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Acute amiodarone-induced lung toxicity

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Abstract *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.

Key words Amiodarone · Acute amiodarone · Induced pulmonary toxicity (APT) · Adult respiratory distress syndrome (ARDS) · Ventilation · High oxygen concentrations

Introduction

The toxic effects of amiodarone on the lung are well recognised, but the rapid onset of those effects, especially in the presence of high inspired oxygen concentrations, are perhaps not adequately appreciated. This may be a potential problem in the Intensive Care Unit (ICU) where amiodarone is frequently used in the treatment of tachydysrhythmias in patients with acute respiratory distress syndrome (ARDS) requiring very high inspired oxygen concentrations. The finding of typical histological appearances of acute amiodarone pulmonary toxicity at post mortem examination of a patient thought to have died from ARDS prompted a review of post mortem findings in patients with a clinical diagnosis of ARDS over the last 3 years.

Materials and methods

Using the ICU and Pathology Department databases, ten cases of ARDS were identified who had undergone post mortem examination in the last 3 years. This represents a small proportion of the total number of ARDS patients treated, reflecting our low post mortem rate. The patients' clinical details were reviewed, including age, duration of stay, cause of ARDS, other clinical diagnoses, duration of inspired oxygen content at 100 % and dose and duration of amiodarone treatment. Amiodarone (Cordarone X, Sanofi Pharma) was infused according to a standard protocol; 300 mg of

Table 1 Clinical details

Case no.	Age	ICU stay (days)	Cause of ARDS	Duration of FIO$_2$ (days)		Amiodarone dose/duration
				> 50 %	100 %	
1.	82	12	Aspiration Acute renal failure	12	4	300 mg; 900 mg/day for 4 days
2.	72	3	ARDS (unknown origin) Acute renal failure	3	2	300 mg; 900 mg/day for 3 days
3.	50	6	Acute renal failure Renal carcinoma	4	1	300 mg; 900 mg/day for 1 day, 600 mg/day for 1 day
4.	72	17	ARDS Pneumonia	14	7	300 mg; 900 mg/day for 1 day
5.	75	14	Sepsis Acute renal failure	13	6	300 mg; 900 mg/day for 8 days, 200 mg/day for 2 days
6.	66	4	Perforated duodenum	4	4	300 mg; 900 mg/day for 1 day. Further 300 mg + 600 mg/day for 1 day
7.	76	5	Pneumonia Aspiration	5	5	300 mg; 900 mg/day for 1 day
8.	32	3	Staphylococcal septicaemia	3	3	None
9.	79	6	Pulmonary fibrosis Valvular heart disease	5	4	None
10.	52	12	Sub-arachnoid haemorrhage Perforated duodenal ulcer Pneumothorax	6	2	None

a solution of 1.2 g in 500 ml 5 % dextrose over 1 h followed by 900 mg over the subsequent 23 h and thereafter as clinically dictated. The lung histology was reviewed without knowledge of the patients' clinical details. All cases had a minimum of three blocks of lung tissue (range 3–7) and routine H & E sections were examined.

Results

The patient's clinical details are described in Table 1. During their ICU stay three patients received no amiodarone, two received 24 h, two received 48 h, and three received longer than 48 h of amiodarone therapy. Patients 2, 3, 5 and 6 died while on amiodarone treatment.

The post mortem histological findings are described in Table 2. Three principal patterns of lung pathology were seen in these patients: hyaline membrane disease with or without accompanying desquamation of alveolar macrophages, and lipoid pneumonia. The three patients who received amiodarone for longer than 48 h all showed extensive lipoid pneumonia. None of the three patients who did not receive amiodarone nor the four receiving 48 h or less had changes of endogenous lipoid pneumonia. All ten patients received sedation and a variety of drugs including inotropes and antibiotics, none of which are noted for lung toxicity. Patients 1, 3, 4, 5, 7, 8, and 10 received parenteral nutrition.

Table 2 Post mortem findings

Case no.	Blocks (no)	Hyaline membrane disease	Lipoid pneumonia	Desquamated alveolar macrophages
1.	3	Minimal	+++	–
2.	5	Minimal	+++	–
3.	3	++	–	+++
4.	4	+	–	+
5.	4	Minimal	++	–
6.	5	+++	–	+++
7.	4	++	–	–
8.	6	+	–	+++
9.	6	+++	–	++
10.	7	+	–	+++

* Extensive pneumonia with widespread foamy change in polymorphs

Discussion

Amiodarone is an extremely effective therapy for supraventricular dysrhythmias and has been used successfully in patients with sepsis and ARDS in whom supraventricular tachydysrhythmias (SVTs) may lead to profound haemodynamic disturbances and can be resistant to treatment. Our experience of three commonly used agents, amiodarone, digoxin and verapamil showed

that a sustained response occurs most frequently with amiodarone, which consequently is our first line management of SVTs associated with sepsis [1]. Other workers have reported a high incidence of recurrent dysrhythmias in patients after a 24 h course of amiodarone and suggest that treatment should be continued for several days until the patient's overall condition is more stable [2].

