Observational Study

Medicine®

OPEN

Comedication with interacting drugs predisposes amiodarone users in cardiac and surgical intensive care units to acute liver injury

A retrospective analysis

Yunn-Fang Ho, BPharm, MD, PhD[a,b,c], Hsin-Ying Chou, MSc[a], Jan-Show Chu, MD, PhD[e], Ping-Ing Lee, MD, PhD[d,*]

Abstract

Risk factors and underlying mechanisms for liver injury associated with amiodarone remain elusive. This study aimed to investigate the drug-related covariates for acute liver injury by amiodarone—an intriguing compound of high lipophilicity, with a long half-life and notable efficacy.

The medical, pharmacy, and laboratory records of new amiodarone users admitted to the cardiac or surgical intensive care units of a medical center were examined retrospectively. A Cox regression model with time-varying dose-related variables of amiodarone was utilized to estimate the hazard ratio (HR) of amiodarone-associated liver injury while adjusting for concomitant therapy and relevant covariates.

Of the 131 eligible patients among 6,572 amiodarone users (46,402 prescriptions), 6 were identified as amiodarone-associated liver injury cases. In comparison to controls (n = 125), this liver injury cohort (n = 6) had significantly higher numbers of amiodarone-interacting (2.7 ± 2.0 vs 0.9 ± 0.9 drugs, $P = .02$) and hepatotoxic (3.8 ± 0.8 vs 2.5 ± 1.7 drugs, $P = .03$) comedications. The number of comedications with amiodarone-interacting potential (HR 2.07, 95% confidence interval [CI] 1.02–4.22, $P = .04$) and amiodarone cumulative doses standardized by body surface area (HR 6.82, 95% CI 1.72–27.04, $P = .01$) were independent risk factors for liver injury associated with amiodarone.

Drug-related (amiodarone cumulative dose, interacting drugs) factors were significant predictors of amiodarone-associated acute liver injury. A prudent evaluation of each medication profile is warranted to attain precision medicine at the level of patient care, especially for those treated by medications with complex physicochemical and pharmacokinetic properties, such as amiodarone.

Abbreviations: AAD = antiarrhythmic drug, AF = atrial fibrillation, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BSA = body surface area, cDose = cumulative dose, DDI = drug–drug interaction, DILI = drug-induced liver injury, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, ICU = intensive care unit, IV = intravenous, log *P* = octanol-water partition coefficient, Ninth Revision –Clinical Modification, PH = proportional hazards, $t_{1/2}$ = half-life, T-bil = total bilirubin, ULN = upper limit of normal, VT = ventricular tachycardia.

Keywords: adverse drug reaction, drug-induced liver injury, intensive care unit, risk factor

1. Introduction

The health care burden among the critically ill is substantial. Up to 78.0% of patients requiring intensive care had cardiac arrhythmias, including ventricular tachycardia (VT) and atrial fibrillation (AF).[1–4] Amiodarone, an iodinated benzofuran derivative with distinct physicochemical (high lipophilicity) and pharmacokinetic properties (long half-life, $t_{1/2}$), is an effective and widely used antiarrhythmic drug (AAD).[5–11] In fact, it is the most commonly prescribed rhythm controller as documented previously.[2,12–14]

Nonetheless, amiodarone is infamous for its risk of end organ toxicity and undesired drug–drug interactions (DDIs). Fatal adverse reactions include pulmonary fibrosis, liver cirrhosis, and cardiac arrest subsequent to bradycardia; while the clinically relevant DDIs between amiodarone and many other pharmaceuticals lead to subtherapeutic (treatment failure) or supratherapeutic (toxicity) effects.[15,16] To minimize risks, regular monitoring of organ functions and vigilant detection of clinically relevant DDIs during amiodarone therapy are recommended.[7,10,15–19]

Editor: Inyang Nora Osemene.

The study was supported by a research grant from the National Science Council (NSC 102-2320-B-002-005), Taiwan, ROC.

The authors have no conflicts of interest to disclose.

[a] Graduate Institute of Clinical Pharmacy, [b] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [c] Department of Pharmacy, [d] Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, [e] Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University; Department of Pathology, Taipei Medical University Hospital, Taipei, Taiwan.

[*] Correspondence: Ping-Ing Lee, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 8, Chung-Shan S. Road, Taipei 10041, Taiwan (e-mail: pinging@ntu.edu.tw).

