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Phlebitis in Amiodarone Administration

Incidence, Contributing Factors, and Clinical Implications

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Abstract and Introduction

Abstract

Background Intravenous amiodarone is an important treatment for arrhythmias, but peripheral infusion is associated with direct irritation of vessel walls and phlebitis rates of 8% to 55%.

Objectives To determine the incidence and factors contributing to the development of amiodarone-induced phlebitis in the coronary care unit in an academic medical center and to refine the current practice protocol.

Methods Medical records from all adult patients during an 18-month period who received intravenous amiodarone while in the critical care unit were reviewed retrospectively. Route of administration, location, concentration, and duration of amiodarone therapy and factors associated with occurrence of phlebitis were examined. Descriptive statistics and regression methods were used to identify incidence and phlebitis factors.

Results In the final sample of 105 patients, incidence of phlebitis was 40%, with a 50% recurrence rate. All cases of phlebitis occurred in patients given a total dose of 3 g via a peripheral catheter, and one-quarter of these cases (n = 10) developed at dosages less than 1 g. Pain, redness, and warmth were the most common indications of phlebitis. Total dosage given via a peripheral catheter, duration of infusion, and number of catheters were significantly associated with phlebitis.

Conclusions Amiodarone-induced phlebitis occurred in 40% of this sample at higher drug dosages. A new practice protocol resulted from this study. An outcome study is in progress.

Introduction

Intravenous amiodarone has been an important treatment option for patients with ventricular tachyarrhythmias since the 1990s and more recently has improved the management of atrial arrhythmias. Amiodarone is a known irritant of blood vessels and has reported rates of phlebitis ranging from 8% to 54.5%.[1–4] Phlebitis rates as high as 25% have been reported with the use of concentrations greater than 1.5 mg/mL.[5] In attempts to prevent this local irritation and reduce factors that contribute to phlebitis, drug dosages and concentration have been altered; delivery systems, drug pH, and additives have been modified;[1] and intravenous sites have been systematically rotated more

frequently.[6] Despite these modifications, little change has occurred in the incidence of phlebitis.[4]

At Stanford University Medical Center, Palo Alto, California, a group of concerned cardiac care and arrhythmia nurses met to examine the magnitude of the problem and modify the current practice protocol. A retrospective study on the incidence and predisposing factors contributing to the development of phlebitis in patients given intravenous amiodarone in the cardiac care unit (CCU) was conducted.[7]

Background

The literature on amiodarone-induced phlebitis delineates the following problems: vessel irritation during administration; additional drug variables that affect vessel irritation, such as concentration, solution dilution, and speed of administration; and other therapeutic risk factors.

Amiodarone was first introduced in 1961 as a drug for treating angina. Today intravenous amiodarone is the gold standard for managing patients with rhythm-related tachyarrhythmias and is listed as the first-line therapy in the American Heart Association's Advanced Cardiac Life Support algorithms for ventricular tachycardia/ventricular fibrillation.[8] The package insert for the Cordarone brand of amiodarone hydrochloride (Wyeth Laboratories) recommends use of a filter during administration at higher concentrations because of the precipitate that can cause phlebitis. Amiodarone is currently available from several manufacturers (eg, Nexterone, Prism Pharmaceuticals/Baxter, and amiodarone hydrochloride intravenous injection, APP Pharmaceuticals LLC).

Thrombophlebitis and Amiodarone

Amiodarone-induced thrombophlebitis was initially described in case reports.[9–11] The graphic descriptions of marked tissue injury in these early reports gave reason for further evaluation of the incidence and clinical significance of thrombophlebitis. In a prospective study of 20 patients receiving amiodarone for recent-onset atrial fibrillation, Kreiss et al[5] found that thrombophlebitis was the most common side effect, occurring in 5 of the 20 patients (25%). Thrombophlebitis was the most common adverse reaction associated with intravenous amiodarone, at a rate of 8% among 550 patients, in a metaanalysis of 18 random-controlled trials of patients with atrial fibrillation who received intravenous amiodarone.[12] In a retrospective review by Mowry and Hartman[3] of 339 hospitalized patients who had received intravenous amiodarone, the incidence of thrombophlebitis was 10.6%.

