Original Article

Clinical outcomes of adverse cardiovascular events in patients with acute dapsone poisoning

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Objective Adverse cardiovascular events (ACVEs) account for a large proportion of the morbidities and mortalities associated with drug overdose emergencies. However, there are no published reports regarding outcomes of ACVEs associated with acute dapsone poisoning. Here, the authors retrospectively analyzed ACVEs reported within 48 hours of treatment in patients with acute dapsone poisoning and assessed the significance of ACVEs as early predictors of mortality.

Methods Sixty-one consecutive cases of acute dapsone poisoning that were diagnosed and treated at a regional emergency center between 2006 and 2014 were included in the study. An ACVE was defined as myocardial injury, shock, ventricular dysrhythmia, cardiac arrest, or any combination of these occurring within the first 48 hours of treatment for acute dapsone poisoning.

Results Nineteen patients (31.1%) had evidence of myocardial injury (elevation of serum troponin-I level or electrocardiography signs of ischemia) after dapsone overdose, and there were a total of 19 ACVEs (31.1%), including one case of shock (1.6%). Fourteen patients (23.0%) died from pneumonia or multiple organ failure, and the incidence of ACVEs was significantly higher among non-survivors than among survivors (64.3% vs. 21.3%, P=0.006). ACVE was a significant predictor of mortality (odds ratio, 5.690; 95% confidence interval, 1.428 to 22.675; P=0.014).

Conclusion The incidence of ACVE was significantly higher among patients who died after acute dapsone poisoning. ACVE is a significant predictor of mortality after dapsone overdose, and evidence of ACVE should be carefully sought in these patients.

Keywords Dapsone; Intoxication; Cardiac injury; Troponin I; Mortality

Capsule Summary

What is already known
Adverse cardiovascular events (ACVEs) account for a large proportion of deaths related to acute drug overdose. However, the implications of ACVE after acute dapsone poisoning are not well known.

What is new in the current study
ACVE occurred in 19 of 61 patients (31.1%) during the first 48 hours after acute overdose. Early ACVE was a significant predictor of mortality.

INTRODUCTION

Dapsone is a bacteriostatic sulfone antibiotic that has been used as a major component in multidrug treatment of leprosy since the 1940s.[1,2] The adverse effects of dapsone at therapeutic doses include neutropenia, thrombocytopenia, eosinophilic pneumonia, aplastic anemia, hemolysis, neuropathy, hepatitis, and agranulocytosis, and acute adverse effects include, nausea, vomiting, abdominal pain, methemoglobinemia, seizure, and coma.[3,4] Hypersensitivity myocarditis has also been associated with dapsone at therapeutic doses.[5-8]

Adverse cardiovascular events (ACVEs) account for a substantial proportion of the morbidity and mortality associated with drug overdose emergencies,[9] but little is known of the implications of ACVEs arising as a result of acute dapsone overdose, specifically ACVEs that are identified by elevated troponin levels.

New cases of leprosy are rare at Wonju Severance Christian Hospital, but dapsone use is still relatively common in our area (Wonju, Korea) because there was a leper colony nearby during the 1960s and 1970s. Dapsone poisoning is known to have a high mortality rate.[10] We wanted to determine the frequency and nature of ACVEs associated with dapsone poisoning, and to examine the relationship between ACVEs and mortality in cases of acute dapsone poisoning.

Accordingly, we determined the incidence of ACVE within 48 hours of the start of treatment and compared general characteristics, including ACVE, in survivors and non-survivors; based on this, we evaluated the significance of ACVE as an early predictor of mortality in cases of acute dapsone poisoning.

METHODS

Study design and data collection

This was a retrospective observational study that included consecutive patients diagnosed with acute dapsone poisoning at a regional emergency center between January 2006 and June 2014. Serum high sensitivity troponin I levels (hs-TnI; Siemens Healthcare Diagnostics, Newark, DE, USA; normal range <0.046 ng/mL) were measured in all included patients. Dapsone ingestion was confirmed by patients or guardians, and dapsone toxicity was confirmed by the treating emergency physician and verified by serum methemoglobin levels. The study exclusion criteria were age <18 years, end-stage renal disease, and the absence of serum TnI measurement during the first 48 hours after arrival at the emergency department.

The following data were obtained from the medical records of the included patients: age, gender, amount ingested, underlying disease, initial symptoms and signs, initial Glasgow Coma Scale (GCS) score, initial systolic blood pressure, and treatment, including methylene blue, gastric irrigation, activated charcoal, and multidose activated charcoal. Electrocardiograms, when available, were reviewed by an experienced cardiologist (HSO) and ventricular dysrhythmias and signs of ischemic change were noted. Serum methemoglobin, hs-TnI, and beta-type natriuretic peptide levels at the time of initial presentation were also recorded. Data collection was conducted by two emergency physicians who were blinded to the study objectives and hypothesis. Both underwent training before data collection to reduce bias by disagreement.

