Acute lung affection in an endurance-trained man under amiodarone medication

Akute Pneumonitis bei einem trainierten Individuum unter Amiodaron-Behandlung

Abstract

Patients undergoing treatment with amiodarone can develop severe pulmonary side effects. This effect, which is often highly underestimated, can lead to dyspnea, pneumonitis, and further fibrosis. A recent change in the labeling of amiodarone by the American Food and Drug Administration (FDA) supports this suspicion. Tracing the symptoms back to the causing agent can be difficult, as shown in our report.

The subject of this case report is an endurance-trained 65 year old male marathon runner who appeared with atrial fibrillation during a routine check up in autumn 2003. After medical cardioversion with flecainide a complaint free interval of 8 months was followed by a relapse, which resulted in a change of medication to amiodarone. Due to misunderstandings the patient kept on taking the amiodarone loading dose for six weeks and returned with severe dyspnea on exertion.

Losses in CO diffusing capacity, a lowered macrophages count and a positive lymphocyte transformation test were the only first hand clinical evidence of amiodarone intoxication, despite the sensation of dyspnea. This case shows that special care has to be taken in treatment with amiodarone. Side effects can be hard to trace and do not evidently show a clear connection to amiodarone.

Keywords: pneumonitis, dyspnoe, vital capacity, amiodarone

Introduction

Amiodarone was initially developed in 1961 as a treatment for angina. It was commonly used throughout Europe as an anti-anginal medication, and was soon found to restrain arrhythmias. However, first descriptions of amiodarone induced pulmonary toxicity (AIPIT) were published in 1980 by Rotmensh [1]. Numerous investigations took place in the 1980s in order to find the pathomechanism of amiodarone lung damage. AIPIT is a relatively common side effect with a reported incidence of 2 to 15 percent per year [1], [2]. It is known that AIPIT is up to nine times more likely in patients with preexisting lung disease [3]. Our case report wants to point out, that this also relates to well trained healthy subjects and ought not to be underestimated.
Diagnosing the pulmonary side effects of amiodarone induced damages is like looking for a needle in a haystack, since no secure clinical marker is known to proof Aipt. Several methods have to be combined to conclude the quest, such as bodyplethysmography, BAL, blood parameters, and clinical signs.

Case presentation

The patient agreed to the use of his clinical data and written informed consent was obtained for this report. The endurance-trained 65 year old male marathon runner (175 cm; 75 kg) appears in a very good state of physical fitness. Before the diagnosis of atrial fibrillation in autumn 2003 no cardiac or pulmonary diseases were known. Since 1976 the patient repeatedly took part in various marathon runs (15 complete runs) and achieved his best time in 3 hours and 15 minutes. Also he took part in numerous half-maraathons and short-distance competitions (since 1976 a total count of 29,300 km training distance). In preparation for each marathon he embarked upon a 12 week training period, with three 15 km runs a week and additional physical workout in a gym. While exercising for a marathon atop the Chinese wall in 2002 the patient underwent a special physical examination program at the University Hospital in Freiburg, Germany, Dept. for rehabilitation, prevention and sports medicine, showing no evidence of cardiac or pulmonary complications or hypertension. During a routine check up in August 2003 atrial fibrillation and perpetual arrhythmia was diagnosed by his local physician. He was sent to the University Hospital in Freiburg to undergo medical cardioversion with flecainide and anticoagulatory treatment with phenprocoumon, followed by ASS. After primary conversion with 4 x 100 mg flecainide a stabilizing dose of 2 x 100 mg flecainide was prescribed, but several relapses occurred for the following 9 to 11 months due to bad compliance in medicine intake. The relapses were also treated with flecainide. There were no signs of oedema, extrasystole or lung complications, such as dyspnea on exertion; blood pressure rose to 150/90 mmHg, but this did not receive any special attention.