Phlebitis (or thrombophlebitis) is an inflammation of the vein wall characterized by pain, tenderness, edema, erythema, and an increase in local temperature[13–15] (Figure 1). In a descriptive study[2] of 355 patients treated in an inpatient unit during a 3.5-month period, pain was the first symptom of phlebitis. Other signs and symptoms included redness, tenderness, swelling, and warmth at the intravenous site. Uslusoy and Mete[2] also noted that phlebitis can cause sepsis, which requires additional diagnostic interventions and treatments, increases hospital length of stay, and increases stress and costs for patients.

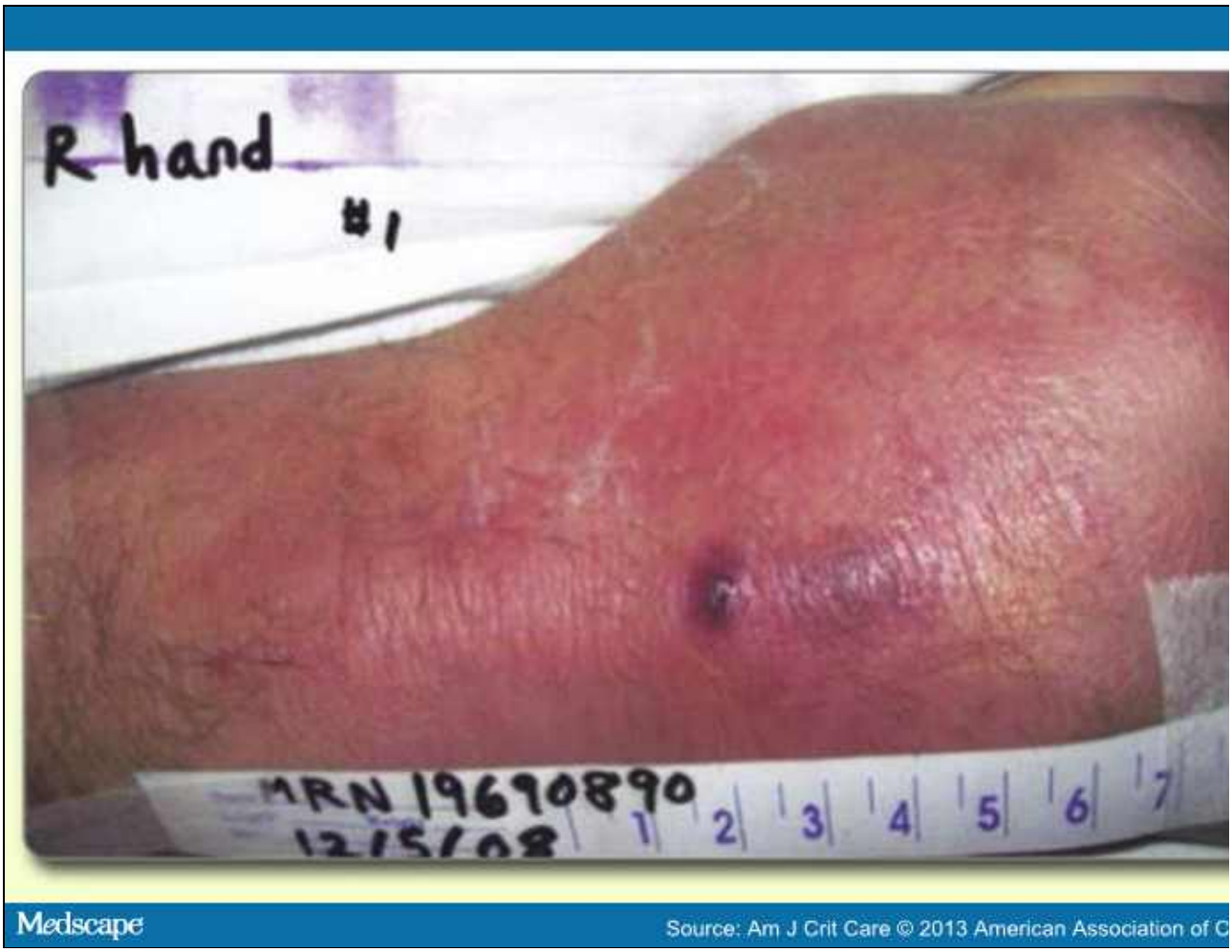

Figure 1.