ACVE was defined by at least one of the following: 1) myocardial injury as evidenced by hs-TnI elevation within 48 hours of presentation or electrocardiography (ECG) signs of ischemia including ST elevation, ST depression, or T wave inversion; 2) shock, as defined by hypotension requiring vasopressor support; 3) ventricular dysrhythmia, including ventricular tachycardia, ventricular fibrillation, or torsades des pointes; and 4) cardiac arrest.[11-16] We included only ACVEs that were apparent during the first 48 hours because we wanted to identify early predictors of mortality and minimize the possibility that an ACVE was secondary to malfunction of other organs or systems or multiple organ failure in the terminal stage.

General characteristics of each case of acute dapsone poisoning, including mortality and the incidence of ACVE, were assessed, and we compared characteristics of survivors and non-survivors to examine the relationship between ACVEs and mortality. This study was approved by the institutional review board of Wonju College of Medicine, Yonsei University.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics ver. 20 (IBM, Armark, NY, USA). Categorical variables were presented as frequencies and percentages, and continuous variables as medians and interquartile ranges after assessment for normality using the Shapiro-Wilk test. The chi-square test or Fisher's exact test was used to compare categorical variables and the Mann-Whitney U-test was used to compare continuous variables. Predictors of mortality were identified by multiple logistic regression analysis. P-values of <0.05 were considered statistically significant.

RESULTS

Characteristics of patients with acute dapsone poisoning

Among 74 consecutive patients who had acute dapsone poisoning during the study period, 61 patients (16 men [26.2%], age 18

to 91 years, median 67 years) were included in this retrospective study and 13 were excluded (five who were < 18 years old, one with end stage renal disease, and seven who did not have serum hs-TnI measurements within 48 hours of arrival).

The amount of dapsone ingested varied from 300 mg (3 × 100 mg tablets) to 3 g (30 × 100 mg tablets). The pills were ingested intentionally in all cases. Hypertension was the most common cardiovascular risk factor. Common signs and symptoms at initial presentation were cyanosis (40 patients, 65.6%), dyspnea (30 patients, 49.2%), and headache (8 patients, 13.1%). Other symptoms included nausea, vomiting, general weakness, dizziness, and seizures (Table 1).

ACVE in the form of myocardial injury occurred in 19 patients (31.1%); among them, 12 (19.7%) had elevated hs-TnI and 10 (16.4%) had ECG changes (4 with ST depression and 6 with T wave inversion); shock was reported in one patient in this group (1.6%). No cases of ventricular dysrhythmia or cardiac arrest were noted.

Table 1. General and laboratory characteristics of patients with acute dapsone poisoning

Characteristics	Value (n = 61)
Age (yr)	67 (51–79)
Male sex	16 (26.2)
Ingestion dose (mg)	500 (375–1,375)
Time from ingestion to ED arrival (hr)	10.0 (3.0–13.9)
Underlying disease	
Diabetes mellitus	16 (26.2)
Hypertension	32 (52.5)
Hyperlipidemia	1 (1.6)
Initial symptoms and signs	
Cyanosis	40 (65.6)
Dyspnea	30 (49.2)
Headache	8 (13.1)
Initial Glasgow Coma Scale	15 (12–15)
Systolic blood pressure (mmHg)	136 (120–152)
Initial methemoglobin (%)	34.6 (27.0–40.0)
Initial high sensitivity TnI (ng/mL)	0.015 (0.007–0.030)
β-natriuretic peptide (pg/mL)	56.83 (14.66–88.55)
Use of methylene blue	59 (96.7)
Gastric irrigation	24 (39.3)
Activated charcoal	39 (63.9)
Multidose activated charcoal	9 (14.8)
Adverse cardiovascular events	19 (31.1)
Myocardial injury	19 (31.1)
Elevation of TnI	12 (19.7)
Ischemic change of ECG	10 (16.4)
Shock	1 (1.6)
Ventricular dysrhythmia	0 (0)
Cardiac arrest	0 (0)
Mortality	14 (23.0)

Values are presented as median (interquartile range) or number (%).
ED, emergency department; TnI, troponin I; ECG, electrocardiography.

Median initial hs-TnI and beta-type natriuretic peptide levels were 0.015 ng/mL and 56.83 pg/mL, respectively. Regarding treatment, 59 patients (96.7%) received methylene blue and nine (14.8%) received multidose activated charcoal. Fourteen of the 61 patients (23.0%) ultimately died from pneumonia or multiple organ failure (Table 1).

Comparison of survivors and non-survivors

There were 14 non-survivors and 47 survivors (77.0%). As a group, the non-survivors were older than the survivors (median age 80 vs. 64 years, P = 0.005) and had significantly lower GCS scores at arrival. The rate of ACVE was significantly higher among the non-survivors (64.3% vs. 21.3%, P = 0.006). Finally, there was a significant difference in median total dose of methylene blue between non-survivors and survivors (2,425 vs. 800 mg, P = 0.004) (Table 2).

Multiple logistic regression analysis showed that among age, initial GCS score, and presence of ACVE, only ACVE (odds ratio, 5.690; 95% confidence interval, 1.428 to 22.675; P = 0.014) was significantly associated with mortality (Table 3).