After an interval of 11 months of treatment with flecainide, anti-coagulation and recurring relapses the medication was changed to amiodarone. At this time the patient already felt slight sensations of dyspnea due to atrial fibrillation. On July 1, 2004 he was advised to take an initial loading dose of 4x200 mg amiodarone for three days; anticoagulatory treatment was kept. On July 5, despite subjective well-being, atrial arrhythmia was still present. The loading dose medication was set to 5x200 mg amiodarone for the next three days. On July 8 the ECG showed a regular sinus rhythm with a first degree a-v block. The continuing medication was set to a dose of 1x200 mg amiodarone per day. Due to a misunderstanding the patient kept on taking the loading dose for the following six weeks. Routine lung function on July 21, 2004 showed no abnormalities (Figure 1). However, after that he experienced an increasing sensation of dyspnea on exertion and lowered resilience. This led to emergency treatment in the university hospital in Freiburg on August 12, 2004.

The patient showed a severe dyspnoe. Blood levels of amiodarone (1.4 μg·ml⁻¹) and its degradation product desethylamiodarone (0.9 μg·ml⁻¹) were nonetheless within normal limits. In a chest radiography and chest HR-CT with contrast medium no signs of amiodarone induced changes in lung parenchyma, interstitial tissue or fibrosis could be detected. No high-attenuation infiltrates could be detected by the radiologist.

In order to evaluate a specific T-lymphocyte activation due to amiodarone a lymphocyte proliferation test (LPT) was performed. The result was highly positive showing a SI of 15.1 with 100 pmol amiodarone clearly exceeding the individual threshold value of 5.1. In contrast, lymphocytes from a healthy person disclosed a SI of 2.9 as the highest value not exceeding the individual threshold value of 3.7.

Due to the possibility of lung affections under amiodarone and the patient’s dyspnea, bronchofibroscopy, functional lung testing, bodyplethysmography and carbon monoxide diffusing capacity (D_LCO) was measured. Bronchofibroscopy showed marginal signs of an acute bronchitis. A bronchial lavage (BAL) was taken from the upper left bronchus which showed a reduced percentage of macrophage cell count (74%), neutrophil granulocytes (10%) and a discrete CD⁴⁺-prominent lymphocytosis (15%) with a CD⁴⁺/CD⁸⁺-Quotient of 0.17.

Bronchofibroscopy records and analysis of blood gases and D_LCO were available from July 2004 and showed no signs of lung disease or affection. After the high dose intake of amiodarone lung function analysis showed a significant reduction in the D_LCO with no relevant changes in Vital Capacity and FEV₁ (Figure 1). During standardized six minute walking test losses in PaO₂ (minimal value
A presumptive diagnosis of an amiodarone-induced pulmonary disease was made clinically, according to the results of the BAL with the positive LPT. The only change made was to discontinue the use of amiodarone. In addition nebivolol 5 mg/d was given for five days to reduce sensations of arrhythmia. Anticoagulatory treatment was kept. As can be seen in Figure 1, complete remission of D\(_{LCO}\) to normal values was achieved and maintained through follow-up inspections. No signs of other amiodarone-induced side effects could be detected. In a follow up inspection in February 2005 at the department of cardiology cardiac function proved to be a stable sinus rhythm, long term ECG and blood pressure controls did not show any pathological evidence. Lung function stabilized at normal values.

**Discussion**

In this case, an endurance-trained individual developed pneumonitis while receiving an accidentally high dose of amiodarone. The most common side effects of amiodarone therapy are skin discoloration, photodermatitis, hepatitis and hepatic cellular necrosis, thyroid dysfunction, corneal deposits, paresthesia, tremor, ataxy, drug interactions, and bone marrow suppression [4], [5], [6], none of which could be found in our patient. Etiology of amiodarone lung toxicity is still not understood in all its details, but it is believed that a sequence of events damages the mitochondrial functions and ATP regeneration in lung cells [7]. A favored attribute of amiodarone is its long half life. On the contrary this leads to accumulation of DEA, which is even more destructive than amiodarone, in peripheral tissue, contributing to its toxicity in the lung [7]. A reduced percentage of macrophages, an increase in neutrophiles and CD\(_{4+}\)/CD\(_{8+}\) lymphocytes in BAL fluids in comparison to normal are a common finding, but does not allow a differentiation between amiodarone induced pneumonitis and other comparable forms [3]. Thus, BAL can be a good method for differential diagnosis in patients examined for A IPT [8].

