

## **Amiodarone and Pulmonary Toxicity 06.08.07**

1: Pharmacotherapy. 2007 Apr;27(4):616-8.

Fatal pulmonary toxicity after a single dose of cyclophosphamide.

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Cyclophosphamide is a chemotherapeutic agent with the potential to cause pulmonary toxicity, most commonly in the form of diffuse alveolar damage. Cyclophosphamide-induced pulmonary toxicity is extremely rare and often difficult to recognize because of presence of confounding factors, including use of other cytotoxic drugs, radiation pneumonitis, oxygen toxicity, pulmonary infections, and malignancies. The lung toxicity caused by cyclophosphamide is accelerated when cyclophosphamide is combined with amiodarone, an antiarrhythmic agent also capable of lung toxicity. We describe a patient with non-Hodgkin's lymphoma who developed fatal pulmonary toxicity after a single dose of cyclophosphamide in the setting of long-term amiodarone use.

PMID: 17381391 [Pubmed - in process]

### Related Links

Lung toxicity associated with cyclophosphamide use. Two distinct patterns. [Am J Respir Crit Care Med. 1996] PMID:8970380

Amiodarone and cyclophosphamide: potential for enhanced lung toxicity. [Bone Marrow Transplant. 2001] PMID:11438830

Long-term gonadal toxicity after therapy for Hodgkin's and non-Hodgkin's lymphoma. [Ann Hematol. 1994] PMID:8167175

Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. [Drugs. 2003] PMID:12662126

Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. [Cancer. 2001] PMID:11745270

2: Toxicol. Sci. 2003 Sep;75(1):169-80. Epub 2003 Jun 27.

Differential effects of pirfenidone on acute pulmonary injury and ensuing fibrosis in the hamster model of amiodarone-induced pulmonary toxicity.

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Pulmonary toxicity, including fibrosis, is a serious adverse effect associated with the antidysrhythmic drug amiodarone (AM). We tested the potential usefulness of pirfenidone against AM-induced pulmonary toxicity in the hamster model. Intratracheal AM administration resulted in pulmonary fibrosis 21 days posttreatment, as evidenced by an increased hydroxyproline content and

histological damage. Dietary pirfenidone administration (0.5% w/w in chow), for 3 days prior to and continuously after AM, prevented fibrosis and suppressed elevation of pulmonary transforming growth factor (TGF)-beta1 mRNA content at 7 and 21 days post-AM. Protection against AM-induced lung damage was not observed when supplementation with pirfenidone was delayed until 7 days following AM administration, suggesting that alteration of early events in AM lung toxicity is necessary for the protective effect of pirfenidone. Both AM and bleomycin, another pulmonary fibrogen, caused inflammation 24 h after intratracheal dosing, measured as increased lactate dehydrogenase activity, protein content, and cellular alterations in bronchoalveolar lavage fluid, with the response to AM markedly greater than that to bleomycin. Administration of AM, but not bleomycin, also caused whole lung mitochondrial dysfunction, alveolar macrophage death, and an influx of eosinophils into the lung, of which pirfenidone was able to decrease only the latter. We conclude that: (1) AM induces alveolar macrophage death and severe, acute pulmonary inflammation with associated eosinophilia following intratracheal administration; (2) mitochondrial dysfunction may play an early role in AM pulmonary injury; and (3) pirfenidone decreases AM-induced pulmonary fibrosis in the hamster, probably through suppression of TGF-beta1 gene expression.

Publication Types:

Comparative Study

Research Support, Non-U.S. Gov't

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Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. [Inflammation. 2000] PMID:10921510

Use of tetrandrine to differentiate between mechanisms involved in silica-versus bleomycin-induced fibrosis. [J Toxicol Environ Health A. 1999] PMID:10406349

Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. [J Pharmacol Exp Ther. 1999] PMID:10490926

3: J. Pharmacol. Exp. Ther. 2003 Jan;304(1):277-83.

Attenuation of amiodarone-induced pulmonary fibrosis by vitamin E is associated with suppression of transforming growth factor-beta1 gene expression but not prevention of mitochondrial dysfunction.

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Amiodarone (AM) is an efficacious antidysrhythmic agent that can cause numerous adverse effects, including potentially life-threatening pulmonary fibrosis. The current study was undertaken to investigate potential protective mechanisms of vitamin E against AM-induced pulmonary toxicity (AIPT) in the hamster. Three weeks after intratracheal administration of AM (1.83 micromol), increased pulmonary hydroxyproline content and histological damage were observed, indicative of fibrosis. These effects were preceded by increased pulmonary levels of transforming growth factor (TGF)-beta1 mRNA at 1 week post-AM, which remained elevated 3 weeks post-AM. Dietary supplementation with vitamin E resulted in rapid pulmonary accumulation of the vitamin, and prevention of AM-induced increases in TGF-beta1, hydroxyproline, and histological damage. Although dietary supplementation also markedly elevated lung mitochondrial vitamin E content, it did not attenuate AM-induced inhibition of mitochondrial respiration or disruption of mitochondrial membrane potential in vitro, or lung mitochondrial respiratory inhibition resulting from in vivo AM administration. These results suggest that vitamin E reduces the extent of pulmonary damage after AM administration via down-regulating TGF-beta1 overexpression but that it does not modify AM-induced mitochondrial dysfunction, a potential initiating event in AIPT.

