodarone, similar to the response to other drugs, e.g. to nitrofurantoin, hexamethonium and bisulphan (16). Literature reports one case of hemoptysis which occurred in a patient in the first days of amiodarone therapy (7).

The characteristic changes in the image of the lungs, obtained in high-resolution computer tomography (HRCT), confirming the presence of inflammatory alterations, are extensive, heterogeneous, ground grass-type areas (8). The ground grass image is the result of the translucency decrease in the pulmonary tissue caused by the presence of fluid or cellular infiltrations in the alveolar spaces and in their immediate surroundings.

The principal diagnostic test, evaluating the functional effects of the above-described radiological changes is spirometry in which – depending on the type of inflammation and stage of its development – restrictive, obturative and mixed changes may occur. However, restrictive changes are most frequently described. Their characteristic features are decreased pulmonary vital capacity (VC), or forced vital capacity (FVC) (9, 11), at Tiffenau index value comprised within the standard (or above the standard) – FEV_1%VC or FEV_1%FVC. In the cases of inflammatory alterations or in pulmonary tissue fibrosis, restriction of pulmonary ventilation of mixed nature may occur in which besides the decrease of FVC and FEV_1 (forced expiratory volume in one second) the value of FEV_1%FVC decreases.

Cabin whole body plethysmography makes it possible to perform the measurement of pulmonary volumes, unavailable to the spirometric test, including functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC), as well as the airways resistance. In the case of the development of fibrous alterations after amiodarone treatment, plethysmography makes it possible to reveal the restrictive changes involving the decrease of FRC, RV and TLC. Application of this method guarantees high accuracy, repeatability and the lowest dependence on co-operation with the patient.

In the presence of radiological changes and clinical symptoms, a sensitive indicator of pulmotoxicity of amiodarone is the decrease of diffusion capacity of the lungs for carbon dioxide (DL_{CO}) (5, 9, 16). It is an exponent of the lesion of alveoli and the alveolo-capillary barrier. To determine DL_{CO} by single inhalation method, the patient inhales a mixture of gases containing 0.3% CO and 10% He, holding their breath for a specific period of time (10 seconds). The inhaled gases diffuse in the amount depending on the state of pulmonary stroma, through the capillary walls into the blood, thus changing their partial pressure in the exhaled air. The advantage of this method is administering a small amount of CO to the patient, so the test can be repeated after 20–30 minutes. According to American Thoracic Society

(ATS), to obtain the repeatability of test results, two performed DL_{CO} measurements may differ between themselves maximally by 10% of the mean value, or by 3 ml/min/mmHg CO (15). The DL_{CO} examination is a very useful test evaluating the extent of lung damage which may be used to monitor the course of disease and evaluation of treatment effectiveness. However, the DL_{CO} measurement also depends on other factors, such as blood flow through capillaries, hemoglobin concentration and irregularity of pulmonary ventilation.

In the diagnostics of amiodarone-induced pneumonia Gallium[67] scintigraphy can be a helpful test. This test reveals homogenous, generalized, increased marker capture in both lungs, more intensive than in the liver. Gallium[67] is a sensitive but unspecific marker, indicating inflammatory changes occurring after amiodarone treatment. Therefore, to establish the diagnosis, besides a positive scintigraphy result, the presence of specific clinical criteria is necessary (9).

A good indicator of amiodarone-induced pulmotoxicity is the level of cancer-associated serum antigen (CASA). Amiodarone induces the increase of mucus and mucin protein MUC-1 production in the respiratory passages. The level of MUC-1 in the peripheral blood is determined by means of monoclonal antibodies detecting mucin protein epitopes during marking of the CASA antigen by means of the ELISA method. The increase of the level of this antigen also occurs in neoplastic (malignant) diseases. It is a useful marker in the difficult diagnosis of amiodarone pulmotoxicity and in differentiating it from congestive heart failure, because in both cases the radiological image may be similar (5). Pulmonary alterations induced by amiodarone should also be differentiated from bacterial or viral pneumonia, congestive heart failure, pulmonary embolism, neoplastic processes and connective tissue diseases.