Medicine (2018) 97:37(e12301)

Received: 5 December 2017 / Accepted: 16 August 2018

http://dx.doi.org/10.1097/MD.0000000000012301

Liver injury associated with amiodarone is not uncommon. The incidences of elevated liver enzymes and hepatitis or cirrhosis were observed to be 15% to 30% and < 3%, respectively.[16] Although amiodarone per se,[20–24] hypoxia (e.g., hepatic hypoperfusion),[25,26] or polysorbate 80 (a co-solvent in parenteral formulations),[27–29] have been postulated to be responsible for these effects, the exact underlying mechanisms or risk factors for hepatic damage remain elusive. Frail individuals under intensive care are usually treated with complex drug regimens. This intricate polypharmacy might elicit substantial interactions with amiodarone and, hence, contribute to the occurrence of drug-induced liver injury (DILI). Alternatively, DILI could solely be the consequence of comedication with hepatotoxic pharmaceuticals in the complex polypharmacy treatment.

A full assessment is more feasible among patients under critical care due to the availability of complete and detailed medical documents. This study, with particular emphasis on incorporating drug-related covariates such as comedications (DDI and DILI potential) and amiodarone doses (daily and cumulative), aims to evaluate the incidence of amiodarone-related acute liver injury, the frequencies of DILI and DDI coprescriptions, and possible risk factors for amiodarone-associated acute liver injury in the settings of cardiac and surgical intensive care units (ICUs) using medical records at a medical center in Taiwan.

2. Patients and methods

2.1. Study design and population

We performed a retrospective cohort study of patients > 18 years of age who began amiodarone therapy from February 1, 2011 to January 31, 2013 at the cardiac and surgical ICUs of a medical center (Fig. 1). The study was approved by the Research Ethics Committee of the National Taiwan University Hospital.

Adult patients (age ≥ 18 years) who initiated amiodarone therapy at cardiac and surgical ICUs with baseline and follow-up alanine aminotransferase (ALT) and total bilirubin (T-bil) levels were eligible for the study. To minimize potential confounding effects, the exclusion criteria included recent users of amiodarone (patients who took amiodarone within the previous 6 months prior to the ICU admission), amiodarone therapy initiated at settings other than the target ICUs, and patients who had baseline liver function abnormalities apparently caused by factors other than amiodarone (e.g., escalating trends of liver biochemistry values prior to amiodarone initiation). The latest laboratory data within 6 months before amiodarone therapy were recorded as the baseline level. Moreover, individuals with apparent underlying liver or biliary tract diseases were also excluded, including patients with hepatitis (i.e., viral, alcoholic, autoimmune, or nonalcoholic steatohepatitis), parenchymal liver diseases, liver abscess, liver cirrhosis, portal hypertension, hepatic coma, biliary tract disorders, hepatorenal syndrome, or hepato-biliary malignancy.