Publication Types:

Research Support, Non-U.S. Gov't

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Effects of vitamin E on cytotoxicity of amiodarone and N-desethylamiodarone in isolated hamster lung cells. [Toxicology. 2001] PMID:11543907

Induction of c-jun and TGF-beta 1 in Fischer 344 rats during amiodarone-induced pulmonary fibrosis. [Am J Physiol Lung Cell Mol Physiol. 2001] PMID:11597910

Disruption of mitochondrial function and cellular ATP levels by amiodarone and N-desethylamiodarone in initiation of amiodarone-induced pulmonary cytotoxicity. [J Pharmacol Exp Ther. 2001] PMID:11504831

4: Intensive Care Med. 1998 Jun;24(6):626-30.

Comment in:

Intensive Care Med. 1999 Feb;25(2):242-3.

Acute amiodarone-induced lung toxicity.

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**OBJECTIVE:** To investigate any relationship between the pathological features of amiodarone-induced pulmonary toxicity (APT) and clinical use of amiodarone in patients dying from acute respiratory distress syndrome (ARDS). **DESIGN:** Retrospective study. Review of clinical and pathological findings of patients dying from ARDS. **SETTING:** Intensive Care Unit (ICU) and Pathology Department of University hospital. **SUBJECTS:** Ten patients with clinical diagnosis of ARDS, who died in ICU and underwent post mortem examination. **INTERVENTIONS:** Case note review of clinical details; independent review of histological specimens. **MEASUREMENT AND RESULTS:** Over a 3-year period, ten patients underwent post mortem examination, of whom seven had received amiodarone. Three patients who received longer than 48 h of amiodarone had histological changes of widespread lipoid pneumonia, a recognised pattern of APT. **CONCLUSIONS:** Acute amiodarone pulmonary toxicity is a definite pathological entity in ICU patients. High oxygen concentrations may be a risk factor, while pre-existing pathology, e. g. ARDS, may mask its development. Amiodarone should be used with caution in this group of patients.

PMID: 9681788 [Pubmed - indexed for MEDLINE]

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Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? [Chest. 2001] PMID:11451849

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Can amiodarone pulmonary toxicity be predicted in patients undergoing implantable cardioverter defibrillator implantation? [Pacing Clin Electrophysiol. 1993] PMID:7508601

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Evaluation of reactive oxygen species involvement in amiodarone pulmonary toxicity in vivo and in vitro.

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Amiodarone (AM) is an effective antidysrhythmic agent, restricted in use by the development of adverse effects, including potentially fatal AM-induced pulmonary toxicity (AIPT). Although the pathogenesis of AIPT is unknown, an oxidant mechanism has been proposed. The present study evaluated the role of reactive oxygen species (ROS) in AM-induced toxicity. The effect of inhibiting lung antioxidant defense on in vivo development of AIPT was evaluated in hamsters. Lung glutathione reductase activity was inhibited by 66%, 6 hours following administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (20 mg/kg i.p.).

When AM (1.83  $\mu\text{mol}$ ) was administered intratracheally 6 hours after BCNU, toxicity was enhanced, as indicated by lung hydroxyproline content and histological evaluation 21 days later. However, BCNU treatment did not affect AM-induced alterations in lung glutathione, suggesting that the increased toxicity was not due to decreased antioxidant capacity following BCNU. The effect of BCNU on AM cytotoxicity in vitro was evaluated using rabbit lung alveolar macrophages. Incubation with 5  $\mu\text{M}$  BCNU for 2 hours caused greater than 95% inhibition of glutathione reductase activity. However, BCNU treatment had no effect on 146  $\mu\text{M}$  AM-induced cytotoxicity, as assessed by lactate dehydrogenase latency following 12 hours of incubation. Rabbit macrophages loaded with 2',7'-dichlorofluorescein, which is oxidized by ROS to fluorescent 2',7'-dichlorofluorescein (DCF), were used to evaluate ROS generation by AM. Incubation of macrophages with AM (73 or 146  $\mu\text{M}$ ) for 1 hour, with or without the catalase inhibitor sodium azide (1 mM), did not result in DCF formation. Overall, these results do not support the hypothesis that AIPT is due to ROS action.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 9029274 [Pubmed - indexed for MEDLINE]

