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Prehospital amiodarone may increase the incidence of acute respiratory distress syndrome among patients at risk^{☆,☆☆}

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Abstract

Purpose—Amiodarone has been implicated as a risk factor for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) when used in the hospital. This study aims to estimate whether prehospital amiodarone also increases the risk of ALI/ARDS.

Materials—Adult patients admitted to 22 centers with at least 1 risk factor for developing ALI were recruited. In a secondary analysis of this cohort, the prehospital use of amiodarone was documented on admission, and the patients followed for the primary outcome of ALI and secondary outcomes of ARDS, the need for invasive ventilation, and mortality. Dose/duration of amiodarone therapy was not available. Propensity matching was performed to account for imbalances in being assigned to amiodarone. The adjusted risk for ALI/ARDS was then estimated from a conditional logistic regression model of this propensity-matched set.

Results—Forty of 5584 patients were on amiodarone at the time of hospitalization; of those, 6 developed ALI, with 5 progressing to ARDS. In comparison, 371 patients not on amiodarone developed ALI, with 224 having ARDS. After propensity score matching, the prehospital use of amiodarone was not statistically associated with an increased risk for all ALI (odds ratio [OR], 1.8; 95% confidence interval [CI], 0.7–5.0; $P = .25$), invasive ventilation (OR, 1.9; 95% CI, 1.0–3.6; $P = .059$), or in-hospital mortality (OR, 1.2; 95% CI, 0.5–2.9; $P = .75$); but its use appeared to significantly increase the risk for ARDS (OR 3.8; 95% CI, 1.1–13.1; $P = .036$).

Conclusions—Prehospital use of amiodarone may independently increase the risk for ARDS in patients who have at least 1 predisposing condition for ALI.

Keywords

Acute lung injury; Acute respiratory distress syndrome; Amiodarone

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1. Introduction

Amiodarone pulmonary toxicity (APT) has been reported in a variety of forms including mild airway illness, pleural disease, organizing pneumonia, solitary parenchymal lesions, alveolar hemorrhage, chronic interstitial pneumonitis, and the rare but potentially fatal acute respiratory distress syndrome (ARDS) [1]. Several mechanisms for APT pathogenesis have been proposed, including an indirect immunologic reaction manifesting as pneumonitis, direct toxic injury via oxidative stress, and by angiotensin enzyme pathway activation [1,2].

Association of amiodarone therapy with pneumonitis dates back to 1980 [3], although reports of fatal outcomes did not follow until later [4]. Initially, amiodarone-related deaths were associated with dosages of 400 to 800 mg daily; however, recent case series from our institution suggest that amiodarone-related pulmonary injury can occur at the lower maintenance dosage of 200 mg daily [5]. Amiodarone-related acute lung injury (ALI) and ARDS are life threatening and have been described in specific clinical settings including postangiography, lung surgery, and cardiac surgery [6–9].

Because the treatment of ALI/ARDS is significantly limited once the condition is established, the mission of the US Critical Illness and Injury Trials Group (USCIITG)–Lung Injury Prevention Study Investigators is to identify modifiable risks for ALI/ARDS and potentially offer strategies to actually prevent its occurrence. With the frequent use of amiodarone as an effective therapy for both supraventricular and ventricular arrhythmias, we hypothesized that amiodarone may pose an increased risk for ALI/ARDS in patients requiring immediate hospitalization. To date, there have not been any investigations of the effect of the prehospital use of amiodarone on the subsequent development of ALI/ARDS. Because it is not possible to test this hypothesis in a clinical trial, we performed a propensity score–based analysis of a large prospective cohort of patients requiring hospitalization to estimate the risk of prehospital amiodarone use on the development of ALI/ARDS.

2. Methods

The USCIITG investigated 5584 patients admitted to 22 hospitals to evaluate the Lung Injury Prediction Score (LIPS) [10]. With the exception of 3 centers, all data were collected prospectively. Several exploratory subgroup analyses including the effect of amiodarone on ALI/ARDS were preplanned. The study was approved and overseen by the institutional review board at each participating center.