In the case of occurrence of pulmotoxicity symptoms, it is necessary to discontinue amiodarone treatment and apply glucocorticotherapy (methylprednisolone, prednisone) (10, 11, 16). Clinical improvement usually occurs after 2–4 weeks, and the subsidence of radiological alterations – after 2–3 months. Using corticosteroids in these cases is regarded by some authors as controversial, as the principal pathomechanism of pulmotoxicity is not of immunological nature (11). However, the administration of glucocorticosteroids accelerates the regression of inflammatory changes in the lungs, restricts the scope of fibrosis and decreases dyspnea in these patients. In obliterative bronchiolitis and BOOP, it is very advantageous to start corticosteroid treatment early, which allows for regression of alterations and decreases mortality (8).

Pulmotoxicity is an especially dangerous side-effect of amiodarone administration, because it can lead to severe respiratory insufficiency, ending in death. However, there are clinical situations, in which amiodarone reveals distinct superiority over other antiarrhythmic drugs. Perhaps it is more advantageous to use this drug in emergency situations than in the long-lasting, supportive therapy, because its toxicity depends on the dose and length of administration period, i.e. on the total dose. It also seems advisable to limit the treatment of arrhythmia with amiodarone only to cases in which the remaining antiarrhythmic drugs are ineffective, or contraindicated. Before the beginning of long-lasting (chronic) amiodarone therapy, the initial chest radiogram and a spirometric test should be performed, and then, during treatment, spirometric and radiological monitoring should be conducted, especially in the persons from high risk groups and those reporting symptoms concerning the respiratory system (cough, dyspnea, pain in the chest). The side-effects of amiodarone of pulmonary origin should be detected as early as possible because quick discontinuation of this drug and administration of glucocorticotherapy makes it possible to avoid severe pulmonary complications.

Amiodarone still belongs to classic drugs influencing repolarization of heart cells. Its various effects on the cardiovascular system in the states of severe ventricular and supraventricular arrhythmias may save patients' lives. However, the administration of this drug should depend on the evaluation of clinical situation, potentially increasing the risk of side-effects in relation to the respiratory system. The risk factors of the development of pulmonary complications of amiodarone treatment should

always be taken into consideration, and the necessity of its administration should be connected with activities aiming at early diagnostics of alterations within the respiratory system.

