not directly specified in the initial product labeling, spontaneous adverse event reports ("MedWatch" reports) received by the US Food and Drug Administration (FDA) and reports from the medical literature, which were highlighted in a review by Ashrafian and Davey,¹ suggest that amiodarone-induced lung toxicity may develop within days to weeks of the initiation of therapy.

From the initial marketing through December 2002, the FDA received approximately 2,000 domestic, clinically serious adverse event reports in association with amiodarone. (In this case, *clinically serious* is defined as an outcome of death, disability, or hospitalization [initial or prolonged] that is life-threatening or requires intervention to prevent permanent impairment/damage.) Based on the Medical Dictionary for Regulatory Activities coding, the most frequent events to be included among these reports were dyspnea (264 reports), pneumonia (178 reports), lung disorder not otherwise specified (173 reports), and pulmonary fibrosis (161 reports). The total number of reports received by year (1,941), including the subset of reports (hatched bar) coded for any parenchymal lung injury (280 reports), is shown in Figure 1. Absolute report counts of parenchymal lung injury have increased to remain in proportion (14% on average) with increases in all clinically serious reports for amiodarone. Spontaneous reports submitted/collected by the FDA represent an unknown fraction of all incident cases, but a frequency of 1 to 10% has been suggested.² Thus, the actual number of amiodarone-associated adverse events may be larger (by 10-fold to 100-fold) than the counts presented herein. However, an increasing number of report counts over time does not necessarily mean that the rate of clinically serious reports is increasing, as these counts are unadjusted for use and might simply reflect increasing use. (Due to the large numbers included in this analysis, unreviewed [ie, crude] report counts have been used in lieu of reviewed "case counts," and thus may include duplicate cases or cases in which the association between an event and amiodarone is unknown.)

In consideration of these and other data¹⁵ of amiodarone-associated parenchymal lung injury, the Cordarone label was updated in April 2003 to include the following statements: "There have been reports of acute onset (days to weeks) pulmonary injury in patients treated with oral Cordarone with and without initial IV therapy. Symptoms included pulmonary infiltrates on radiograph, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death. Patients with preexisting pulmonary disease have a poorer prognosis if pulmonary toxicity develops. Use of a lower loading and maintenance doses of amiodarone may decrease the incidence of amiodarone-induced pulmonary toxicity."

Allen Brinker, MD, MS
Michael Johnston, RPh
Food and Drug Administration
Rockville, MD

References

A Frequent Error in Etiology of Round Pneumonia

To the Editor:

I have read with great interest the article by Durning et al (July 2003).¹ Our experience with round pneumonia² and Q fever³ has permitted us to detect various methodologic errors that make some comments and conclusions in this report questionable.

Figure 1. Trends in receipt of clinically serious, domestic spontaneous adverse event reports (1,941) in association with amiodarone (all forms) with further indication of the subset of reports coded for parenchymal lung injury (n = 280). Adverse Event Reporting System database, 1986–2002. The hatched section of each bar represents the subset of reports coded for parenchymal lung injury.
First, the microbiologic study did not include agents of atypical pneumonia (Q fever, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*). Serologic tests such as seroconversion, elevated IgM in acute stage, or urinary antigens were absent; perhaps this explains why the etiologic organism was not identified.

Second, the authors performed a MEDLINE search that was restricted to the English language. This leads to a serious self-limitation. In the world’s first medical database there are, as well as the English-language articles, the abstracts and the medical subject headings that offer essential information about the published reports in non-English-language journals.2,3

Third, in Table 1, which reviews 18 case reports of round pneumonia in adults, 14 cases are shown without etiology (75%). The search for agents of atypical pneumonia appears in none of them.