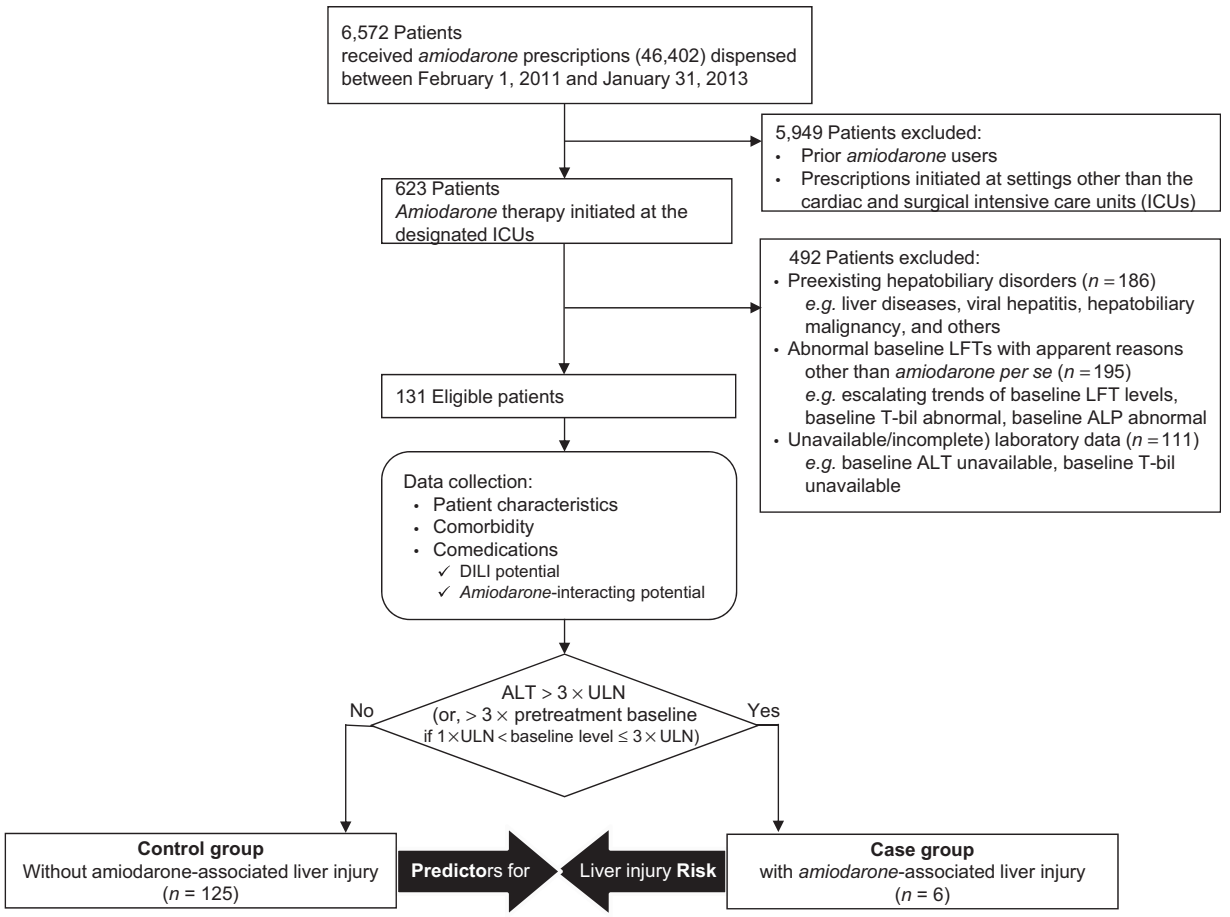

Figure 1. Patient selection and study flow. ALP = alkaline phosphatase, ALT = alanine aminotransferase, ICUs = intensive care units, LFTs = liver function tests, T-bil = total bilirubin, ULN = upper limit of normal.

Recent users or those ineligible were excluded (as summarized in Fig. 1).

2.2. Data source

The study utilized data from relevant medical charts, electronic medical records, laboratory data files, and pharmacy dispensing datasets. Relevant patient-level outpatient visit, ER visit, and hospitalization data were collected. Patient demographic information, *International Classification of Diseases,* Ninth Revision—Clinical Modification (ICD-9-CM) diagnosis and procedure codes, prescriptions details (amiodarone and concurrent medications), and laboratory data [liver biochemistry values: serum ALT, T-bil and, if available, aspartate aminotransferase (AST), direct bilirubin, and alkaline phosphatase (ALP) levels during baseline and amiodarone use] were all recorded (as listed in Table 1). Prescription details including the drug names, formulations, strength or concentrations, dosages, frequencies or rates, routes of administration, and dates of initiation and discontinuation were also noted. The cumulative dose of amiodarone for each patient was also calculated. A factor of 0.5 was applied for the oral-to-intravenous (IV) amiodarone dosage conversion (equivalent dosage) to account for oral bioavailability (approximately 0.5).[19]

2.3. Definition of amiodarone-associated liver injury

Patients who developed liver function abnormalities without other apparent causes during amiodarone therapy or within 7 days after discontinuation were regarded as amiodarone-related liver injury cases. Liver function abnormality was defined as ALT levels 3 or more times the upper limit of normal (ULN) (or $> 3 \times$ pretreatment baseline if the baseline level was

Table 1

Patient demographics and univariate analysis for amiodarone-associated liver injury.