Phlebitis of the right hand.

Amiodarone-induced phlebitis has been attributed to the mechanical and chemical effects of the particulate matter introduced during injection.[16] Amiodarone may break down into particles during storage because of the drug's physical instability, poor quality control, or poor compounding processes. Crystallization of amiodarone may occur at the time of administration if the solubility limits of the drug are approached during dilution and mixing in the bloodstream.[17]

Ward et al[18] and Ward and Yalkowsky[19] examined amiodarone-induced phlebitis with thermal measurement to distinguish rates of infusion and the consequences. They found that rapid dilution of the formulation is an important variable in the determination of phlebitis. A slow injection into a constantly flowing bloodstream or a slow injection rate into a large blood volume both produce a rapid dilution. A very slow injection (especially if into a large vessel such as the femoral vein) will eliminate precipitation because the drug becomes soluble before nucleation can occur. Similarly, injection into small veins (such as those of the wrist) should be avoided because the low rate of blood flow would result in a high local venous concentration of drug and an increased likelihood of precipitation and purulence.[15]

Using a rabbit ear model and a thermographic camera, Ward and Yalkowsky[17] and

Ward et al[18] were able to detect temperature changes during infusion of amiodarone. Despite the use of a filter, precipitation within the vessel depended on the ratio of the rate of injection to the rate of blood flow. Precipitation was directly correlated with phlebitis.[19]

Yalkowsky et al[15] found a relatively high incidence of adverse reactions at the infusion site in patients receiving a continuous infusion and paradoxically found that a single dose seemed to be better tolerated than a lower dose given over several hours.

The research by Ward, Yalkowsky and their colleagues also showed that amiodarone may be a direct irritant to the vessel wall, because it can leach out plasticizers in polyvinyl chloride tubing. Leaching increases at higher concentrations and lower flow rates. Their findings clearly indicate the link between the time of amiodarone administration and the clinical findings of inflammation, redness, tenderness, pain, increased temperature, edema, swelling, and a palpable cord and vein.[20] Most important, phlebitis can lead to thrombus formation and even death.[15]

Thrombophlebitis is a common complication of intravenous therapy; it can cause marked pain, swelling, fever, and tissue loss and may increase hospital costs by increasing length of stay.[9] The range of reported rates of occurrence and contributing factors related to thrombophlebitis is wide. Contributing factors include the material, length, and lumen size of the cannula; the skill of the person inserting the cannula; the character of the material infused; the frequency of changes of intravenous dressings; and host factors, such as age, sex, and underlying disease.[13,14]

The wide variations in amiodarone-induced phlebitis most likely are due to the varied populations of patients studied, the small sample sizes of most of the studies, and different methods and practices of drug administration. Understanding the mechanisms and pathophysiology of the development of amiodarone-induced phlebitis and the changes in the drug solution and its delivery methods and technology (cannulas, intravenous containers) have not altered the occurrence of the complication to date. Understanding when phlebitis occurs and its relationship to dosage and concentration of amiodarone is needed to devise improved practice guidelines.

Methods

Design

The goals of this retrospective descriptive study were to determine the incidence of amiodaronerelated phlebitis, which variables contribute to the development of phlebitis, and practice standards to minimize the risk of phlebitis.

Sample and Setting

The study was conducted in the CCU at Stanford Hospital and Clinics, Stanford, California, where a large number of patients with arrhythmias are treated with amiodarone. Once the study was reviewed and approved by the Stanford review board, a list of sequential CCU patients who received amiodarone was compiled from pharmacy records for April 2008 through January 2009. A total of 18 patients were excluded because they had sepsis, they had never received intravenous amiodarone, or the presence or absence of phlebitis could not be determined. The final sample consisted of 105 patients. The electronic health records of the 105 patients were reviewed.

Independent variables of interest were based on a review of the literature and clinical judgment. They included patients' biodemographic characteristics, use of other irritant

drugs, drug dosages, and variables associated with use of an intravenous catheter.

Phlebitis, the dependent variable, was determined by the documented presence and degree of pain, swelling, redness, and temperature at the intravenous site and the decision of at least 2 members of the study team that the patient had phlebitis.

