

Predictors of mortality in patients with suspected propofol infusion syndrome

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Objectives: To identify predictors of mortality in patients with suspected propofol infusion syndrome and to develop a simple scoring system to identify patients with suspected propofol infusion syndrome who are most at risk of death.

Design: Retrospective, database analysis.

Setting: MEDWATCH system.

Participants: Reports (1989–2005) where propofol was associated with ≥ 1 of 24 published propofol infusion syndrome clinical manifestations.

Interventions: None.

Measurements and Main Results: After comparison of demographic and clinical manifestations between survivors and non-survivors, a multivariate logistic regression model was built through a stepwise selection process and then used to develop a simplified mortality scoring system. Of 1139 patients with suspected propofol infusion syndrome, 342 (30%) were fatal. Death was more likely if patients were ≤ 18 yrs (odds ratio [95% confidence interval], 2.3 [1.7–3.2]), male (1.3 [1.1–1.7]), received a vasopressor (1.8 [1.3–2.5]), or had the following clinical manifestations: cardiac (3.8 [2.88–4.91]), metabolic acidosis (3.7

[2.7–5.0]), renal failure (1.9 [1.4–2.6]), hypotension (1.8 [1.3–2.3]), rhabdomyolysis (1.8 [1.3–2.3]), or dyslipidemia (2.0 [1.2–3.4]). The multivariable modeling process found that cardiac symptoms, rhabdomyolysis, hypotension, metabolic acidosis, renal failure, and age each affected survival, although significant interactions existed between some of these factors. Based on the combination of the presence or absence of the six factors in the multivariate model, a propofol infusion syndrome mortality risk score of 0 to 4 resulted in a predicted %/observed % mortality for each score of 0 (10%/10%), 1 (24%/24%), 2 (47%/44%), 3 (72%/81%), and 4 (89%/83%).

Conclusions: A number of characteristics are independently associated with higher mortality in patients with suspected propofol infusion syndrome, only some of which are currently reflected in the package insert. Further research should focus on prospectively evaluating the mortality scoring system in patients with suspected propofol infusion syndrome. (Crit Care Med 2008; 36:2281–2287)

KEY WORDS: propofol; propofol infusion syndrome; adverse drug event; risk factors; mortality; outcomes; critical care; sedation

Propofol is an anesthetic agent that has been widely used as a sedative in the intensive care unit (ICU) for nearly 20 yrs (1). Although propofol is generally considered a safe agent when prescribed based on product labeling recommendations, a troublesome syndrome known as the propofol infusion syndrome (PRIS) has

been reported with its use (2–28). PRIS was first described in 1992 in a case series of five pediatric ICU patients, who developed metabolic acidosis with bradyarrhythmia and progressive myocardial failure resulting in death while receiving high-dose propofol ($>83 \mu\text{g}/\text{kg}/\text{min}$ [$5 \text{ mg}/\text{kg}/\text{hr}$]) for >48 hrs (5). Since this report, 38 cases of PRIS have subsequently been published in both adults and children with an associated mortality rate exceeding 80% (29, 30).

PRIS-associated clinical manifestations vary widely and have been reported to include rhabdomyolysis, myocardial failure, acute renal failure, severe metabolic acidosis, bradyarrhythmias, cardiac arrest, dyslipidemias, and hypotension (31). Postulated risk factors for PRIS include propofol doses $>83 \mu\text{g}/\text{kg}/\text{min}$, a duration of therapy >48 hrs, concomitant use of catecholamine vasopressors or glucocorticoids and age <18 yrs (29–31). Other potential risk factors include patients having an inborn error of mito-

chondrial fatty acid oxidation or who receive a ketogenic diet (4, 28). Recently, the product labeling of propofol has been changed to increase the prescriber's awareness of PRIS. Current labeling advocates the optimization of hemodynamic and oxygen delivery parameters in all ICU patients treated with propofol in addition to the discontinuation of propofol if metabolic acidosis, rhabdomyolysis, hyperkalemia, and/or rapid progressive heart failure occur during therapy (32).