Covariate	Study cohort (n = 131)	Amiodarone-asssociated liver injury(ALT $> 3 \times$ ULN, or $> 3 \times$ pretreatment baseline)		P
		Yes (n = 6)	No (n = 125)	
Patient characteristics				
Gender (male)	89 (67.9%)	3 (50.0)	86 (68.8%)	.38
Age, years	67.3 ± 12.5 (29.1–90.4)	72.2 ± 12.4 (52.7–88.1)	67.1 ± 12.5 (29.1–90.4)	.33
18–65	49 (37.4%)	1 (16.7%)	48 (38.4%)	.41
> 65	82 (62.6%)	5 (83.3%)	77 (61.6%)	
Height, cm	161.2 ± 7.8 (141.8–178.0)	158.7 ± 10.8 (147.0–175.0)	161.3 ± 7.7 (141.8–178.0)	.42
Weight, kg	64.1 ± 11.9 (41.6–96.6)	58.5 ± 9.4 (48.0–68.6)	64.4 ± 12.0 (41.6–96.6)	.24
Body surface area (BSA, m^2)	1.69 ± 0.18 (1.30–2.14)	1.60 ± 0.18 (1.40–1.83)	1.69 ± 0.18 (1.30–2.14)	.30
Body mass index (BMI, kg/m^2)	24.6 ± 3.9 (15.2–35.9)	23.1 ± 1.6 (21.8–26.0)	24.7 ± 4.0 (15.2–35.9)	.24
Allergy/social history				
Drug allergy	16 (12.2%)	1 (16.7%)	15 (12.0%)	.55
Smoking				.84
No	80 (61.1%)	3 (50.0%)	77 (61.6%)	
Previous	30 (22.9%)	2 (33.3%)	28 (22.4%)	
Current	21 (16.0%)	1 (16.7%)	20 (16.0%)	
Drinking (alcohol)				.69
No	108 (82.4%)	5 (83.3%)	103 (82.4%)	
Previous	8 (6.1%)	0 (0%)	8 (6.4%)	
Current	15 (11.5%)	1 (16.7%)	14 (11.2%)	
Liver Biochemistry values (baseline)				
Alanine aminotransferase (ALT, U/L)	20.8 ± 10.0 (3–79)	30.5 ± 26.3 (12–79)	20.4 ± 8.7 (3–41)	.77
Bilirubin, total (T-bil, mg/dL)	0.65 ± 0.20 (0.14–1.00)	0.61 ± 0.28 (0.14–0.98)	0.65 ± 0.19 (0.25–1.00)	.87
Comorbidity				
Number of comorbid diagnoses	6.1 ± 3.4 (0–20)	7.8 ± 3.7 (3–12)	6.0 ± 3.4 (0–20)	.16
Disease				
Heart diseases	119 (90.8%)	6 (100%)	113 (90.4%)	
Hypertension	91 (69.5%)	5 (83.3%)	86 (68.8%)	.67
Hypotension	8 (6.1%)	1 (16.7%)	7 (5.6%)	.32
Aneurysm	1 (0.8%)	0 (0%)	1 (0.8%)	
Shock	5 (3.8%)	0 (0%)	5 (4.0%)	
Endocrine disorders	70 (53.4%)	4 (66.7%)	66 (52.8%)	.68
Pulmonary disorders	15 (11.5%)	1 (16.7%)	14 (11.2%)	0.53
Chronic kidney disease	23 (17.6%)	1 (16.7%)	22 (17.6%)	
Stroke	13 (9.9%)	0 (0%)	13 (10.4%)	
Benign prostatic hypertrophy	12 (9.2%)	1 (16.7%)	11 (8.8%)	.44
Comedications				
With DILI potential	110 (84.0%)	6 (100%)	104 (83.2%)	.59
Number of meds with DILI potential	2.5 ± 1.7 (0–7)	3.8 ± 0.8 (3–5)	2.5 ± 1.7 (0–7)	.03
With amiodarone-interacting potential	81 (61.8%)	5 (83.3%)	76 (60.8%)	.41
Number of meds with DDI potential	1.0 ± 1.1 (0–5)	2.7 ± 2.0 (0–5)	0.9 ± 0.9 (0–4)	.02

Data are presented as either cases (%) or mean ± SD (range).

DDI = drug–drug interaction, DILI = drug-induced liver injury, meds = medications, ULN = upper limit of normal.

*Wilcoxon rank-sum test for continuous variables or Fisher's exact test for categorical variables.

slightly higher than reference range, i.e., $1 \times$ ULN $<$ baseline level $\leq 3 \times$ ULN).[30,31] During amiodarone therapy, the first date the patient presented with elevated ALT levels as defined above was deemed the event date. Cases of amiodarone-associated liver injury and nonliver injury controls were followed-up for 3 months from the event date or until the date of last amiodarone use, respectively.

2.4. Comedications of hepatotoxic or amiodarone-interacting potential

Comedications taken concurrently were also recorded for further assessment. The potentially hepatotoxic agents, described as comedications of hepatotoxic potential or medications with DILI potential, examined in the study included certain nonsteroidal anti-inflammatory drugs, anti-infectives, anticonvulsants, anti-psychotics, antidepressants, angiotensin-converting enzyme inhibitors, furosemide, antilipemic agents, antidiabetic agents, antineoplastic and immunomodulatory agents, and acetaminophen.[19,30,32–34]

The DDI list of moderate or major severity of concern to amiodarone included anticoagulants (warfarin, dabigatran, and rivaroxaban), antiarrhythmics (diltiazem and quinidine), antihypertensives (atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, and metoprolol), digoxin, statins (HMG-CoA reductase inhibitors: atorvastatin, fluvastatin, rosuvastatin, and simvastatin), anti-infectives (azithromycin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, metronidazole, rifabutin, atazanavir, darunavir, lopinavir, and ritonavir), analgesics (fentanyl and lidocaine), clonazepam, ziprasidone, zolpidem, theophylline, cyclosporine, sirolimus, methotrexate, and iohexol.[19,35]

2.5. Statistical analysis

The data are described as mean ± standard deviation (SD) for continuous variables and as frequencies (percentage, %) for categorical variables; for their comparison, we used the Wilcoxon rank-sum test and Fisher's exact test, respectively.