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Investigation of the role of oxidative stress in amiodarone-induced pulmonary toxicity in the hamster. [Can J Physiol Pharmacol. 1994] PMID:7954092

Disruption of mitochondrial function and cellular ATP levels by amiodarone and N-desethylamiodarone in initiation of amiodarone-induced pulmonary cytotoxicity. [J Pharmacol Exp Ther. 2001] PMID:11504831

Effects of vitamin E on cytotoxicity of amiodarone and N-desethylamiodarone in isolated hamster lung cells. [Toxicology. 2001] PMID:11543907

Effects of dietary vitamin E supplementation on pulmonary morphology and collagen deposition in amiodarone- and vehicle-treated hamsters. [Toxicology. 1999] PMID:10378474

Comparison of the in vivo pulmonary toxicity of amiodarone and des-oxo-amiodarone in the hamster. [Toxicol Appl Pharmacol. 1994] PMID:8048071

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Mechanisms in the pathogenesis of amiodarone-induced pulmonary toxicity.

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Although amiodarone is a highly efficacious antidysrhythmic agent, the drug produces numerous adverse effects. The most critical of these is pulmonary toxicity because of the potential for mortality. This review examines the experimental model systems used to study amiodarone toxicity, summarizes the current state of knowledge regarding the processes involved in amiodarone-induced pulmonary toxicity (AIPT), and includes a discussion of potential future

directions. Possible contributing processes to initiation of AIPT include phospholipidosis, altered calcium ion regulation, generation of reactive oxygen species, formation of an amiodarone aryl radical, and perturbation of cellular energy production. In addition, an immune response to the parent compound or to a metabolite could play a role. It is expected that elucidation of the mechanism(s) of AIPT will lead to safer antidysrhythmic agents and (or) to effective treatments for the prevention or amelioration of AIPT.

Publication Types:

Research Support, Non-U.S. Gov't  
Review

PMID: 8834480 [Pubmed - indexed for MEDLINE]

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An evaluation of possible mechanisms underlying amiodarone-induced pulmonary toxicity. [Proc Soc Exp Biol Med. 1996] PMID:8751986

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Resistance of the hamster to amiodarone-induced pulmonary toxicity following repeated intraperitoneal administration. [Toxicol Lett. 1994] PMID:8085270

Intratracheal amiodarone administration to F344 rats directly damages lung airway and parenchymal cells. [Toxicol Appl Pharmacol. 2003] PMID:12691727

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Pulmonary complications after long term amiodarone treatment.

Roca J, Heras M, Rodriguez-Roisin R, MagriÃ±Ã J, Xaubet A, Sanz G.

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**BACKGROUND:** Amiodarone hydrochloride is an antiarrhythmic agent useful in arrhythmias refractory to standard therapy. Although interstitial pneumonitis is known to be its most serious side effect, several aspects of amiodarone lung toxicity are still controversial. **METHODS:** Pulmonary side effects were examined in a sample of 61 symptomless patients (mean (SD) age 55 (7) years) who had had long term treatment with amiodarone (daily maintenance dose 400 mg), selected from 482 men attending the University of Barcelona myocardial infarction project. To allow for the confounding effects of coronary artery disease and tobacco history on lung function, 46 patients who had taken amiodarone for more than one year were matched with a control group from the same population. Subjects underwent measurement of lung volumes, arterial blood gas analysis and an incremental bicycle exercise test. **RESULTS:** Most lung function values were close to predicted values, though there was a small increase in resting alveolar-arterial oxygen tension difference (A-aDO<sub>2</sub>) at rest (4.8 (1.4) kPa in both groups). There were no differences in the results of forced spirometry or static lung volumes between the two groups, or in the fall in A-aDO<sub>2</sub> from rest to exercise. There was a small difference between the amiodarone and the control

group in transfer factor for carbon monoxide corrected for lung volume (KCO 1.67 (0.3) and 1.83 (0.3) mmol min<sup>-1</sup> kPa<sup>-1</sup> l<sup>-1</sup> respectively) and in exercise capacity (140 (25) and 120 (30)w). Only three patients showed lung function impairment consistent with pneumonitis. No relation between lung function measures and cumulative doses of amiodarone or desethylamiodarone was found. CONCLUSIONS: The prevalence of clinically evident pulmonary side effects was 4.9%, which is lower than that reported in studies in which higher daily maintenance doses of amiodarone were given. The slightly lower KCO values and lower work load achieved by the patients taking amiodarone suggest a small effect of amiodarone in doses of 400 mg on lung function. A role for individual susceptibility to pulmonary complications of amiodarone treatment is suggested.