Although PRIS is associated with a high mortality rate and propofol is widely used in the ICU, the small number of published case reports of PRIS leave the demographic and clinical factors associated with PRIS, particularly those factors associated with death, poorly characterized. One recent study attempted to analyze deaths associated with the administration of propofol; however, its utility as a guide for identifying PRIS was limited given that many of the PRIS-associated clinical manifestations that have been re-

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ported in published case reports were excluded and that only cases associated with death were evaluated (33). Given the high-mortality associated with PRIS, we sought to 1) identify predictors of mortality in patients receiving propofol who had PRIS-associated clinical manifestations, and 2) propose a simple scoring system to identify patients with suspected PRIS who are at most risk of death.

METHODS

Published case reports of PRIS were identified via a MEDLINE search (1950–June 2006) using one or more of the following search terms: propofol, PRIS, rhabdomyolysis, and adverse drug events (3–28, 31, 34). The references listed at the end of each case report were manually searched to identify additional possible cases of PRIS. Both pediatric and adult reports were included. From the identified cases ($n = 43$), a list of the most common PRIS-associated clinical manifestations was tabulated and grouped under nine different categories. The categories and the frequency of each clinical manifestation was reported among the 43 cases, included 1) rhabdomyolysis ($n = 25$); 2) cardiac ($n = 69$) including asystole ($n = 6$), bradyarrhythmias ($n = 14$), bradycardia ($n = 14$), Brugada-like electrocardiogram pattern ($n = 6$), cardiac arrest ($n = 6$), myocardial failure ($n = 5$), pulseless electrical activity ($n = 6$), and ventricular tachycardia/fibrillation ($n = 12$); 3) metabolic acidosis ($n = 24$) (including lactic acidosis); 4) hypotension ($n = 16$); 5) hepatic ($n = 14$); made up of hepatomegaly ($n = 7$), hepatic steatosis ($n = 4$), and transaminitis ($n = 3$); 6) renal ($n = 34$); made up of anuria ($n = 4$), oliguria ($n = 6$), renal failure ($n = 11$), and hyperkalemia ($n = 13$); 7) hypoxia ($n = 5$); 8) hyperthermia ($n = 12$); and 9) dyslipidemia ($n = 16$) made up of hypertriglyceridemia ($n = 9$) and lipemia ($n = 7$). This study received expedited approval from the Institutional Review Board at Tufts-New England Medical Center before its completion.

Under the Freedom of Information Act, we requested all case reports submitted to the Food and Drug Administration's MEDWATCH Adverse Event Reporting System database from the years 1989 through 2005 in which one or more of the above PRIS-associated clinical manifestations was reported in a patient who received propofol. MEDWATCH is the world's largest repository of adverse drug events, particularly those that are relatively rare (35, 36). Although published case reports of PRIS suggest that it is comprised of more than one of these clinical manifestations, the exact combination of clinical factors is not well elucidated and thus the authors deemed it important to include patients with as few as

one of the identified PRIS clinical manifestations (29, 30, 37). An experienced critical care pharmacist (JJF) manually screened each case and entered it into a Microsoft Access database (Microsoft Corp., Redmond, WA). Cases were excluded if: a) none of the PRIS-associated clinical manifestations were present, b) the survival status of the patient was unknown, c) the case matched only one word of a multiple-word clinical manifestation (e.g., atrial fibrillation rather than ventricular fibrillation), or d) the PRIS-associated clinical manifestation could be clearly explained by another documented clinical event (e.g., anaphylactic shock), or e) the report represented a follow-up report for the same patient (Fig. 1). A second investigator (MK) verified and validated each case entered into the database.

Various patient, reporting, dosing, and concomitant medication characteristics were compared between patients with suspected PRIS who died and those who survived. These included age in years (also stratified by <18 yrs and ≥ 18 yrs), gender, type of report (i.e., expedited, periodic, or direct), suspected role of propofol (i.e., primary or secondary), geographic origin of report (i.e., North American vs. non-North American), report source (i.e., health professional or unknown), brand of propofol (i.e., Diprivan vs. generic formulation) propofol dose, propofol duration, use of corticosteroid, or catecholamine vasopressors therapy during suspected PRIS event and the identified PRIS clinical manifestations. Chi-square tests

were used to compare the distributions for each characteristic between patients who died and those who survived.