DISCUSSION

There was a greater incidence of ACVE development within the first 48 hours of treatment for dapsone poisoning than we anticipated, and the rate of early ACVE was significantly higher in non-survivors than in survivors (Table 2). Logistic regression analysis confirmed a significant association between early cardiac injury and mortality, and ours is the first study to report this finding in relation to acute dapsone poisoning. Evaluation for early signs of ACVE, such as serum hs-TnI levels > 0.046 ng/mL or ECG changes characteristic of ischemia, should be a part of the initial prognostic workup for patients with acute dapsone poisoning.

TnI is useful for detecting acute myocardial injury because it is expressed as a cardiac-specific isoform.[17] Experimental data strongly suggest that TnI leaks from cells only after membrane disruption following myocardial cell death.[18] High-sensitivity troponin assays permit early detection of circulating TnI resulting from transient ischemia or inflammatory myocardial injury.[19] In the present study, all of the patients who had early ACVE after dapsone overdose had myocardial injury. Only three of 12 patients with elevated serum hs-TnI levels had ECG changes consistent with ischemia. Therefore, we suggest that both ECG and serum TnI level should be used to check for myocardial injury in patients with acute dapsone poisoning.

Two mechanisms of cardiotoxicity related to dapsone-induced ACVE have been proposed. First, methemoglobinemia may lead to myocardial cell death because of reduced oxygen delivery to the

Table 2. Comparison of survivors and non-survivors

Characteristic	Survivors (n = 47, 77.0%)	Non-survivors (n = 14, 23.0%)	P-value
Age (yr)	64 (51–78)	80 (68–83)	0.005
Male sex	14 (29.8)	2 (14.3)	0.318
Ingestion dose (mg)	500 (288–1,375)	875 (425–2,188)	0.503
Underlying disease			
Diabetes mellitus	11 (23.4)	5 (35.7)	0.490
Hypertension	24 (51.1)	8 (57.1)	0.689
Hyperlipidemia	1 (2.1)	0 (0)	1.000
Initial symptoms and signs			
Cyanosis	28 (59.6)	12 (85.7)	0.109
Dyspnea	23 (48.9)	7 (50.0)	0.944
Headache	8 (17.0)	0 (0)	0.180
Initial Glasgow Coma Scale	15 (13–15)	13 (9–14)	0.009
Systolic blood pressure (mmHg)	135 (120–150)	138 (130–166)	0.274
Initial methemoglobin (%)	33.6 (23.1–39.7)	37.8 (31.6–40.9)	0.162
Initial hs-TnI (ng/mL)	0.014 (0.006–0.015)	0.039 (0.013–0.556)	0.007
β-natriuretic peptide (pg/mL)	36.24 (12.29–88.52)	63.48 (54.32–147.12)	0.138
Use of methylene blue	45 (95.7)	14 (100)	1.000
Total dose of methylene blue (mg)	800 (450–1,500)	2,425 (1,285–3,840)	0.004
Gastric irrigation	18 (38.3)	6 (42.9)	0.759
Activated charcoal	32 (68.1)	7 (50.0)	0.216
Multidose activated charcoal	7 (14.9)	2 (14.3)	1.000
Adverse cardiovascular events	10 (21.3)	9 (64.3)	0.006

Values are presented as median (interquartile range) or number (%).
hs-TnI, high sensitivity troponin I.

Table 3. Early predictors of mortality

	Odds ratio	95% confidence interval	P-value
Age	1.030	0.979–1.083	0.256
Adverse cardiovascular events	5.690	1.428–22.675	0.014
Glasgow Coma Scale	0.876	0.712–1.078	0.212

cells. Second, reduced intravascular volume, vascular resistance, or myocardial contractility due to myocardial stunning may lead to cardiogenic shock.[20]

Only one patient in our study population developed shock requiring vasopressor support during the first 48 hours of treatment, and there were no cases of ventricular dysrhythmia or cardiac arrest.

We did not include cases of shock and cardiac arrest associated with multiple organ failure during the late period in our analysis because we wanted to identify early predictors of mortality. Our comparison of non-survivors and survivors showed that median age, median initial GCS score, total dose of methylene blue, and incidence of ACVE differed significantly between these two groups. We attributed the finding that non-survivors were older than survivors to weaker physiologic defense mechanisms among the older patients, and we also attributed the lower GCS scores and higher rate of ACVEs among non-survivors to this age difference. We speculated that the differences in total dose of methy-

lene blue were related to the persistence of methemoglobinemia in non-survivors compared to survivors.

This study has some limitations that bear consideration. First, it was conducted using a retrospective design at a single hospital, and as a result, not all relevant assessment parameters were included, especially initial symptoms and past history. Serum beta-type natriuretic peptide was checked in 36 (59.0%) out of 61 patients, and echocardiography results as a measure of cardiac function in patients with ACVE, were not included in the analysis. Further studies are required to clarify these details. Nonetheless, our finding of a significant association between early indicators of ACVE and mortality in cases of acute dapsone poisoning should prompt physicians in the emergency department to consider checking serum biomarkers and ECG for early signs of ACVE in all patients who present with dapsone overdose.

The incidence of ACVE was significantly higher among patients who died after acute dapsone poisoning. ACVE is a significant predictor of mortality after dapsone overdose, and evidence of ACVE should be carefully sought in these patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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