Intravenous amiodarone has an onset of action of between 1 and 30 min. Its high lipid solubility and huge volume of distribution of up to 148 l/kg mean that plasma therapeutic monitoring is inappropriate. The highest levels of the drug are found in adipose tissue, the liver and lungs. It is eliminated by hepatic and intestinal metabolism with less than 1% excreted by the kidneys and hence no dosage adjustments are required in renal failure.

Cases 1, 2, and 5 received between 3 and 8 days treatment with amiodarone at a dose of 900 mg daily in view of recurrent SVT; these relatively large doses are within dosage recommendations [3].

There appear to be two distinct patterns of presentation of amiodarone pulmonary toxicity (APT). Two-thirds of cases consist of an insidious onset of a non-productive cough, dyspnoea, weight loss and, occasionally, fever. This is associated with diffuse interstitial infiltrates on chest X-ray. This type of reaction rarely begins before two months of therapy and seldom in patients receiving less than 400 mg daily. The second type of presentation is associated with a more acute onset. The chest X-ray shows a predominant alveolar pattern not uncommonly involving the peripheral area of the lung. This presentation is typically associated with fever, mimicking pneumonia and, in severe cases, ARDS [4].

There are a number of reports of acute amiodarone pulmonary toxicity presenting as ARDS, following cardiac or general surgery in patients on long-term amiodarone therapy [5–7]. In one of these series, the incidence of post-operative pulmonary complications was substantially greater in patients receiving amiodarone; 8 out of 11 patients receiving amiodarone pre-operatively experienced post-operative complications compared to only two of nine patients not on amiodarone undergoing similar surgery. Of the eight on amiodarone treatment with pulmonary complications six were exposed to a high intra-operative inspired oxygen concentration (greater than 50%) [7]. Post-operative acute APT has also been noted after short-term amiodarone prophylaxis for atrial fibrillation following thoracic surgery [8]. Three out of eleven patients receiving amiodarone prophylaxis developed ARDS after pneumonectomy, while none of the 21 receiving placebo or verapamil developed this complication. In the affected patients, amiodarone treatment lasted only 2–3 days (dose 2150–3750 mg I. V.).

The mechanism of action of amiodarone toxicity remains unknown although several theories have been postulated. Amiodarone is known to inhibit phospholipase and the resulting phospholipidosis may cause direct cell injury [9]. Type II alveolar epithelial cells, bronchiolar epithelium and interstitial fibroblasts eventually show vacuolation. Extra-pulmonary involvement takes the form of similar vacuoles in the lymph nodes, circulating blood, liver, thyroid, GI tract and skin [10]. Another possibility is that cell damage may be mediated in part by toxic oxygen free radicals and this may explain the link between APT and a high FIO_2 [6]. The immunological system is also implicated in APT with raised counts of polymorphonuclear leukocytes, t-suppressor and cytotoxic lymphocytes being found in patients exhibiting amiodarone toxicity [4].

The post mortem appearances of ARDS consist of diffuse alveolar damage at various stages of evolution. These changes range from pulmonary oedema, congestion and haemorrhage to typical hyaline membrane disease and changes of an organizing pneumonia, depending on the duration of the terminal illness. It should be appreciated that different stages of this pathological process are usually present at the same time in any one specimen. It is not usual to see intra-alveolar foamy macrophages (as distinct from desquamated macrophages) in patients with ARDS.

An endogenous-type pattern of lipoid pneumonia is a well recognised pattern of amiodarone-induced lung injury. Three of our patients (1, 2 and 5) show the typical appearances of an endogenous lipoid pneumonia (Fig. 1a). These patients all received longer than 48 h of amiodarone therapy. Given the time course between the initiation of therapy and death in these patients, it is clear that such reactions can evolve rapidly. This group of patients did show small traces of typical hyaline membrane disease but in no case did this histological pattern coincide with the lipoid pneumonia, the two patterns occurring in different areas of the lung. In none of these cases did hyaline membrane change constitute more than 5–10% of the abnormalities noted. Three of our patients (3, 6 and 9) showed florid changes of hyaline membrane disease (Fig. 1b) with no evidence of lipoid pneumonia. Two of these patients had received amiodarone for 48 h while one received none.