The risk for mortality was measured for those factors found to have statistically significant associations with death and was expressed as an odds ratio (95% confidence interval). This univariate analysis excluded those variables (i.e., country of origin, duration of propofol therapy, and concomitant use of glucocorticoids) where the amount of missing data in the Adverse Event Reporting System report was deemed to be too large to allow analysis (i.e., $\geq 25\%$). The multivariable logistic regression model was built by first doing a stepwise analysis for the PRIS clinical manifestations and demographic parameters that were statistically significant in the univariate analysis. As a second step, the other covariates were forced into the resulting model, and removed sequentially if not significant. Two-way interactions between clinical manifestation variables with each other and with age (<18 and ≥ 18 yrs) were also allowed to step into the model. In the model building process, a p value ≤ 0.05 was used to retain variables in the final model. For presentation purposes, the final model was reparameterized to more easily interpret interactions.

To develop a reproducible, quantifiable means for assessing the risk for death in patients with suspected PRIS, a simple scoring scheme was developed based on the coefficients from the logistic regression model. A score ranging from 0 to 4 based on the presence or absence of PRIS clinical manifesta-

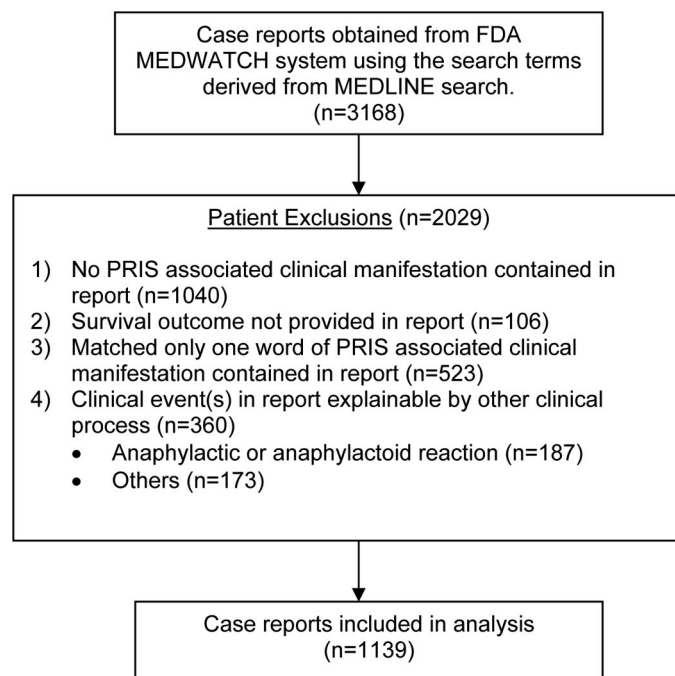


Figure 1. Description of cases that were excluded from the analysis. FDA, Food and Drug Administration; PRIS, propofol infusion syndrome.

tions and related demographic factors was computed for each patient in the data set. To evaluate the performance of this score as related to mortality, a logistic regression model was run using the score as the single predictor variable. Actual and predicted death rates were calculated for each score value (0–4), the receiver operator curve area was computed, and the Hosmer-Lemeshow lack-of-fit test was run. All statistical comparisons were performed using the SAS system for Windows (9.1.3) (The SAS Institute, Cary, NC). A *p* value <0.05 was considered statistically significant for all analyses.