LPT gauges the frequency of antigen-specific T cells, i.e. high stimulation indices indicate a high number of cells proliferating after the recognition of the specific antigen. LPT is frequently used to differentiate chronic beryllium disease and sarcoidosis [9], [10], [11] or to estimate adverse effects of anti-tuberculosis therapy [11]. These tests are specific and can differentiate between different causative agents, which are also indicated by the clear difference in SI between patient and control [11]. We did not determine the sub-population of T cells reacting in the amiodarone LPT, however, due to the decreased CD\(_{4+}/CD_{8+}\) ratio it is feasible that CD\(_{4+}\) cells are important in the pathophysiology of amiodarone induced pneumonitis and may represent the proliferating sub-population in LPT.

Patients who develop lung damages often show increased blood levels of amiodarone and even higher levels of DEA [12]. These parameters, too, do not allow a diagnosis of amiodarone induced lung damages, since other reports also point out, that amiodarone-induced side effects can occur without elevated blood levels of amiodarone or DEA [13]. Therefore blood concentrations prove not to be a reliable indicator for the occurrence of side effects. In April 2003 the Food and Drug Administration (FDA) approved a change in the labeling of amiodarone and the pulmonary side effects are now clearly noted. Retrospective studies stated that an amiodarone intake of more than 400 mg per day leads to an estimated 10% to 17% of lung damages in patients of which 10% turned out to be fatal [14]. Adams et al. [15] estimate the pulmonary side effects even at 27%. The most common changes developing from amiodarone intoxication are dyspnea, pneumonitis and pulmonary fibrosis. KudenChuck et al. [16] point out that there is only a weak correlation between the degree of exposure to amiodarone (in dosage and duration of treatment) and the development of lung affections; the only predictive risk in developing adverse effects are initial abnormalities in pulmonary function such as a reduced D\(_{LCO}\) and pathological findings in chest x-ray. Additionally there is an increasing role of amiodarone induced ARDS in patients with pre-existing lung damages and surgical patients [3], [14]. Ott et al. [17] show that even low dose treatment (200 mg per day) is a risk factor for developing lung damages ranging from mild symptoms such as cough to ARDS. Therefore it is notable that not even a low dose of amiodarone is presently a safe medication, but may decrease the incidence of pulmonary side effects [18]. It is noteworthy that our patient did not show any signs of amiodarone or DEA intoxication in his blood, despite his high dosage and prolonged intake. The most wide spread varying parameter is D\(_{LCO}\). Most patients with amiodarone lung damages show a greater loss in D\(_{LCO}\) than normal patients. Adams et al. [15] show that there was a mean loss of 20.3% in D\(_{LCO}\) levels in patients under treatment with amiodarone than in comparison with normal subjects. On the other hand it is shown by Gleadhill et al. [1] that an isolated fall in D\(_{LCO}\) does not necessarily require a discontinuation of amiodarone treatment when no clinical signs of intoxication are given. Therefore, an unchanged D\(_{LCO}\) value appears to be a reliable negative predictor of pulmonary toxicity. Pulmonary function testing is also not proven to be statistically relevant for diagnosis, since it does not allow to a distinction from other pulmonary diseases [19]. In our case, no changes in VC and FEV\(_{1}\) could be measured (Figure 1).

Despite that our patient did not show any evidence of amiodarone induced lung changes for the first three weeks of his high dose intake. The first notable changes occurred in the time period July 21 to August 12, 2004 (Figure 1). The time span, in which AIPT develops varies from acute onset up to long term affection. Dusman et al. [12] noted AIPT from the sixth day of treatment up to the 60th month, with the highest incidence occurring
during the first 12 months. Hypersensitivity pneumonitis can occur early in treatment [6]. Even though amiodarone side effects are more likely to occur with increasing duration of treatment and cumulating dosage [13]. In patients of the ICU following thoracic surgery acute AIPT and ARDS can develop within 2 days postoperative and may turn out fatal, especially in these patients [3], [20]. There is no specific treatment for an amiodarone affected lung. Corticosteroids might be helpful to reduce inflammation, but are not intended for general usage. Reversibility of pulmonary changes, even fibrosis, by discontinuation of amiodarone treatment is a well described phenomenon [21], [22], [17].

Conclusions

Our case report, although a single one can act as a reminder of the clinical uncertainties of amiodarone use and patient compliance. Amiodarone is surely a safe and very effective anti-arrhythmic drug, but should be administered with a close clinical monitoring and the lowest dosage possible for arrhythmia control. 

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