Fourth, neither were the most relevant articles in English-language journals about etiology of round pneumonia browsed. Round pneumonia constitutes an atypical radiologic presentation of pulmonary infections and is very rare in adults. Q fever is a world zoonosis caused by *Coxiella burnetii* (*Rickettsiae*) that was first described by Derrick in 1937 in Australia.4 Its usual clinical presentation is as pneumonia,5 and so should be included in the diagnostic work of pneumonia. Various authors5–7 have studied the radiologic presentation of Q fever pneumonia in adults, all of them in the English language. Pickworth et al5 noticed, in a series of 21 cases, that sometimes (4 cases, 19%) the lesion became rounded (2 to 7 cm in diameter) during resolution, and concluded that the appearance of round pneumonia should alert to possible Q fever. Gordon et al6 assessed, retrospectively, chest radiographs of 25 patients with epidemic and sporadic Q fever pneumonia and demonstrated multiple round pneumonia in 14% of sporadic cases and in 45% of epidemic. Millar et al7 have studied the chest radiographs on hospital admission of 32 cases of Q fever serologically confirmed, and the more frequent lung changes encountered (78%) were multiple round segmental consolidations (from one to seven), 5 to 10 cm in diameter, and usually situated in the lower lobes. Some lesions became round during resolution. They concluded that the finding of a single or multiple round pneumonia was found to be good evidence that the patient had “Q fever.”

Q fever is, probably, the first cause of round pneumonia in adults. However, in the 21st century, some authors continue to think that round pneumonia is most often caused by *Streptococcus pneumoniae* without reference to Q fever.5,8,9 The diagnostic work in round pneumonia should include agents of atypical pneumonia especially Q fever.

Durning et al10 state that the “treatment of adults with round pneumonia is not similar to that of individuals with lobar pneumonia.” Therapy with antibiotics in these cases should be effective against the common pathogens causing lobar pneumonia5 but also against Q fever: old and new macrolides (erythromycin and clarithromycin) and new quinolones (levofoxacin) are curative and prevent chronic Q fever.

**References**


9 Wagner AL. Round pneumonia and focal organizing pneumonia are different entities [letter]. AJR Am J Roentgenol 1999; 172:549

A Concussive Clinical Coincidence

To the Editor:

I arrived on Monday to begin a 2-week stint as attending in our medical ICUs. The first patient was an elderly lady, who had been in hospital for a month with newly diagnosed HIV and *Pneumocystis carinii* pneumonia. She unexpectedly experienced grand mal seizures and was intubated for airway protection. Brain imaging and lumbar puncture were unrevealing. Her status epilepticus was complicated by aspiration pneumonia-related septic shock, with prolonged hypotension requiring pressors for > 48 h. Acute tubular necrosis developed, which was beginning to resolve by my advent to the service. The patient had been in a deep coma for 3 days since cessation of her seizures. She did not move to deep pain, her pupils were minimally reactive, and she triggered the ventilator occasionally. The house officers presented her as a case of anoxic encephalopathy—the diagnosis suggested by the consulting neurologist. “When did she code?” I queried. “She didn’t” was the response. She remained in her slumber, essentially unchanged, except that she began to move her left arm, nonpurposefully, to deep pain. An EEG demonstrated a paucity of activity—no seizures, but brain waves that portended a very poor prognosis. The consulting neurologist pronounced that there was little or no hope of meaningful survival. Although I felt uncomfortable, not understanding the mechanism of her coma and still suspicious that it was related to multiorgan failure and polypharmacy, the brain waves seemed like incontrovertible evidence that her chances were very poor. I arranged for a family meeting to discuss ongoing management. I have been, historically, the typical “he—he” the last one to give up on patients. And for days, the housestaff and nurses were adamant that we were doing our patient no favors by keeping her alive, languishing on the ventilator.

The patient’s daughter and her husband, both in their mid-30s, arrived for the meeting. They were polite and thoughtful, but clearly distressed by what was happening. I explained that our patient remained in a deep coma, with little change, likely as a result of multiorgan failure and polypharmacy, the brain waves seemed like incontrovertible evidence that her chances were very poor. I was adamant that we were doing our patient no favors by keeping her alive, languishing on the ventilator.

Although it may hold out false hope to some, this approach

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**Correspondence to:** Enrique Antón, MD, PhD

Hospital de Zamarraga

Guipúzcoa, Spain

Enrique Antón, MD, PhD

Hospital de Zamarraga

20700-Zamarraga, Guipúzcoa, Spain; e-mail: lceanton@hzuzn.osakidetz.net

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