RESULTS

Of the 3168 cases contained in the Food and Drug Administration MEDWATCH report, 2029 were excluded (Fig. 1). Of the 1139 suspected PRIS cases that were included in the analysis, 342 (30%) were fatal. Most of these 1139 cases involved adults (≥ 18 yrs) ($n = 817$; 80%), identified propofol as the primary suspect drug ($n = 725$; 70%), were reported in an expedited manner ($n = 960$; 84%) by a health care professional ($n = 725$; 64%) and involved brand name Diprivan ($n = 705$; 62%) (Table 1). The average age for the adults was 51.7 ± 18 yrs and for children 8.9 ± 6.2 yrs. The propofol infusion dose exceeded $83 \mu\text{g}/\text{kg}/\text{min}$ ($5 \text{ mg}/\text{kg}/\text{hr}$) in 88 (68%) of the 129 cases, where dose was reported. Duration of therapy was reported in 136 (12%) of 1139 cases and exceeded 48 hrs in 54% of these 136 cases. Because dose-related data were not available for nearly 90% of the study sample, these data were not explored as markers for mortality in either the univariate or multivariable logistic regression analyses. Patients with suspected PRIS who died were more likely to be younger than 18 yrs ($p < 0.0001$), male ($p < 0.0028$), from outside North America ($p = 0.0028$), have received propofol ≥ 48 hrs ($p = 0.0029$) and had been concomitantly treated with catecholamine therapy ($p = 0.0009$). Only 44 (4%) of the reports contained the term “propofol infusion syndrome.”

The order of frequency of the PRIS-associated clinical manifestations were cardiac (43.7%), followed by hypotension (34.0%), rhabdomyolysis (27.0%), hepatic (24.1%), renal (23.5%), metabolic acidosis (20.1%), hypoxia (17.5%), hyperthermia (11.6%), and dyslipidemia (5.3%) (Table 2). Cardiac abnormalities, hypotension, rhabdomyolysis, renal failure, metabolic acidosis, and dyslipidemia were more likely to occur in patients who

Table 1. Demographic characteristics of potential PRIS cases and comparison between survivors and nonsurvivors (n [%])

Demographic Variable	All Cases ($n = 1139$)	Died ($n = 342$)	Survived ($n = 797$)	<i>p</i> ^a
Age				
Adult (≥ 18 yrs)	817 (80)	222 (71)	595 (85)	<0.0001
Pediatric (<18 yrs)	199 (20)	92 (30)	107 (15)	
	NR: 123 (11)			
Gender				
Female	511 (47)	138 (42)	373 (49)	0.0256
Male	584 (53)	194 (58)	390 (51)	
	NR: 44 (4)			
Type of report				
Expedited	960 (84)	285 (83)	675 (85)	0.461
Periodic	57 (5)	15 (4)	42 (5)	
Direct	122 (11)	42 (12)	80 (10)	
	NR: 0 (0)			
Source of report				
North America	307 (27)	109 (32)	198 (25)	0.0028
Foreign	546 (48)	168 (49)	378 (47)	
	NR: 286 (25)	65 (19)	221 (28)	
Report source				
Health professional	725 (64)	222 (65)	503 (63)	0.5531
Unknown	410 (36)	118 (35)	292 (37)	
Company representative	0.4 (4)	2 (1)	2 (0.3)	
	NR: 0 (0)			
Role of propofol				
Primary suspected drug	725 (70)	253 (74)	542 (68)	0.1126
Secondary suspected drug	343 (30)	89 (26)	254 (32)	
Concomitant drug	1 (0.1)	0	1 (0.1)	
	NR: 0 (0)			
Manufacturer				
AstraZeneca (Diprivan)	705 (62)	207 (61)	498 (63)	0.0177
Generic	384 (34)	111 (33)	273 (34)	
Other	50 (4)	24 (7)	26 (3)	
	NR: 0 (0)			
Propofol dose				
$\geq 83 \mu\text{g}/\text{kg}/\text{min}$	88 (8)	50 (15)	38 (5)	0.104
<83 $\mu\text{g}/\text{kg}/\text{min}$	41 (3)	17 (5)	24 (3)	
	NR: 1010 (89)			
Duration of propofol therapy				
≥ 48 hrs	74 (7)	26 (8)	8 (0.01)	0.0029
<48 hrs	62 (5)	48 (14)	54 (7)	
	NR: 1003 (88)			
Concomitant use of glucocorticosteroids	111 (10)	37 (11)	74 (9)	0.424
Concomitant use of vasopressors	169 (15)	69 (20)	100 (13)	0.0009

^aDied vs. survived.