A code book was generated and tested for use in data collection. After data collection, the code book was reviewed for accuracy and completeness, and a phlebitis diagnosis was determined.

Data Analysis

Data were analyzed by using SAS, Version 9.1 (SAS Institute Inc). Analyses consisted of descriptive statistics, including minimum, 25th, 50th (median), and 75th quartiles, and maximum; 2 x 2 tables for dichotomous variables with odds ratios, 95% confidence intervals, and Fisher exact tests; Wilcoxon/Mann-Whitney tests on (transformed) continuous variables; and logistic regression to detect relationships among study variables.

The results provided estimates of which factors were predictive of phlebitis. Because many of values for the continuous variables were highly skewed to the right, the log transformation approximately normalized the values, and the transformed values were used in the analyses.

Results

Description of the Sample

The study sample consisted of 75 men and 30 women with a mean age of 66 years. Among the subsample of 101 patients with atrial fibrillation, 67 (66.3%) were treated with amiodarone. Among the whole sample of 105 patients, 32 (30.5%) received amiodarone for ventricular arrhythmias. and summarize the patients' biodemographic data. The biodemographic variables did not differ significantly between patients who had phlebitis and those who did not. Both groups had low ejection fractions shown by echocardiography, and many had concomitant risk factors for coronary artery disease, including overweight, hypertension, diabetes, and peripheral vascular disease.

Table 1. Dichotomous biodemographic sample characteristics

Variable	Phlebitis				Odds ratio[a]		*P* [b]
	Yes (n = 42)		No (n = 63)				
	No.	%	No.	%	Estimate	Exact 95% CI	
Male sex	32	76	43	68	1.49	0.57–4.06	.51
Ventricular tachycardia	17	40	15	24	2.18	0.85–5.52	.08
Atrial fibrillation (n = 101; 40 yes, 61 no)	22	55	45	74	0.43	0.17–1.01	.06
Cardiomyopathy	23	55	30	48	1.29	0.55–3.05	.55
Coronary artery disease	24	57	31	49	1.37	0.58–3.26	.55

Hypertension (n = 104; 42 yes, 62 no)	23	55	32	52	1.13	0.48–2.69	.84
Diabetes (n = 104; 42 yes, 62 no)	6	14	20	32	0.35	0.10–1.04	.06
Peripheral vascular disease (n = 104; 42 yes, 62 no)	2	5	3	5	0.98	0.08–8.99	>.99
Potassium	20	48	36	57	0.68	0.29–1.61	.43
Intravenous vancomycin (n = 104; 42 yes, 62 no)	13	31	29	47	0.51	0.20–1.25	.15
Intravenous nafcillin (n = 104; 41 yes, 63 no)	1	2	0	0	∞	0.08, ∞	.39

[a] Values greater than 1 imply higher risk of phlebitis, for example, men have a higher risk than do women.
[b] Two-tailed, obtained by Fisher exact test.

Table 2. Continuous biodemographic sample characteristics

Variable	Phlebitis	No.	Minimum	Quartile			Maximum	*P* [a]
				25th	50th (median)	75th		
Age, y	Yes	42	35.0	57.0	66.5	74.0	91.0	.92
	No	63	31.0	57.0	64.0	79.0	93.0	
Weight, kg								
Men	Yes	32	63.0	80.5	89.0	108.0	154.0	.11
	No	42	52.0	71.0	83.5	99.0	246.0	
Women	Yes	10	49.0	61.0	75.0	88.0	105.0	.42
	No	19	40.0	56.0	66.0	81.0	223.0	
Ejection fraction, %	Yes	42	17.0	25.0	35.0	55.0	62.0	.41
	No	55	12.0	25.0	35.0	50.0	65.0	
Albumin, g/dL	Yes	40	1.60	2.20	2.50	2.95	4.00	.46
	No	62	0.00	1.90	2.55	2.90	4.00	
Creatinine, mg/dL	Yes	42	0.70	1.10	1.70	2.30	6.40	.35
	No	63	0.30	1.20	1.70	3.00	6.50	
White blood cell count, x 10^3/μL	Yes	42	4.80	9.00	13.50	20.70	35.70	.53
	No	63	0.20	9.50	13.80	20.90	49.50	
Stay, days	Yes	42	3.00	7.00	13.00	20.00	143.00	.77
	No	63	2.00	7.00	14.00	23.00	138.00	

SI conversion factors: to convert albumin from g/dL to g/L, multiply by 10; to convert

creatinine from mg/dL to µmol/L, multiply by 88.4.
[a]Two-tailed Wilcoxon/Mann-Whitney test on transformed variable.