2.1. Study population

Details of the study population have been described previously [10]. Briefly, adult patients (>18 years) admitted to academic and community acute care hospitals were eligible to participate if they had at least 1 major risk factor for ALI, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery (including major cardiac and lung surgery). Patients were excluded if they had ALI at the time of admission, were transferred from an outside hospital, died in the emergency department, were admitted for comfort or hospice care, or were readmitted to a hospital during the study period.

2.2. Predictor variables

The exposure of interest was amiodarone therapy determined at the time of hospital admission as documented in the medical record. Detailed data on dose, or duration, or continuation of amiodarone therapy were not available. Baseline characteristics consisting of demographic information and clinical data (comorbidities, medications, vital signs, laboratory studies) were collected at the time of hospital admission or preoperatively at the time of elective surgery. These clinical variables were used to generate the LIPS score as a measure of the baseline risk of developing ALI/ARDS at the time of admission [10], as well as the Acute Physiology and Chronic Health Evaluation (APACHE) II score as a measure of disease severity.

2.3. Outcome variables

The primary outcome was the development of ALI during the hospitalization as determined by the Standard American-European Consensus Conference criteria [11]: development of acute, bilateral pulmonary infiltrates, and hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$ —ALI, $\text{PaO}_2/\text{FiO}_2 < 200$ —ARDS) in the absence of clinical signs of left atrial hypertension as the explanation for pulmonary edema [10]. Secondary outcome measures included the occurrence of ARDS, the need for invasive ventilation, and in-hospital mortality. Patients were followed for the duration of their hospital stay up to 90 days.

2.4. Statistical analyses

Patients were categorized into 2 groups on the basis of whether they were receiving amiodarone therapy or not at admission. The entire cohort was used to report the unadjusted risk for ALI/ARDS and other binary outcome variables, conferred by the prehospital use of amiodarone.

To adjust for the inherent selection bias introduced by the observational design of the study, a propensity score analysis was performed to account for differences in the 2 groups of patients who were or were not taking amiodarone at admission. To approximate randomization, we used all available data captured at baseline to generate a logistic regression model for being on amiodarone. The patient's baseline risk for developing lung injury based on the LIPS score and the severity of illness from the APACHE II score were also incorporated into the model. The probability of being on amiodarone (ie, the propensity score) was then derived from this model for each patient. Subsequently, each patient on amiodarone was matched by their propensity score by a greedy algorithm (the shortest Euclidean distance within the caliper width of ± 0.03) to identify up to 4 subjects not on amiodarone [12]. Finally, using each matched set as a stratum, a conditional logistic regression model was used to estimate the association (odds ratio [OR]) of amiodarone with ALI/ARDS. Identical procedures were performed to estimate the risk that amiodarone posed for the other secondary outcomes.

Risk estimates are reported as ORs with their 95% confidence intervals (CI). A *P* value of less than .05 was considered statistically significant. Fisher exact test was used to compare contingency tables, and when appropriate, the *t* test was used to compare distributions of

continuous variables. All statistical analyses were performed using JMP 8.0 statistical software and SAS 9.1.3 (SAS Institute Inc, Cary, NC).

3. Results

As previously described [10], 5584 of the 5992 eligible patients were enrolled into the LIPS cohort between March and August of 2009. The median age of the entire cohort was 57 years (interquartile range, 43–70 years), and the majority were white (63%) and male (57%). On admission, their severity of illness reflected by the APACHE II score was 9 (interquartile range, 5–14).

Of the 5584 patients, only 49 (<1%) were on amiodarone at the time of admission. Six of these patients subsequently developed ALI, most of whom (5) met the criteria for ARDS. In comparison, of the remaining 5535 patients not on amiodarone, 371 developed ALI, with 224 meeting the criteria for ARDS (Fig. 1). The unadjusted univariate risk for ARDS when on amiodarone was increased (OR, 2.7; 95% CI, 1.1–6.9; $P = .049$), but not significantly for all ALI (OR, 1.9; 95% CI, 0.8–4.6; $P = .14$). In addition, there was an apparent increase in the risk for requiring invasive ventilation (OR, 1.9; 95% CI, 1.1–3.4; $P = .031$) and death (OR, 3.1; 95% CI, 1.4–7.1; $P = .012$).