NR, not reported; PRIS, propofol infusion syndrome.

died. Results of the univariate logistic regression analyses indicated that death was more likely if patients were <18 yrs (odds ratio [95% confidence interval]; 2.30 [1.68–3.17]), male (1.34 [1.04–1.74]), receiving a vasopressor (1.76 [1.26–2.47]), or if one of the following PRIS clinical manifestations was present: cardiac symptoms (3.76 [2.88–4.91]), hypotension (1.78 [1.37–2.32]), rhabdomyolysis (1.76 [1.34–2.32]), renal (1.92 [1.44–2.55]), metabolic acidosis (3.66 [2.71–4.95]), or dyslipidemia (1.98 [1.17–3.36]) (Table 3).

The multivariate logistic regression model revealed statistically significant interactions between rhabdomyolysis and

hypotension as well as rhabdomyolysis and renal failure. Separate odds ratios from the final model were computed for each possible combination of renal failure, hypotension, and rhabdomyolysis to allow for the odds of death to be compared between the combinations of these factors. These adjusted odds ratios are presented in Table 4. Although ranked in order from highest to lowest, we note that there is statistical uncertainty in these estimates, and the span of the confidence intervals must also be considered when interpreting these results. The highest adjusted odds ratios for mortality were found for the presence of hypotension and rhabdomyolysis (with or without

Table 2. Frequency of clinical manifestations associated with PRIS and comparison between survivors and nonsurvivors (n [%])

	All Cases (n = 1139)	Died (n = 342)	Survived (n = 797)	<i>p</i> ^a
Cardiac	498 (44)	226 (66)	272 (34)	<0.0001
Cardiac arrest	231 (20)	139 (41)	92 (12)	<0.0001
Bradycardia	195 (17)	76 (22)	119 (15)	0.0028
Vtach/Vfib	177 (16)	83 (24)	94 (12)	<0.0001
Myocardial failure	116 (10)	61 (18)	55 (7)	<0.0001
Bradyarrhythmia	60 (5)	19 (6)	41 (5)	0.736
Hypotension	387 (34)	148 (43)	239 (30)	<0.0001
Rhabdomyolysis	307 (27)	120 (35)	187 (24)	<0.0001
Hepatic	275 (24)	78 (23)	197 (25)	0.4898
Transaminitis	263 (23)	72 (21)	191 (24)	0.285
Hepatic steatosis	51 (5)	17 (5)	34 (4)	0.598
Hepatomegaly	19 (2)	8 (2)	11 (1)	0.247
Renal	268 (24)	110 (32)	158 (20)	<0.0001
Renal failure	253 (22)	102 (30)	151 (19)	<0.0001
Oliguria/anuria	47 (4)	12 (4)	35 (4)	0.49
Hyperkalemia	78 (7)	50 (15)	28 (4)	<0.0001
Metabolic acidosis	229 (20)	123 (36)	106 (13)	<0.0001
Hypoxia	199 (18)	63 (18)	136 (17)	0.58
Hyperthermia	132 (12)	39 (11)	93 (12)	0.898
Dyslipemia	60 (5)	27 (8)	33 (4)	0.0093
Hypertriglyceridemia	52 (5)	20 (6)	32 (4)	0.174
Lipemia	16 (1)	12 (4)	4 (0.5)	<0.0001

^aDied vs. survived.

PRIS, propofol infusion syndrome; Vtach, ventricular tachycardia; Vfib, ventricular fibrillation.