Incidence and Indications of Phlebitis

Among the 105 patients in the sample, 42 had phlebitis, an incidence of 40%. In patients who had had phlebitis before, the recurrence rate was 50%. Among patients with recurrent phlebitis, the total dosage of amiodarone delivered via a peripheral catheter was significantly higher ($P < .001$) than the total dosage among the other patients.

The most common reported indications of phlebitis, in descending order of frequency, were pain (45 patients), redness (31), warmth (11), edema (10), swelling (5), and hardness (4). A mean of 3 signs or symptoms was reported for each episode of phlebitis. These indications were reported in the electronic health record when a catheter was discontinued.

Factors Contributing to Phlebitis

Factors associated with the development of phlebitis included amiodarone dosage (peripheral and total) and duration of amiodarone administration. The number of central and peripheral intravenous catheters inserted as a result of the phlebitis was also significantly higher in the patients who had phlebitis than in the patients who did not (Figures 2 and 3).

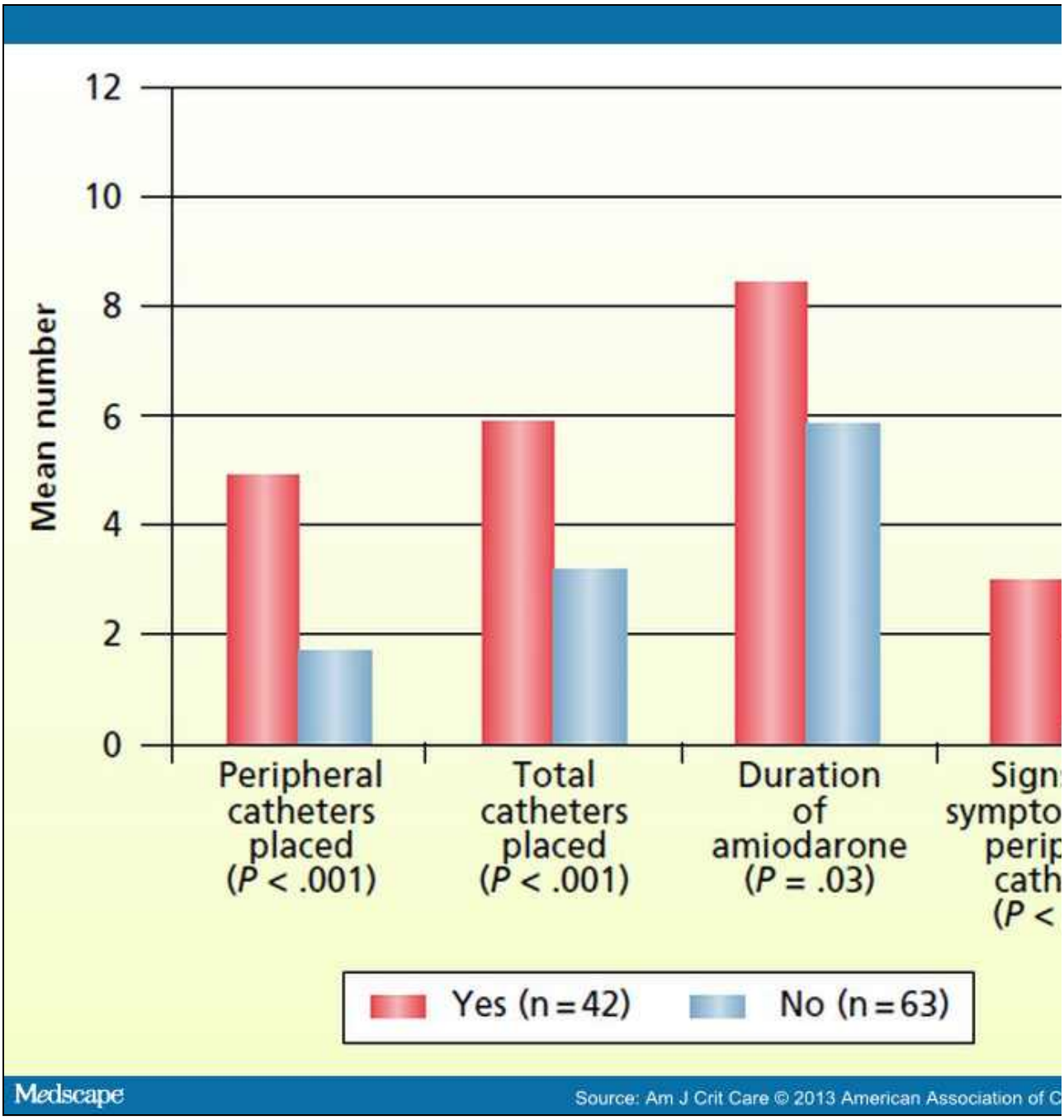

Figure 2.

Variables that differed significantly between patients with and without phlebitis (yes/no).