Cox's proportional hazards (PH) model with time-dependent covariates (called the "Cox's model") was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for each independent covariate in predicting the risk of amiodarone-related acute liver injury. The formulations (IV and oral) and dosages of amiodarone were taken into account in the PH models. Time-dependent covariates included daily doses (on the event day), the 3-day dosage (an aggregate dosage from the prior 72 hours till the DILI event), the cumulative dose (cDose, the total dosage from therapy initiation until the event date), and the body surface area (BSA)-standardized dose of either the daily, 3-day, or cDose.

The following categories of covariates were considered as candidates in the stepwise variable selection procedure for this regression model: patient characteristics (11 items; Table 1), comorbidity (10 items; Table 1), concomitant therapy (4 covariates; medications with DILI or amiodarone-interacting potential, Table 1), and amiodarone use (1 item) plus covariates for depicting daily/3-day/cDose amiodarone dosages (12 items; time-dependent variables, described above). Generalized additive models were used to detect the nonlinear effects of continuous covariates when appropriate.

All analyses were performed using the *R* statistical software (version 3.2.0, R Foundation for Statistical Computing, Vienna, Austria).[36] Significant differences were assumed when the P was $\leq .05$.

3. Results

Of the 6572 patients receiving a total of 46,402 amiodarone prescriptions, amiodarone therapy was initiated in 623 individuals (9.5%) in cardiac and surgical ICUs. The study cohort of 131 patients (21.0%), new amiodarone users and had baseline and follow-up liver biochemistry results, ultimately met the inclusion criteria for further analysis. The percentage of males, mean age, ALT level, T-bil level, and number of comorbidities were 67.9%, 67.3 ± 12.5 years, 20.8 ± 10.0 U/L, 0.65 ± 0.20 mg/dL, and 6.1 ± 3.4 diagnoses, respectively (Table 1). The proportions of comedicating with DILI (84.0%) or clinically significant amiodarone-interacting (61.8%) potential were high. The mean numbers (± SD) of DILI and DDI comedications were 2.5 ± 1.7 and 1.0 ± 1.1 drugs, respectively.

Six subjects exhibited ALT levels $>$ 3 times the ULN (n = 4) or the pretreatment baseline (n = 2; $1 \times$ ULN $<$ baseline levels $< 3 \times$ ULN) during amiodarone therapy. Five of 6 hepatic injury cases received initial amiodarone administration intravenously. Each of the 6 cases of amiodarone-associated liver injury (100%) were co-prescribed 2 or more DILI potential medications, and 5 (83.3%) had amiodarone-interacting comedications. Ampicillin/sulbactam (IV) and acetaminophen were the most commonly observed DILI coprescriptions. The most frequently encountered DDI comedications were fentanyl (IV) and carvedilol.

The univariate analysis of covariates related to patient characteristics and comorbidity showed no significant difference between liver injury cases and non-injury controls (Table 1). The difference in the baseline ALT levels between the 2 groups was also insignificant (30.5 ± 26.3 vs 20.4 ± 8.7, $P = .77$; Table 1). However, the ALT levels of the liver injury cases ranged from 160 to 637 U/L on the event dates. The length of ICU stays (31.7 ± 37.5 vs 7.0 ± 6.8, $P = .003$) and the length of hospital stays (76.0 ± 66.3 vs 19.3 ± 14.4, $P < .001$) for DILI cases were also considerably prolonged compared to those of the controls (Table 2). Most interestingly, the number of comedications consisting of either DILI potential drugs (3.8 ± 0.8 vs 2.5 ± 1.7, $P = .03$) or amiodarone-interacting agents (2.7 ± 2.0 vs 0.9 ± 0.9, $P = .02$) was notably higher in the DILI case group.

The latency period, from the start of therapy to the onset of laboratory evidence of liver injury, of the case cohort ranged from 1 to 10 days (mean, 4.3 ± 3.4 days). In contrast to this apparently *acute* hepatocellular injury effect, the time-to-recovery was relatively lengthy (up to 3 months; mean, 45.6 ± 32.1 days) (Table 2). Multivariate analyses using Cox's PH model demonstrated that the number of comedications with DDI potential (HR, 2.07; 95% CI, 1.02 to 4.22; $P = .04$) and the BSA-standardized cumulative dose (cDose/BSA, g/m^2; HR, 6.82; 95% CI, 1.72 to 27.04; $P = .01$) were independently associated with risk of amiodarone-associated liver injury (Table 3).