Table 3. Potential clinical and demographic predictors of PRIS: Univariate analysis (n [%])

	Mortality Rate, n (%)	Odds Ratio (95% Confidence Interval)	<i>p</i>
Cardiac			
Present (n = 498)	226 (45)	3.76 (2.88–4.91)	<0.0001
Not present (n = 641)	116 (18)		
Hypotension			
Present (n = 387)	148 (38)	1.78 (1.37–2.32)	<0.0001
Not present (n = 752)	194 (26)		
Rhabdomyolysis			
Present (n = 307)	120 (39)	1.76 (1.34–2.32)	<0.0001
Not present (n = 832)	222 (27)		
Renal			
Present (n = 268)	110 (41)	1.92 (1.44–2.55)	<0.0001
Not present (n = 871)	232 (27)		
Metabolic acidosis			
Present (n = 229)	123 (54)	3.66 (2.71–4.95)	<0.0001
Not present (n = 910)	219 (24)		
Dyslipidemia			
Present (n = 60)	27 (45)	1.98 (1.17–3.36)	0.012
Not present (n = 1079)	315 (29)		
Use of catecholamines			
Present (n = 169)	69 (41)	1.76 (1.26–2.47)	0.0012
Not present (n = 970)	273 (28)		
Gender			
Male (n = 584)	194 (33)	1.34 (1.04–1.74)	0.0254
Female (n = 511)	138 (27)		
Age			
Under 18 (n = 199)	92 (46)	2.30 (1.68–3.17)	<0.0001
18 or older (n = 817)	817 (27)		

PRIS, propofol infusion syndrome.

the presence of renal failure). The presence of cardiac involvement alone was independently associated with a greater likelihood of death. Another significant interaction was found between metabolic

acidosis and age. Although both younger age and presence of metabolic acidosis were risk factors, their effects were not multiplicative. The receiver operator curve area for this model was 0.765.

The multivariate logistic regression model coefficients, standard errors, and associated *p* values are presented in Table 5. Point values for the presence/absence of each predictor or combination of predictors, based on the values of the model coefficients, rounded to either 1, 0, or –1, are also presented in Table 5. To compute a mortality risk score for a patient with suspected PRIS, the point values for each of their characteristics is totaled. For example, if a patient had cardiac involvement (1 point), rhabdomyolysis and hypotension (1 point for rhabdomyolysis, 1 point for both), and was under age 18 years (1 point) they would have a total of 4 points. The receiver operator curve area from the logistic regression model using the mortality risk score as the sole independent variable was 0.744 with the odds ratio for a 1-point increase of 2.89 (2.43–3.40). The results of the Hosmer-Lemeshow test failed to show a statistically significant lack-of-fit (*p* = 0.40). The predicted death rate (from the mortality risk score model) and the observed death rate (from the entire database) are presented in Table 6. For example, a patient having a PRIS score of 1 would have a predicted mortality rate of 24%, whereas a PRIS score of 4 would predicate a mortality rate of 89%.

DISCUSSION

The increasing awareness of PRIS in the medical community, and its inherently high mortality rate, have led to concerns regarding the routine use of this agent in clinical practice in the ICU, particularly in children (29–31, 37–39). Our study is the first to identify clinical predictors of mortality in patients with suspected PRIS and to propose a scoring system to aid clinicians in estimating risk for mortality in this population. Scoring systems such as this have been shown to improve the ability of clinicians to identify complex syndromes (40). The patient factors associated with higher mortality that our analysis identified are consistent with the PRIS-related symptoms contained in published case series and supports recent revisions to the propofol package insert by regulatory authorities (37). Our findings also highlight the need to educate critical care clinicians regarding PRIS given that only 4% of the MEDWATCH reports identified PRIS by name in the report.

Recently, Wysowski and Pollock (33) reviewed and analyzed MEDWATCH re-

Table 4. Adjusted odds ratios for death based on multivariable logistic regression model