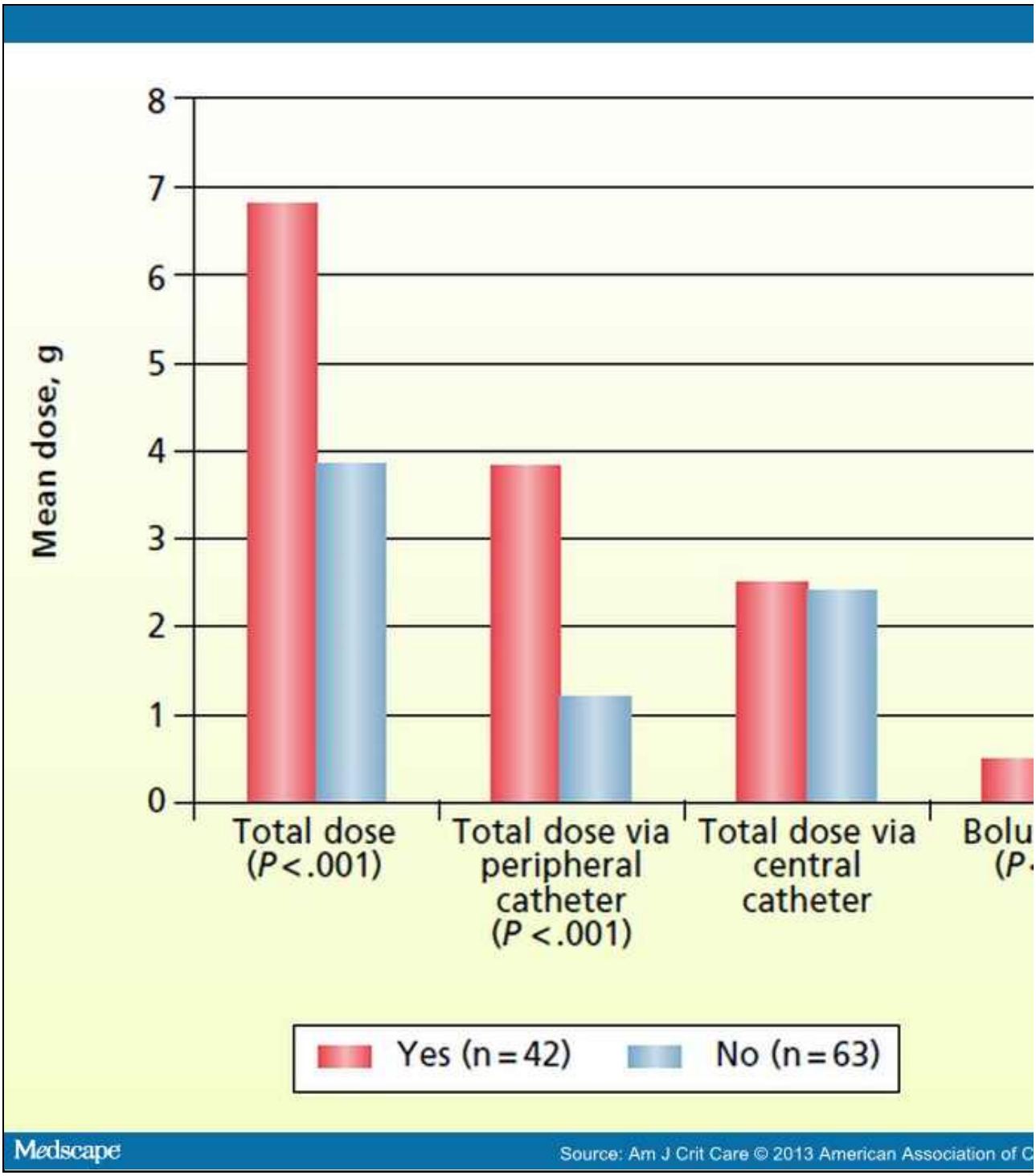

Figure 3.

Amiodarone dose (log-transformed data) in patients with and without phlebitis (yes/no).

Variables associated with amiodarone dosage included the amount delivered via a central catheter (4.8 mg/mL; 1200 mg in 250 mL at either 1.0 or 0.5 mg/min), a peripheral catheter (1.8 mg/mL; 450 mg in 250 mL at either 1.0 or 0.5 mg/min), or as a bolus dose (usually 150 mg) and total amiodarone dose.

Dosage variables analyzed included total dosages delivered via a central catheter, via a

peripheral catheter, and as a bolus and total amiodarone dose (central dose + peripheral dose + bolus dose). All dosages except those delivered via a central catheter were significantly higher in the patients who had phlebitis than in the patients who did not.

Most episodes of phlebitis occurred in patients who had a total doses of 3 g of amiodarone delivered via a peripheral catheter. Among the 42 patients in whom phlebitis developed, 10 (24%) had received total dosages of amiodarone less than 1 g at the time of occurrence, and the complication commonly occurred within 24 hours of treatment.

The number of days amiodarone was administered was significantly greater in patients who had phlebitis than in patients who did not. Duration of administration was defined as the time from the first intravenous dosage until discontinuation of the drug. Although duration of administration was significantly longer ($P < .05$) for patients who had phlebitis (8.21 days) than for patients who did not (5.94 days), duration was also highly correlated with total amiodarone dosage (r=0.91, P<.001) and total dose delivered via peripheral catheters ($r = 0.61$, $P < .001$). The longer the duration of administration, the higher the total dosage of amiodarone.

The number of peripheral catheters and the total number of catheters inserted was significantly greater in the patients who had phlebitis than in the patients who did not (Figure 2). Intravenous catheters included percutaneously inserted central catheters, trialysis catheters, and catheters inserted in the internal jugular, femoral, and subclavian veins. Peripheral catheters were inserted in the left or right forearm, the hands, and the antecubitus.