The third pattern of pulmonary injury is characterised by desquamative interstitial pneumonia (Fig. 1c), which is a recognised marker of diffuse alveolar damage. Five of our cases showed this pattern to a major extent, three in association with significant hyaline membrane disease elsewhere in the sections and two in relative isolation. The presence of desquamated alveolar macrophages in association with hyaline membrane disease may cause difficulty when reviewing the autopsy histology of patients who have died with clinical ARDS. It is important to appreciate the morphological difference between these macrophages, which have a slightly granular and often pigmented (lipofuschin) cy-

Figs. 1 A–C Photomicrographs showing principal patterns of pulmonary disease. **A** Endogenous lipoid pneumonia (amiodarone-type pattern; index case) (H & E × 266) **B** Hyaline membrane disease (H & E × 66) **C** Desquamative pneumonia (H & E × 266)
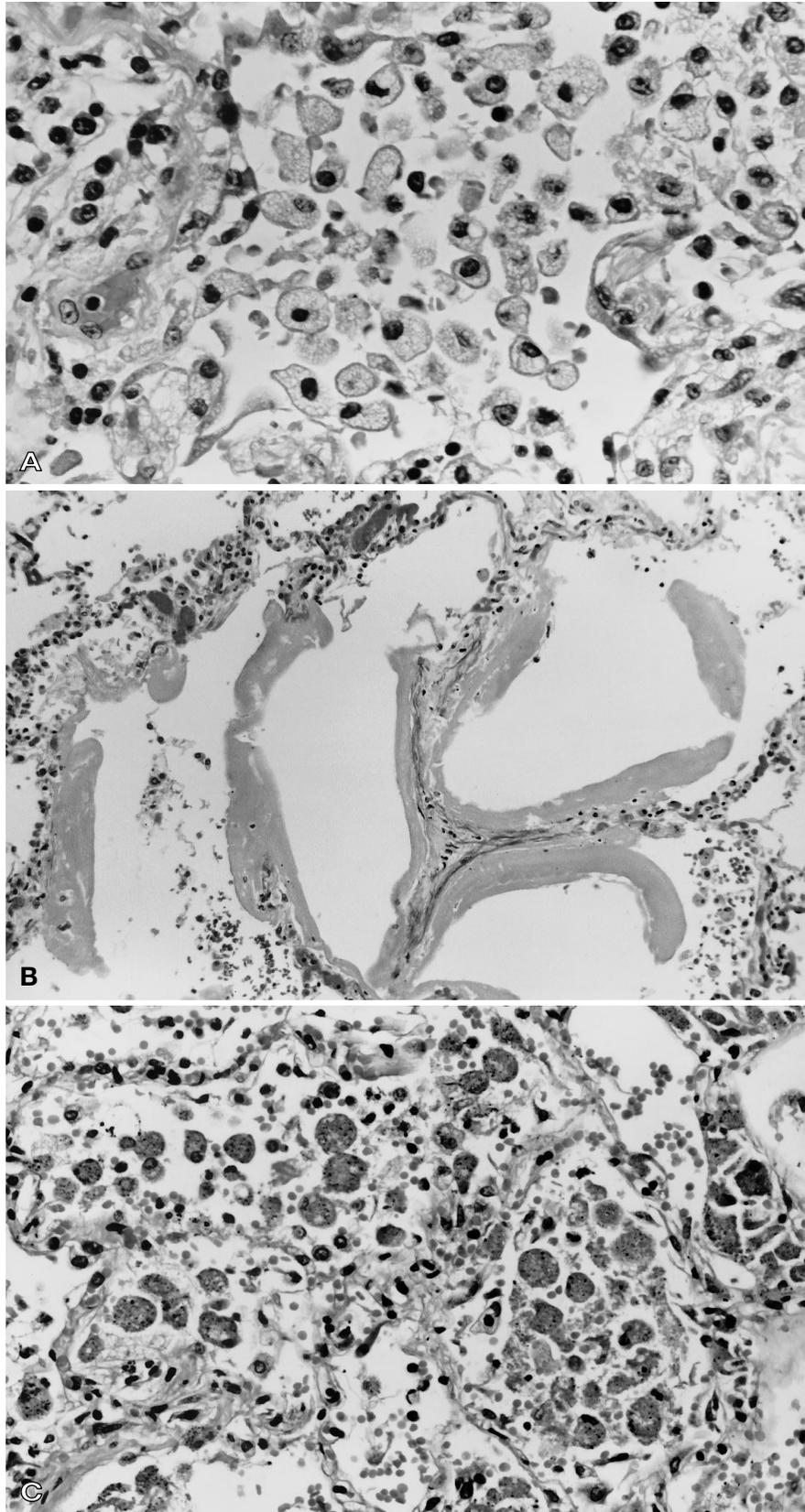
toplasm, from the truly foamy cytoplasm of the macrophages found in amiodarone-related lipoid pneumonia.

This represents, to our knowledge, the first report of amiodarone-induced lung injury in patients being treated acutely for critical illness-associated SVT. In view of its efficacy in treating this dysrhythmia, we do not recommend that amiodarone be discarded in this situation. Nevertheless this report, coupled with past evidence, strongly suggests an increased risk of acute APT in patients receiving high concentrations of oxygen. Furthermore APT in these patients may be difficult to detect clinically when associated with existing ARDS. In view of the widespread lipoid pneumonia with characteristic appearance of the foamy macrophages, bronchoalveolar lavage might be a useful diagnostic tool to detect the problem. Amiodarone should be used with care in patients with ARDS, with early discontinuation as soon as the dysrhythmia is controlled.

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