Interaction	Odds Ratio (95% Confidence Interval)
Hypotension and rhabdomyolysis and renal failure	
Hypotension and rhabdomyolysis	8.45 (4.1–17.42)
Hypotension and rhabdomyolysis and renal failure	7.07 (3.45–14.52)
Hypotension and renal failure	3.09 (1.71–5.57)
Rhabdomyolysis and renal failure	1.76 (1.01–3.07)
Renal failure alone	2.81 (1.77–4.48)
Rhabdomyolysis alone	2.1 (1.27–3.48)
Hypotension alone	1.1 (0.76–1.58)
None of the risk factors	1 (reference)
Metabolic acidosis and age status	
Metabolic acidosis (18 yrs or older)	3.45 (2.24–5.34)
No metabolic acidosis (under 18 yrs)	2.28 (1.48–3.5)
Metabolic acidosis (under 18 yrs)	1.98 (1.06–3.68)
No metabolic acidosis, 18 yrs or older	1 (reference)
Cardiac	
Cardiac alone	4.58 (3.29–6.37)

These odds ratios were computed from a multivariable logistic regression model (Table 5) based on $n = 1003$ patients. The receiver operating characteristic curve = 0.765. The model $\chi^2 = 222.6$, $df = 9$, $p \leq 0.0001$.

Table 5. Multivariable logistic regression model coefficients and mortality scoring scheme points

Term in Model	Beta	se (Beta)	<i>p</i>	Score
Intercept	-2.3852	0.1750	<0.0001	N/A
Rhabdomyolysis	0.7437	0.257	0.0038	1
Hypotension	0.0927	0.186	0.6186	0
Metabolic acidosis	1.2395	0.222	<0.0001	1
Cardiac	1.5211	0.168	<0.0001	1
Renal failure	1.0346	0.237	<0.0001	1
Age under 18 yrs	0.8222	0.219	0.0002	1
Age under 18 yrs and metabolic acidosis	-1.3791	0.415	0.0009	-1
Rhabdomyolysis and hypotension	1.2977	0.395	0.0010	1
Rhabdomyolysis and renal failure	-1.2120	0.390	0.0019	-1

This model is based on $n = 1003$ patients. The receiver operating characteristic curve = 0.765. The model $\chi^2 = 222.6$, $df = 9$, $p \leq 0.0001$.

Table 6. Predicted and observed mortality for each possible point score

Total Mortality Risk Score	Predicted Death % (From Score Model)	Observed Death % (From Database)
0	9.6	9.7 (22/226)
1	23	24 (112/469)
2	47	44 (85/195)
3	72	81 (58/72)
4	88	83 (34/41)

The logistic regression model using the 0 to 4 point mortality risk score as predictor had a receiver operating characteristic curve = 0.744. The odds ratio for a 1 point score increase is 2.87 (95% confidence interval: 2.43–3.40) $p < 0.0001$. The Hosmer-Lemshov test for lack-of-fit $p = 0.40$ ($df = 2$). This model is based on 1003 patients.

ports of death in American patients (both children and adults), when propofol was administered for nonprocedural sedation and it was the primary suspect drug in the report. Reports were generated from marketing to April 2005 and PRIS was defined for the purposes of this analysis as metabolic acidosis and/or rhabdomyol-

ysis with progressive myocardial failure. Of the 21 patients ≤ 16 years of age who died, 15 (71%) had a disorder consistent with the PRIS definition used; of the 68 patients older than 16 years who died, 21 (31%) had a disorder consistent with PRIS using this same definition. Our analysis identified a far greater number of

patients in the MEDWATCH system than Wysowski and Pollock given that we did not limit our analysis to only those cases that were fatal, included reports where propofol was administered for indications other than nonprocedural sedation, analyzed both foreign and American reports, and used a much more liberal definition for PRIS in an effort to identify the risk factors associated with mortality in patients with suspected PRIS.

The results of our analysis corroborate with most, but not all, of the findings from published PRIS case series (10, 29–31, 33). Although the PRIS-related features we identified (i.e., cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure) are similar to those reported by Vasile et al. and Fudickar et al. they differ from those reported by Bray and Cremer et al. (10, 29–31). In these two latter reports, PRIS was also associated with lipemia, hepatic steatosis, and hepatomegaly. While 24% of the cases in MEDWATCH had hepatic manifestations, there was nearly an equal distribution between those who died (23%) and those who survived (25%). When the mortality scoring system proposed in this analysis was applied to those patients in the MEDWATCH cohort with PRIS-related clinical manifestations most commonly identified in the published case reports (i.e., cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure), the mortality rate (74%) was very similar to those in the published reports.