Logistic Regression

Stepwise logistic regression was used to elucidate any factors predictive of phlebitis: age, sex, total dose of amiodarone, total dose delivered via a peripheral catheter, total dose delivered via a central catheter; total dose delivered as a bolus, and duration of administration. Of these, total dose delivered via a peripheral catheter was the only significant predictor ($P < .001$; see).

Table 3. Logisitic regression analysis of dose delivered via a peripheral catheter and occurrence of phlebitis

Analysis of maximum likelihood estimates					
Parameter	***df***	**Estimate**	**SE**	**Wald χ^2**	***P***
Intercept	1	-2.2818	0.5393	17.9	<.001
Peripheral catheter log dose	1	0.3361	0.0765	19.3	<.001

Discussion

An opportunity for change in a current practice protocol emerged when arrhythmia and CCU staff realized that phlebitis was a problem in patients receiving intravenous amiodarone via a peripheral catheter even when the current recommendations for administering the drug were followed. This retrospective study was designed to examine our then-current practice of amiodarone administration, determine if the clinical problem of phlebitis was as large as anticipated, understand factors contributing to the development of phlebitis, and refine a practice protocol to decrease this problem.

The incidence of phlebitis was 40%, with a 50% recurrence rate. Rates in previous

investigations[11–4] varied greatly, from 8% to 55%, most likely because of differences in sampling, methods, and practice standards of the various institutions. However, amiodarone-induced phlebitis still exists, and the incidence has largely been unaffected by use of manufacturers' recommendations and current delivery protocols. Our current practice protocol calls for use of an in-line filter, delivery of the higher recommended concentrations via a central catheter, and delivery of only lower concentrations via a peripheral catheter. The rate of phlebitis in our study suggests that the protocol we were using was not sufficient to prevent or even minimize phlebitis and was in need of refinement.