4. Discussion

This study incorporated comedications of DDI and DILI potentials and amiodarone doses (daily, 3-day, cumulative) as essential covariates to delineate the risks and clinical significance of amiodarone-associated liver injury in ICU settings. Within this critically ill, high comorbidity, and frequent DILI or DDI co-prescription cohort, the incidence of amiodarone-associated liver injury was prudently estimated to be 4.6%. All of the 6 liver-

Table 2

Clinical status and outcomes of the study cohort.

Covariate	Study cohort (n = 131)	Amiodarone-associated liver injury (ALT > 3 × ULN, or > 3 × pretreatment baseline)		P
		Yes (n = 6)	No (n = 125)	
Clinical status				
Length of stay				
ICU stay, days	8.1 ± 11.2 (1–105)	31.7 ± 37.5 (6–105)	7.0 ± 6.8 (1–34)	.003
Hospital stay, days	21.9 ± 22.5 (1–206)	76.0 ± 66.3 (23–206)	19.3 ± 14.4 (1–97)	<.001
Amiodarone-associated liver injury cases				
ALT, U/L, on the event day (n = 6)		324.2 ± 192.7 (160–637)		
Latency (time-to-DILI event, days)		4.3 ± 3.4 (1–10)		
Sequela of liver injury				
Recovery				
Fully		5 (83.3%)		
Partially		1 (16.7%)		
Time to full recovery (days, n = 5)		45.6 ± 32.1 (17–84)		

Data are presented as either cases (%) or mean ± SD (range).

DILI = drug-induced liver injury, ULN = upper limit of normal.

*Wilcoxon rank-sum test for continuous variables or Fisher's exact test for categorical variables.

Table 3

The multivariate analysis of factors associated with amiodarone-associated liver injury by Cox's proportional hazards model.

Covariate	Hazard ratio	95% Confidence interval	P
Number of comedications of amiodarone-interacting potential	2.07	1.02–4.22	.04
Cumulative dose/BSA (cDose/BSA, g/m^2)	6.82	1.72–27.04	.01

BSA = body surface area, DDI = drug–drug interaction.

*In the regression model (n = 131), the adjusted generalized $R^2 = 0.49$ and concordance = 0.90 (SE = 0.12); > 0.7 indicated a very good fit.

injury cases were detected while still on amiodarone therapy, mainly intravenously administered, with latency periods of ≤ 10 days. Patients developed liver injury during amiodarone use had significantly longer lengths of ICU and hospital stays even though their baseline characteristics were comparable to those of controls (Table 1).

Although seemingly justified by instinct, explicit evidence of drug-specific factors for DILI is limited.[37] Two drug-related risks, namely the number of DDI comedications and the BSA-standardized cumulative dose were identified for amiodarone-associated liver injury by a time-dependent multivariate analysis in our study. Amiodarone is unique in its physicochemical (octanol-water partition coefficient, log $P = 7.2$; amphiphilic) and pharmacokinetic ($t_{1/2} \fallingdotseq 58$ days) properties.[18,38] With this composite nature of high lipophilicity and long half-life, it is of interest that the BSA-standardized cumulative dose of amiodarone can predict risk of liver injury; however, the daily dosage and the cumulative dose alone do not have such predictive power.

This study of amiodarone use in critical settings is the first to indicate that interacting comedications should not be overlooked in evaluating complex comedication regimens or complicated cases. Whether amiodarone per se, hypoxia, or co-solvent (parenteral formulation) is causative of *acute* hepatotoxicity remains undetermined.[20–29] Nonetheless, the amiodarone-related risk factors disclosed herein may imply that the physiochemical nature of the compound itself plays a role in invoking DILI. Moreover, one of the 6 patients did not receive IV amiodarone, indicating that a co-solvent in parenteral formulations may not be a requisite. Our finding coincides with an early report that drug *content* (concentration) is also critical with regard to amiodarone-induced hepatic phospholipidosis.[39,40]

In an examination of a dataset including 343 medications, Chen et al[38] recently demonstrated that oral drugs with a high lipophilicity (logP ≥ 3) and a high usual dosage (≥ 100 mg/day) were prone to DILI hazard. Our identification of the BSA-standardized cumulative dose as a predictor for amiodarone-associated liver injury, using the unique approach of analyzing patient medical data, not only underscores Chen et al.'s statement but also indicates the importance of the cumulative dose for drugs with unusually long half-lives and the necessity of taking the patient's stature (e.g., BSA) into consideration when making clinical judgments.