The fact that we completed a systematic analysis of the MEDWATCH database rather than relying solely on a review of published suspected PRIS cases is a major strength of our analysis given that published cases are more apt to report both fatalities and those situations involving multiple PRIS clinical manifestations. The Food and Drug Administration MEDWATCH system collects data from both manufacturer-sponsored clinical trials and voluntary reports from clinicians on a worldwide basis and thus is the largest available repository for adverse drug event data. Its use in characterizing adverse drug events is well established (35, 36, 41). The methodology used to formulate the PRIS clinical manifestations used in the analysis was based on the frequency these manifestations have been reported using all published PRIS case series and concomitant administration of medications such as catecholamine vasopressors. Finally,

the fact that the majority of the cases we identified list propofol as the primary suspected agent makes other causes for the symptoms observed to be unlikely.

Our analysis has a number of potential limitations, many of which relate to the general limitations of using the MEDWATCH system (42–44). These include the large amount of missing data in reports that makes causality challenging to establish, the lack of a link between prescribing patterns and adverse event reporting, the fact that reporting rates are highly variable and dependent on external events (e.g., “dear doctor” letters), that reporters may erroneously assign an adverse event to a drug, and finally that reports are generated from both clinical trials and clinical practice. Despite using a search strategy based on published PRIS case reports, we had to eliminate more than 2000 of the cases either because no PRIS-associated clinical manifestation was present or survival status was unknown. The fact that the majority of cases were reported in an expedited manner suggests that only the most likely cases of suspected PRIS may have been reported. This latter point is particularly important for a syndrome like PRIS that involves conditions commonly observed in ICU patients (e.g., metabolic acidosis).

A number of factors that have been proposed to increase the risk for PRIS were not able to be incorporated in the model either because they were frequently missing in the reports (e.g., dose, bolus administration of propofol, duration of therapy, concomitant use of corticosteroids, or vasopressors), were too infrequent (e.g., dyslipidemia), or are not included in the MEDWATCH reports (e.g., the cumulative dose of propofol administered, severity of illness, presence of airway infection or severe head injury) (31). Lack of a severity of illness score for any of the patients (e.g., Acute Physiology and Chronic Health Evaluation II score) in the database makes it impossible to know whether the patients in our cohort who died were simply a sicker cohort at baseline. Finally, the lack of a documented start date for propofol in most of the cases relative to the development of any of the individual PRIS symptoms made a temporal analysis of PRIS, and the factors associated with death, impossible to conduct.

Further research efforts should focus on prospectively validating the mortality scoring system that we developed in pa-

tients with suspected PRIS. In addition, it is important to study whether the practice of bolusing propofol is a risk factor for PRIS given that studies of smart infusion systems in the ICU have identified propofol to be the most frequent cause for averted overdoses and a close second to heparin as the agent with the highest Intravenous Medication Harm Index (45). In addition, other research efforts should focus on further exploration of the pathogenic mechanisms for PRIS including elucidation of the various clinical sequelae that have been associated with this syndrome. Determining whether certain patient populations are genetically at greater risk for PRIS (e.g., inborn error of mitochondrial fatty acid oxidation) requires further evaluation (29). Only through large, carefully conducted, prospective evaluations of critically ill patients administered propofol will the clinical manifestations most commonly associated with PRIS be identified, the risk factors associated with its development be characterized, and the optimal monitoring strategy to detect PRIS be determined.

By using the Food and Drug Administration MEDWATCH system, we have identified a number of factors that are independently associated with a higher risk for death in patients with suspected PRIS. It is important to note that some of these factors are not reflected in current package insert recommendations (i.e., age <18 yrs, renal failure, hypotension) and thus may be underappreciated by clinicians. Clinicians should carefully monitor their patients receiving propofol for the presence of those PRIS-related factors associated with higher death, and if found to be present, consider alternate sedation regimens.

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