In the propensity score matching process, all 49 subjects on amiodarone were successfully matched to those not on amiodarone, with the majority (44) matched to at least 4 patients, for a total of 235 subjects in the matched set. We analyzed the success of the propensity score matching by comparing important covariates including the severity of illness (ie, APACHE II) and the patient's baseline risk for lung injury (ie, LIPS). The mean APACHE II (14.1 ± 5.8 vs 14.2 ± 6.9 , $P = .97$) and the mean LIPS (4.1 ± 2.6 vs 4 ± 2.3 , $P = .92$) were not different between groups of patients on amiodarone vs those who were not taking amiodarone; this was further confirmed across each matched set in a stratified conditional logistic regression analysis. Similarly, other important covariates were well balanced between the groups after propensity matching (see Table 1).

Using this propensity score-matched sample, the adjusted risks for all ALI, ARDS only, invasive ventilation, and death were computed through a conditional logistic regression model, using each matched set as a strata. In this model, the prehospital use of amiodarone did not significantly increase the risk for all ALI, invasive ventilation, or in-hospital mortality but did suggest a significant increase in the risk for the more severe variant, ARDS (OR, 3.8; 95% CI, 1.1–13.1; $P = .036$) (see Table 2 and Fig. 2.)

4. Discussion

The aim of this study was to investigate whether prehospital amiodarone therapy increases the risk of ALI/ARDS in hospitalized patients with at least 1 risk factor for ALI. Fully established ARDS generally manifests itself after secondary insults subsequent to the initial lung injury, and only a fraction of these patients actually progress to ARDS. Therefore, development of the LIPS model helped to identify those most at risk, alerting clinicians to avoid known “second hit” exposures such as blood transfusions, high-tidal-volume mechanical ventilation, and aspiration, whenever possible [10]. The current study proposes

amiodarone as being another potential “second hit.” Although the data are drawn using standardized collection techniques from a large, prospective observational cohort across 22 academic and community hospitals, prehospital amiodarone use was rare (<1%) and necessitated the use of a propensity score–matched control group. In doing so, an increased risk for the subsequent development of ARDS was found. Although there was no increase in the risk of death, the direction of effect was consistent for the outcomes of all ALI and respiratory failure requiring invasive mechanical ventilation. This is consistent with previous associations observed between amiodarone and ALI/ARDS, but our findings further support that patients on maintenance amiodarone—and not just those given amiodarone immediately—may be at an increased risk for ARDS.

Several potential mechanisms for amiodarone-induced pulmonary toxicity have been proposed. Amiodarone can acutely damage lung tissue indirectly via immunological reactions involving CD8 T-cell lymphocytosis, leading to pneumonitis [2]. Accumulation of amiodarone in macrophage lysosomes results in destabilization of their membranes and release of free oxygen radicals; hospitalized patients might be particularly susceptible to this mode of injury in a setting of a higher inspiratory fraction of inhaled oxygen [1,2]. A third mechanism of APT involves drug’s propensity to up-regulate renin-angiotensin system, inducing apoptosis of alveolar type II pneumocytes [13]. Amiodarone is known for its long half-life of more than 30 days and a slow onset of action [2]. A database review of 237 cases of amiodarone-induced pulmonary toxicity in Australia and United States identified those at an increased risk: patients older than 60 years and those receiving the medication for 6 to 12 months [14]. Overall, no direct relationship between amiodarone dose and pulmonary effect was apparent in this study, although data suggested an increased risk in patients who had received cumulative doses of 101 to 150 g. Nonetheless, APT has been reported to occur as early as the second day of treatment for cumulative doses of 1000 to 1500 mg intravenously [1], and therefore, APT may not always be dose related.