This study is limited by the retrospective nature, sample size, confined setting (critically ill), and single institution (tertiary care). Few liver injury cases were observed in the study. However, the goodness-of-fit measure *concordance* (0.90, se = 0.12; Table 3) of the final Cox's model in our study suggested an acceptable level of discrimination power. Although the enlisted medications with DILI potential were summarized from reliable reference resources and decade-long registries,[19,30,32–34] a more restrictive definition might have been employed because certain medications were with little DILI evidence. Interestingly, the DILI-comedication covariate was not presented as a significant factor for predicting amiodarone-related liver injury despite a more inclusive definition was used in this study. Undoubtedly, further clinical and fundamental studies are required to delineate the exact mechanisms underlying amiodarone-associated *acute* hepatotoxicity.

5. Conclusions

Precision medicine, achieved by networking layers of information from scientific research, clinical practice, social or behavioral

studies, and observations about optimal health care, is now on the horizon.[41–43] This study found that drug-related covariates such as physicochemical properties, interaction profiles, and the BSA-standardized cumulative dose are all important factors when deliberating amiodarone-associated liver injury at the individual patient care level. Factors pertaining to medications are especially of concern in critical care settings where high comorbidity and frequent polypharmacy are common. We sincerely recommend that drug factors, in addition to well-recognized biomedical (molecular, genomic, cellular, physiological, and clinical), behavioral, and environmental factors, should be taken into consideration to make the utmost of precision medicine in the decades ahead.

Acknowledgments

The authors are grateful to Dr Fu-Chang Hu, MS, ScD, for his invaluable statistical discussions. We thank the NTU Hospital Information Technology Office and the Department of Pharmacy for providing relevant electronic medical records and dispensing data.

Author contributions

Conceptualization: Yunn-Fang Ho, Hsin-Ying Chou, Jan-Show Chu, Ping-Ing Lee.
Data curation: Yunn-Fang Ho, Hsin-Ying Chou.
Formal analysis: Yunn-Fang Ho, Hsin-Ying Chou, Ping-Ing Lee.
Funding acquisition: Yunn-Fang Ho.
Investigation: Yunn-Fang Ho, Hsin-Ying Chou, Ping-Ing Lee.
Methodology: Yunn-Fang Ho, Ping-Ing Lee.
Resources: Jan-Show Chu, Ping-Ing Lee.
Supervision: Ping-Ing Lee.
Validation: Yunn-Fang Ho.
Writing – original draft: Yunn-Fang Ho, Hsin-Ying Chou.
Writing – review & editing: Yunn-Fang Ho, Jan-Show Chu, Ping-Ing Lee.