Total dosage of amiodarone delivered via a peripheral catheter was predictive of phlebitis and reinforces the notion that local and not systemic effects of the drug cause phlebitis. This finding indicates that amiodarone is a local irritant of vessel walls and supports the work of Ward, Yalkowsy, and their colleagues.[15,17,19,20] The total dose delivered via a peripheral catheter and the early onset of phlebitis in several patients in our study were pivotal findings for adopting clinical changes in intravenous administration of amiodarone at Stanford Hospital and Clinics. All 42 cases of phlebitis occurred in patients who received a total dose of 3 g of amiodarone via a peripheral catheter, and 10 of the cases developed when the patients had received less than 1 g. The doses used in this study are commonly administered in the first 24 hours of loading. Therefore the first 24 hours are a critical time to monitor a patient and plan for oral or central dosing if the drug is not tolerated or the drug will be continued longer than 24 hours.

We defined phlebitis on the basis of current descriptors of signs and symptoms designated in each patient's electronic health record. When an intravenous catheter was discontinued, signs and symptoms of phlebitis as reasons for discontinuation of the catheter were not always reported in the electronic health record, and no reliable and valid monitoring method for intravenous catheters was available or required for documentation. This situation contributed to the inability to determine the diagnosis of phlebitis in some of the excluded patients and might explain the high number of intravenous catheters that were used in the patients who had phlebitis. Therefore, most likely the initial occurrence of phlebitis was not diagnosed until subsequent catheters were placed and, ultimately, discontinued.

Nursing practice and changes in the system used for electronic health records now include mandatory assessment of peripheral intravenous catheters every 4 hours by using the phlebitis scale of the Infusion Nurses Society[21] embedded in the health records. The scale is a valid and reliable tool[22] that facilitates tracking of the sequelae of infusions and provides ongoing monitoring of phlebitis. Documentation of a catheter's location and reasons for discontinuing a catheter are also required.

Although not a part of our study, the copying and compounding of generic forms of amiodarone and their role in phlebitis may need to be examined.

Study limitations include the retrospective study design and the documentation problems that existed in the electronic health record. Our study was conducted in the CCU at a single site and may unfortunately reflect the ongoing phlebitis problem at other institutions. Our results have been critical in developing a multidisciplinary evidence-based practice protocol for administration of amiodarone at our facility. All members of a team of nursing practice and research clinicians from the CCUs and the arrhythmia group, critical care physicians, and personnel from the pharmacy and the informatics department are involved in the protocol revisions and education for these practice changes to reduce the incidence of amiodarone-induced phlebitis.

These guidelines include use of an in-line filter and dose recommendations for central and peripheral catheters, use of the largest peripheral vessel, change to oral amiodarone within 24 hours of administration of intravenous doses, percutaneous insertion of a central catheter if administration exceeds 24 hours, and the creation of an order set with pharmacy dose information. Changes in nursing practice and in the electronic health record include mandatory assessment of peripheral intravenous catheters by using the phlebitis scale of the Infusion Nurses Society.

Future research is needed to measure the outcome of the new guidelines to ensure that patients' risk for phlebitis is not increased by early percutaneous insertion of a central catheter and to determine if the changes have decreased the incidence of phlebitis.

Sidebar 1

Amiodarone is a known irritant of blood vessels, and phlebitis rates are high.

A total of 105 electronic health records of patients who received amiodarone were reviewed.

Practice guidelines include use of an in-line filter in the largest peripheral vessel and use of a central catheter after 24 hours.

Sidebar 2

eLetters

Now that you've read the article, create or contribute to an online discussion on this topic. Visit **www.ajcconline.org** and click "Responses" in the second column of either the full-text or PDF view of the article.

Sidebar 3

See Also

For more about phlebitis and amiodarone in critical care, visit the *Critical Care Nurse* Web site, **www.ccnonline.org** , and read the article by Boyce and Yee, "Incidence and Severity of Phlebitis in Patients Receiving Peripherally Infused Amiodarone" (August 2012).

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