REFERENCES

1. Baritussio A. et al.: Amiodarone inhibits lung degradation of SP-A and perturbs the distribution of lysosomal enzymes. Am. J. Physiol. Lung Cell. Mol. Physiol., 281, 1189, 2001.
2. Ben-Noun L.: Drug-induced respiratory disorders. Incidence, prevention and management. Drug Saf., 23, 143, 2000.
3. Bolt M. W. et al.: Disruption of mitochondrial function and cellular ATP levels by amiodarone and N-desethylamiodarone in initiation of amiodarone-induced pulmonary cytotoxicity. J. Pharmacol. Exp. Ther., 298, 1280, 2001.
4. Chevalier P. et al.: Amiodarone versus placebo and class IC drugs for cardioversion of recent onset atrial fibrillation: a metaanalysis. J. Am. Coll. of Cardiol., 41, 255, 2003.
5. Devine P. L. et al.: Serum mucin antigen (CASA) as a marker of amiodarone-induced pulmonary toxicity. Dis. Markers, 14, 169, 1998.
6. Dorian P. et al.: Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N. Engl. J. Med., 346, 884, 2002.
7. Goldstein I. et al.: Very early onset of acute amiodarone pulmonary toxicity presenting with hemoptysis. Chest, 111, 1446, 1997.
8. Jessurun G. A. J. et al.: Amiodarone-induced pulmonary toxicity. Predisposing factors, clinical symptoms and treatment. Drug Saf., 18, 339, 1998.
9. Lim K. K., Radford D. J.: Amiodarone pneumonitis diagnosed by gallium-67 scintigraphy. Heart, Lung and Circulation, 11, 59, 2002.
10. Liveriani E. et al.: Amiodarone-induced adult respiratory distress syndrome after nonthoracotomy subcutaneous defibrillator implantation. J. Intern. Med., 249, 565, 2001.
11. Marchlinski F. E. et al.: Amiodarone pulmonary toxicity. Ann. Intern. Med., 97, 839, 1982.
12. McKenna W. et al.: Amiodarone: the experience of the past decade. BMJ, 287, 1654, 1983.
13. Orseck M. J. et al.: Bronchiolitis obliterans organizing pneumonia mimicking multiple pulmonary metastases. Am. Surg., 66, 11, 2000.
14. Priori S. G. et al.: Task force on sudden cardiac death of the European society of cardiology. Eur. Heart J., 22, 1374, 2001.
15. Punjabi N. M. et al.: Measurement variability in single-breath diffusing capacity of the lung. Chest, 123, 1082, 2003.
16. Riley S. A. et al.: Alveolitis after treatment with amiodarone. BMJ, 284, 161, 1982.
17. Rotmensch H. H. et al.: Steady-state serum amiodarone concentrations: relationship with antiarrhythmic efficacy and toxicity. Ann. Intern. Med., 101, 462, 1984.
18. Roy D. et al.: Amiodarone to prevent recurrence of atrial fibrillation. Canadian trial of atrial fibrillation investigators. N. Engl. J. Med., 342, 913, 2000.

SUMMARY

Amiodarone is a widely used antiarrhythmic drug, however, not without numerous side-effects. One of them is a potentially adverse reaction upon the respiratory system which can assume the form of acute respiratory failure, interstitial pneumonitis, parenchymal infiltrates, pleural effusion or bronchiolitis obliterans organizing pneumonia. For this reason prior to the onset of the long-term amiodarone therapy initial chest x-ray and spirometry should be made and in the course of the treatment

spirometry and radiological monitoring should be carried out. Helpful in diagnosing the side-effects of amiodarone use in relation to the respiratory system could also be plethysmography, evaluation of the diffusing capacity, Gallium scintigraphy and cancer-associated serum antigen (CASA). While planning a long-term amiodarone therapy one should consider the risk factors of the development of pulmonary complications and the necessity to use this drug should be connected with the activities aiming at an early diagnosis of the respiratory system dysfunctions.

Powikłania płucne leczenia amiodaronem

Amiodaron jest często stosowanym lekiem antyarytmicznym, niepozbawionym jednak wielu działań ubocznych. Jednym z nich jest potencjalnie niekorzystne działanie w stosunku do układu oddechowego, które może przyjmować postać ostrej niewydolności oddechowej, śródmiąższowego zapalenia płuc, nacieków miąższowych, wysięku opłucnowego lub zarostowego zapalenia oskrzelików z organizującym się zapaleniem płuc. Z tego względu przed rozpoczęciem przewlekłej terapii amiodaronem należy wykonać wyjściowy radiogram klatki piersiowej i badanie spirometryczne, a następnie w trakcie leczenia prowadzić monitorowanie spirometryczne i radiologiczne. Pomocne w rozpoznaniu objawów ubocznych stosowania amiodaronu w stosunku do układu oddechowego mogą być także badania pletyzmograficzne, ocena pojemności dyfuzyjnej, scyntygrafia Galem[67] oraz oznaczenie surowiczego antygenu związanego z rakiem (CASA). Planując przewlekłe leczenie amiodaronem, należy rozważyć czynniki ryzyka rozwoju powikłań płucnych, a konieczność zastosowania tego leku łączyć z działaniami mającymi na celu wczesną diagnostykę zmian w zakresie układu oddechowego.