References

[1] Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. Crit Care Med 1990;18:1383–8.
[2] Reinelt P, Karth GD, Geppert A, et al. Incidence and type of cardiac arrhythmias in critically ill patients: a single center experience in a medical-cardiological ICU. Intensive Care Med 2001;27:1466–73.
[3] Tongyoo S, Permpikul C, Haemin R, et al. Predicting factors, incidence and prognosis of cardiac arrhythmia in medical, non-acute coronary syndrome, critically ill patients. J Med Assoc Thai 2013;96(suppl 2): S238–45.
[4] Yoshida T, Fujii T, Uchino S, et al. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. J Intensive Care 2015;3:19.
[5] Mason JW. Amiodarone. N Engl J Med 1987;316:455–66.
[6] Singh BN. Amiodarone: the expanding antiarrhythmic role and how to follow a patient on chronic therapy. Clin Cardiol 1997;20:608–18.
[7] Goldschlager N, Epstein AE, Naccarelli GV, et al. Practice Guidelines Sub-committee, North American Society of Pacing and Electrophysiology (HRS)A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm 2007;4:1250–9.
[8] Zebis LR, Christensen TD, Thomsen HF, et al. Practical regimen for amiodarone use in preventing postoperative atrial fibrillation. Ann Thorac Surg 2007;83:1326–31.
[9] January CT, Wann LS, Alpert JS, et al. ACC/AHA Task Force Members2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:2246–80.
[10] Sanoski CA, Bauman JL. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. The arrhythmias. Pharmacotherapy: A Pathophysiologic Approach 9th ednMcGraw-Hill Education, New York:2014;207–44.
[11] Xanthos T, Bassiakou E, Vlachos IS, et al. Intravenous and oral administration of amiodarone for the treatment of recent onset atrial fibrillation after digoxin administration. Int J Cardiol 2007;121:291–5.
[12] Fang MC, Stafford RS, Ruskin JN, et al. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. Arch Intern Med 2004;164:55–60.
[13] Vaughan-Sarrazin MS, Mazur A, Chrischilles E, et al. Trends in the pharmacologic management of atrial fibrillation: data from the Veterans Affairs Health System. Am Heart J 2014;168:53–9.e1.
[14] Desai AM, Cavanaugh TM, Desai VC, et al. Trends in the outpatient treatment of atrial fibrillation in the USA from 2001 to 2010. Pharmacoepidemiol Drug Saf 2014;23:539–47.
[15] Siddoway LA. Amiodarone: guidelines for use and monitoring. Am Fam Physician 2003;68:2189–96.
[16] Vassallo P. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA 2007;298:1312–22.
[17] Punnam SR, Goyal SK, Kotaru VP, et al. Amiodarone—a 'broad spectrum' antiarrhythmic drug. Cardiovasc Hematol Disord Drug Targets 2010;10: 73–81.
[18] Package insert (Cordarone, revised March 27, 2015). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018972s047lbl.pdf. Accessed 10 January 2017.
[19] Micromedex Computerized Clinical Information System. Thomson Reuters (Healthcare) Inc., 2016. Available at: https://www.micromedexsolutions.com/micromedex2/librarian/
[20] Fromenty B, Fisch C, Berson A, et al. Dual effect of amiodarone on mitochondrial respiration. Initial protonophoric uncoupling effect followed by inhibition of the respiratory chain at the levels of complex I and complex II. J Pharmacol Exp Ther 1990;255:1377–84.
[21] Vereckei A, Blazovics A, Gyorgy I, et al. The role of free radicals in the pathogenesis of amiodarone toxicity. J Cardiovasc Electrophysiol 1993;4:161–77.
[22] Ribeiro SM, Campello AP, Nascimento AJ, et al. Effect of amiodarone (AMD) on the antioxidant enzymes, lipid peroxidation and mitochondrial metabolism. Cell Biochem Funct 1997;15:145–52.
[23] Waldhauser KM, Török M, Ha HR, et al. Hepatocellular toxicity and pharmacological effect of amiodarone and amiodarone derivatives. J Pharmacol Exp Ther 2006;319:1413–23.
[24] Serviddio G, Bellanti F, Giudetti AM, et al. Mitochondrial oxidative stress and respiratory chain dysfunction account for liver toxicity during amiodarone but not dronedarone administration. Free Radic Biol Med 2011;51:2234–42.
[25] Henrion J, Schapira M, Luwaert R, et al. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore) 2003;82:392–406.
[26] Gluck N, Fried M, Porat R. Acute amiodarone liver toxicity likely due to ischemic hepatitis. Isr Med Assoc J 2011;13:748–52.
[27] Rhodes A, Eastwood JB, Smith SA. Early acute hepatitis with parenteral amiodarone: a toxic effect of the vehicle? Gut 1993;34:565–6.
[28] Rätz Bravo AE, Drewe J, Schlienger RG, et al. Hepatotoxicity during rapid intravenous loading with amiodarone: description of three cases and review of the literature. Crit Care Med 2005;33:128–34.
[29] Souney PF, Cooper WD, Cushing DJ. PM101: intravenous amiodarone formulation changes can improve medication safety. Expert Opin Drug Saf 2010;9:319–33.
[30] Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006;354:731–9.
[31] FDA Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Issued July 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. Accessed 16 August 2017.
[32] Andrade RJ, Lucena MI, Fernández MC, et al. Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512–21.
[33] Björnsson E, Jerlstad P, Bergqvist A, et al. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005;40:1095–101.
[34] Devarbhavi H, Dierkhising R, Kremers WK, et al. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010;105: 2396–404.
[35] Tatro DS. Drug Interaction Facts: the Authority on Drug Interactions. Lippincott Williams & Wilkins, Philadelphia:2014.

[36] R Foundation for Statistical Computing. R: a language and environment for statistical computing. Available at: http://www.R-project.org/2015. Accessed 18 April 2015.
[37] Chalasani NP, Hayashi PH, Bonkovsky HL, et al. Practice Parameters Committee of the American College of GastroenterologyACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:950–66.
[38] Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology 2013;58:388–96.
[39] Pirovino M, Müller O, Zysset T, et al. Amiodarone-induced hepatic phospholipidosis: correlation of morphological and biochemical findings in an animal model. Hepatology 1988;8:591–8.
[40] Farrell GC. Farrell GD. Drug-induced steatohepatitis. Drug-induced Liver Disease Churchill Livingstone, Edinburge:1994; 431–8.
[41] National Research Council. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. National Academies Press, Washington, DC, 2011. Available at: http://www.nap.edu/catalog/13284/toward-precision-medicine-building-a-knowledge-network-for-biomedical-research. Accessed 8 May 2017.
[42] Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–5.
[43] Hawgood S, Hook-Barnard IG, O'Brien TC, et al. Precision medicine: beyond the inflection point. Sci Transl Med 2015;7:300s17.