In line with these biologic mechanisms, previous reports have suggested an increased risk of ARDS from amiodarone use. In a convenience sample of patients undergoing cardiac surgery, 50% of those on amiodarone developed ARDS, whereas none occurred in those not on amiodarone [8]. In another series of patients undergoing placement of an implantable cardioverter-defibrillator, approximately a quarter of those on amiodarone developed ARDS; whereas again, none occurred in patients not receiving amiodarone [9]. In a retrospective review of postmortem biopsies of patients who died of ARDS, 7 of 10 were noted to have received amiodarone; of those, 3 patients who received the drug for more than 48 hours had histologic changes of widespread lipoid pneumonia, a recognized pattern of APT [15]. These studies, however, did not adjust for the baseline risk of ARDS. Furthermore, because these and related reports were on patients in intensive care units or undergoing cardiac or pulmonary surgery, their findings cannot be generalized.

Although our findings are consistent with previous observational reports, most cardiovascular clinical trials where amiodarone was randomly assigned did not demonstrate a significantly increased risk for ALI/ARDS. A few clinical studies have identified an overall increase in respiratory adverse effects [16,17]; however, none have specifically identified ALI/ARDS as being increased, either around the time of surgery [18,19] or with

long-term use [20–23]. One clinical trial that did find a significant increase in ARDS was a nonblinded study of Belgian patients randomized to prophylactic placebo, verapamil, or amiodarone for the prevention of atrial fibrillation after lung cancer surgery [7]. Three of 11 patients in the amiodarone group developed ARDS after a right-sided pneumonectomy compared with none in the other 2 treatment arms. Notably, ARDS is not uncommon after a pneumonectomy, with reported incidence of up to 12% [24]. Thus, although most randomized clinical trials of amiodarone have not noted any concerns for ALI/ARDS, in specific patient contexts such as after a pneumonectomy, immediate prophylactic administration of amiodarone (which is not the intent of this report) may still pose a risk for ARDS.

Our study has several limitations. Although this particular investigation was among the preplanned ancillary studies, it was not the primary aim of the LIPS cohort [10]. Therefore, the potential for unmeasured effects remains. Although the propensity score–based approach helps to minimize the effect of a nonrandom selection, given the complexity and heterogeneity of the disease process in a nonexperimental setting, the risk of missing important confounders and covariates that might provide an alternative explanation for the apparent association cannot be entirely discounted. Furthermore, neither the dose nor the duration of amiodarone therapy before hospitalization or subsequently during the hospital course was available, limiting our interpretation. In addition, our data set did not include several important variables that could have influenced amiodarone use such as arrhythmias, use of anticoagulation, β -blockers calcium channel blockers, and digoxin, to name a few. Finally, given the low prevalence (<1%) of amiodarone use in this cohort, a match design was necessary to ensure valid comparisons. As a result, this led to a reduction in the overall sample size, affecting both the statistical precision (CI width) and power.

This study, despite its limitations, remains clinically informative because it provides a reliable estimate of the risk that prehospital amiodarone use poses on the subsequent development of ALI/ARDS. To support the causal relationship of amiodarone on ALI/ARDS, ideally, requires a randomized controlled trial. Such a study is impractical and unethical. Thus, within the limitations of an observational design, we performed the study prospectively to maintain the temporal relationship by clearly identifying amiodarone use before hospitalization and the development of ALI/ARDS. Furthermore, our findings were consistent across the investigated respiratory outcomes and in agreement with observations by others linking amiodarone to pulmonary toxicity in different contexts and settings. Finally, there are indeed several biologic mechanisms as described above that support the plausibility of a true causal relationship. Overall, despite some of the deficits in the causal argument, we feel that our findings significantly advance the concern that amiodarone contributes in a causal pathway to ARDS.