Publication Types:

Comparative Study

Research Support, Non-U.S. Gov't

PMID: 1609381 [Pubmed - indexed for MEDLINE]

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Serial lung function testing in patients treated with amiodarone: a prospective study. [Am J Med. 1989] PMID:2910095

Long-term low-dose amiodarone therapy in the management of ventricular and supraventricular tachyarrhythmias: efficacy and safety. [Clin Cardiol. 1997] PMID:9098598

Pulmonary effect of amiodarone in patients with heart failure. The Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy (CHF-STAT) Investigators (Veterans Affairs Cooperative Study No. 320). [J Am Coll Cardiol. 1997] PMID:9247526

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Amiodarone-induced injury of human pulmonary artery endothelial cells: protection by alpha-tocopherol.

Kachel DL, Moyer TP, Martin WJ.

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Amiodarone is a potent antidysrhythmic drug that is associated with severe pulmonary toxicity. The mechanism of amiodarone pulmonary toxicity is poorly understood. To investigate the possible involvement of oxygen-derived metabolites in amiodarone-induced injury, <sup>51</sup>Cr-labeled human pulmonary artery endothelial (HPAE) cells were incubated with amiodarone for 18 hr in the presence of various antioxidants and in hypoxic and hyperoxic conditions with cell injury quantified by <sup>51</sup>Cr release, expressed as cytotoxic index. Amiodarone (10-50 microM) directly injured HPAE cells in a concentration-dependent manner, but the injury was not

modulated by altering ambient oxygen concentrations. Furthermore, amiodarone-induced injury (30 microM) was not reduced by the following antioxidants: catalase, superoxide dismutase, ascorbic acid, dimethyl sulfoxide and ethanol. In contrast, toxicity from 30 microM amiodarone was significantly reduced by alpha-tocopherol (alpha-TOC) at 10, 20 and 40 microM from a cytotoxic index of 41.6 +/- 3.5 to 25.5 +/- 7.9, 10.61 +/- 5.4 and 3.1 +/- 2.8, respectively. As revealed by phase microscopy, alpha-TOC (40 microM) prevented any evidence of toxicity to the amiodarone-treated cells. Amiodarone concentrations in the HPAE cells incubated in the presence and absence of alpha-TOC were not significantly different, indicating that alpha-TOC did not interfere with the uptake of the drug by the cells. Similarly, amiodarone did not interfere with the uptake of alpha-TOC by the HPAE cells. Although the specific mechanism of action remains unclear, alpha-TOC affords nearly complete protection in vitro from the cellular injury induced by amiodarone.

Publication Types:

Research Support, U.S. Gov't, P.H.S.

PMID: 2395108 [Pubmed - indexed for MEDLINE]

Related Links

Amiodarone-mediated increase in intracellular free Ca<sup>2+</sup> associated with cellular injury to human pulmonary artery endothelial cells. [Toxicol Appl Pharmacol. 1990] PMID:2315926

Bleomycin-induced pulmonary endothelial cell injury: evidence for the role of iron-catalyzed toxic oxygen-derived species. [J Lab Clin Med. 1987] PMID:2439623

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Life-threatening postoperative pulmonary complications in patients with previous amiodarone pulmonary toxicity undergoing cardiothoracic operations.

Nalos PC, Kass RM, Gang ES, Fishbein MC, Mandel WJ, Peter T.

Amiodarone therapy for cardiac arrhythmias is increasingly being recognized to be associated with pulmonary toxicity. In this report, we describe the case histories of four patients with previously diagnosed amiodarone pulmonary toxicity in whom the adult respiratory distress syndrome developed after cardiothoracic operations for malignant ventricular arrhythmias. Three patients underwent endocardial resection (two died), and a fourth patient had implantation of an automatic defibrillator unit. Radiographic changes and results of pulmonary function testing are evaluated during initial toxicity and preoperatively. These four patients (mean amiodarone dosage of 420 mg/day for 20 months) are compared to 13 other patients undergoing cardiothoracic operations with prior amiodarone treatment (one patient with preoperative pulmonary toxicity) in whom

life-threatening postoperative pulmonary complications did not develop (mean dosage of 550 mg/day for 10 months). Mean preoperative serum amiodarone levels for the four patients were 1.5 micrograms/ml. In the two patients who died, desethylamiodarone levels were 510 and 4,400 micrograms/gm in pulmonary tissue. Histologic examination showed "honeycomb" appearance of the lung with prominent septae, alveolar foamy macrophages, and hyperplasia of alveolar lining cells, consistent with amiodarone pulmonary toxicity. Causes including pump-oxygenator time, oxygen toxicity, anesthetic agents, congestive heart failure, and pulmonary infection superimposed on amiodarone pulmonary toxicity are discussed with a review of the literature.

Publication Types:

- Case Reports
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, P.H.S.

PMID: 3573800 [Pubmed - indexed for MEDLINE]

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Low-dose amiodarone-related complications after cardiac operations. [J Thorac Cardiovasc Surg. 1997] PMID:9240291

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