Unfortunately, if the risk conferred by the prehospital use of amiodarone on ARDS is true, our observational study does not suggest an obvious solution for these patients. Although completely discontinuing amiodarone during the hospitalization may reduce the risk of ARDS, this is unproven and may prove more harmful. Given the half-life of amiodarone, it would seem unlikely that stopping the drug immediately will quickly reverse the risk for ARDS. Specific pharmacologic interventions may be possible and have already been

suggested to protect against amiodarone-induced pulmonary toxicity [25], but whether it will reduce the risk for ALI/ARDS is unknown and requires further study. Alternatively, potentially safer compounds similar to amiodarone [26,27] may be considered in those recognized to be at an increased risk for ALI/ARDS, but these newer agents still lack long-term experience [28] and are not recommended for patients with an ejection fraction below 35%. However, it is reasonable to implement recognized practice strategies that may mitigate the risk for ALI/ARDS and its complications, such as judicious fluid management, limiting transfusions, and adhering to low tidal volumes. Whether early implementation of these and other strategies can actually prevent the development of ALI/ARDS is being currently studied by the USCITG [29]. Until then, clinicians should be alerted to this common subgroup of patients who may be at an increased risk for ARDS and proactively monitor and respond to respiratory complications.

In conclusion, even the prehospital use of amiodarone appears to confer an independently increased risk for the subsequent development of ARDS among patients who require hospitalization with at least 1 predisposing condition for ALI. Further studies are underway to determine whether early identification of these at-risk patients and timely implementation of preventative strategies will prove to be effective.

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Fig. 1.
Frequency of ALI/ARDS in patients on amiodarone and remaining cohort.

Fig. 2.

Amiodarone and the adjusted risk for respiratory complications after propensity matching. Prehospital use of amiodarone did not significantly increase the risk for all ALI or invasive ventilation but did suggest a significant increase in risk for ARDS. The risk of in-hospital mortality was not increased (see Table 2 for specific numeric figures).

Table 1

Group characteristics in the propensity-matched samples

Parameter	Amiodarone (n = 49)	No amiodarone (n = 186)	P
Age (y) ^a	71.2 ± 12.8	71.7 ± 13.1	.87
Sex (male)	55.1%	51.6%	.75
White	70.2%	65.8%	.61
Smoking			
Current	8.7%	15.3%	
Former	34.8%	37.1%	.34
APACHE II ^a	14.18 ± 5.8	14.22 ± 6.9	.97
LIPS ^a	4.10 ± 2.6	4.06 ± 2.3	.92
Comorbidities			
Cardiac surgery	18.8%	22.5%	.55
CHF, NYHA class IV	12.2%	12.9%	1.00
Diabetes	36.7%	37.6%	1.00
Pneumonia	28.6%	27.4%	.86
COPD	22.5%	18.3%	.54
ILD	2.0%	0%	.21
GERD	26.5%	21.5%	.45
Medications			
ACEI/ARB	38.8%	36.0%	.74
Statin	46.9%	40.3%	.42
Aspirin	57.1%	54.8%	.87
PPI	38.8%	39.3%	1.00

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; GERD, gastroesophageal reflux disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton-pump inhibitor.

^aMean ± SD. *t* Test was used for continuous variables, and the Fisher exact test for contingency tables.

Table 2

Amiodarone and the risk for respiratory complications and death in the entire cohort and after adjustment by propensity matching for being on amiodarone

Outcome	Amiodarone	No amiodarone	OR	95% CI	P
Entire cohort (unadjusted)					
Death	14% (7/49)	5% (279/5535)	3.1	1.4–7.1	.012
ARDS only	10% (5/49)	4% (224/5535)	2.7	1.1–6.9	.049
All ALI	12% (6/49)	7% (371/5535)	1.9	0.8–4.6	.14
Invasive ventilation	50% (24/48)	34% (1832/5363)	1.9	1.1–3.4	.031
Propensity-matched set					
Death	14% (7/49)	11% (21/186)	1.2	0.5–2.9	.75
ARDS only	10% (5/49)	3% (5/186)	3.8	1.1–13.1	.036
All ALI	12% (6/49)	6% (12/186)	1.8	0.7–5.0	.25
Invasive ventilation	50% (24/48)	34% (62/180)	1.9	1.0–3.6	.059

Fisher exact test was used to test for significance in the unadjusted set. Conditional logistic regression was used to test for significance in the propensity-matched set. % indicates percentage of subjects in the exposure group having the respective outcome; numerator, count of outcome; denominator, total count of exposure group.