



Propofol infusion syndrome: A lethal condition in critically injured patients eliminated by a simple screening protocol

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ABSTRACT

Propofol infusion syndrome (PIS) is defined by arrhythmia, rhabdomyolysis, lactic acidosis, and unrecognized leads to death. We sought to determine the incidence of PIS in trauma patients and evaluate the efficacy of a prospective screening protocol in this patient population.

Materials and methods: In Phase I of the *before-and-after* study (1st January, 2005–31st December, 2005), trauma patients who received propofol were evaluated. Records were reviewed for demographics, injury severity, propofol time, dose, and rates, laboratory values, and adverse events. Patients were identified with PIS based on two of the following criteria: (1) cardiac arrhythmia/collapse, (2) metabolic acidosis, (3) rhabdomyolysis, and (4) acute kidney injury. Phase II (1st January, 2006–31st December, 2011) consisted of a prospective screening protocol (elevated lactate or creatine phosphokinase (CPK)) to identify patients at risk for PIS.

Results: 207 patients were identified in Phase I. 6 (2.9%) developed PIS with a 50% mortality. No differences were seen in age, gender, or mechanism. PIS patients were more injured (median ISS 44 vs 26, $p = 0.04$; median head AIS 5 vs 4, $p = 0.003$) and received more propofol (median 50,350 vs 9770 mg, $p = 0.001$) with longer infusion times (413 vs 65 h, $p = 0.001$). Sodium, creatinine, and CPK levels were higher in those that developed PIS (160 vs 145 mmol/L, $p = 0.001$; 4.3 vs 1.1 mg/dL, $p = 0.005$; 59,871 vs 520 U/L; $p = 0.002$). Pre-screening PIS incidence was 2.9% (6/207), but after screening (January 2006) the incidence dropped to 0.19% (2/1038, $p < 0.001$).

Conclusions: PIS is a morbid and lethal entity associated with sedation of critically injured patients. A simple screening procedure utilizing serum CPK (<5000 U/L) can essentially eliminate the development of PIS.

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Introduction

Propofol is a sedative drug used for the induction and maintenance of anaesthesia and sedation in the intensive care unit. This agent is advantageous for patients with traumatic brain injuries (TBI) due to multiple factors, including rapid onset of action, short half-life, and moderating effects on intracranial hypertension.¹ The harbinger that this drug may have some adverse consequences came in 1992 with the description of propofol infusion syndrome (PIS) in children by Parke.² In that seminal report, five children admitted for respiratory tract

infections developed metabolic acidosis, bradyarrhythmia, and cardiac failure resulting in death while on propofol. While initially thought to be a toxicity of propofol only in children, this later proved to be false when the first adult case of PIS resulting in death was described in 2000.³ An 18 year-old treated after a motor vehicle collision for cervical spine injuries, facial fractures, extremity fractures, burns, and TBI was sedated with high dose propofol. During the propofol infusion, the patient developed cardiac arrhythmias, metabolic acidosis, rhabdomyolysis (attributed to trauma), and progressed to death.³ Several case reports of PIS have since been described in adults.^{4–18} Defining features of PIS include metabolic acidosis, rhabdomyolysis, acute kidney injury, and cardiac arrhythmia or collapse.^{4,5,19–24}

An index case of PIS was recognized at our institution in August of 2005 in a 27 year-old man with an isolated TBI. As part of the therapy for his TBI, propofol was used for sedation. During the propofol infusion, unexplained rhabdomyolysis and cardiac

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arrhythmias developed. The propofol infusion was stopped. He recovered and was discharged several months later. Following the recognition of the index case, we suspected that more cases might have occurred. We then reviewed our past experience and examined the usage of propofol; more cases of PIS were discovered. We hypothesized that institution of a prospective screening protocol would prevent PIS and allow safe use of propofol in patients with TBI. This report details the studies involving identification of the syndrome and the outcomes of the prospective screening program. The Institutional Review Boards approved the study and granted waiver from informed consent. None of the authors have any conflicts of interest to declare.

Materials and methods

Study Phase I – retrospective syndrome identification and case definition

Following identification of the index PIS case in August 2005, the hospital pharmacy order database (Meditech, Westwood, MA) was reviewed for trauma patients who received continuous infusions of 1% propofol during calendar year 2005. Patients who received continuous infusions of propofol for greater than 24 h were included; patients were excluded if death occurred within 24 h of admission, if propofol was used only for anaesthesia, or if the total dose of propofol was less than 1000 mg. Eligible patient records from the trauma registry (NTRACS, version 3.0, Digital Innovation, Forest Hill, MD) and hospital charts were reviewed for demographic data, mechanism of injury, hospital medications (narcotics, benzodiazepines, anti-hypertensives, diuretics, inotropes, vasopressors, and corticosteroids), injury severity (injury severity score (ISS), admission Glasgow Coma Scale (GCS) score, and head abbreviated injury score (AIS)), associated injuries, maximum intracranial pressure (ICP_{MAX}), peak laboratory values while receiving propofol (creatinine, creatine phosphokinase (CPK), lactate, sodium, osmolality), adverse events, and infectious morbidity. Sodium dose was calculated based on the concentration of hypertonic saline (3% or 7.5%) and quantity abstracted from the electronic medical record (Meditech, Westwood, MA). Propofol infusion time, dose, and rates were abstracted from the trauma intensive care unit (TICU) flow sheets and the electronic medical record (Meditech, Westwood, MA). All data were abstracted by two of the authors.

Patients who developed PIS were identified based on the following criteria: (1) cardiac arrhythmia or collapse, (2) metabolic acidosis, (3) rhabdomyolysis, and (4) acute kidney injury. Patients diagnosed with PIS were required to have two of the four criteria; the events had to begin while receiving propofol and have no other aetiology based on consensus opinion of the authors.^{4,5,19–23} Cardiac arrhythmia was defined as any rhythm other than sinus or sinus tachycardia. Cardiac collapse was defined as cardiac failure in the absence of cardiac disease. Acute kidney injury was defined as elevation of creatinine greater than 50% of baseline. Rhabdomyolysis was defined as elevation of CPK with either myoglobin present in the urine or renal failure. Metabolic acidosis was defined as a decrease in pH (<7.30) with either an elevation of lactate (>4.0 mmol/L), decrease in serum HCO₃ (<22 mmol/L), or increased anion gap (>15). Patients identified with PIS were compared to the remaining ICU patients who received propofol.

Infections were analyzed to examine any potential association with PIS. The following definitions were used: (1) ventilator-associated pneumonia (VAP) – $\geq 10^5$ colony forming units (CFU)/mL on quantitative culture following bronchoalveolar lavage; (2) urinary tract infection (UTI) – $\geq 10^5$ CFU/mL on culture; (3) bacteremia – positive blood cultures from two sites if Gram-positive

organisms and any growth with Gram-negative organisms or *Staphylococcus aureus*; (4) meningitis – any positive cerebrospinal fluid culture.

Study Phase II – screening protocol implementation

Following the identification of PIS, the prospective screening program for early identification of PIS was instituted in patients receiving continuous infusions of propofol. This protocol began January 2006 and continues to present. The protocol consists of daily measurements of serum CPK and lactate while on a continuous propofol infusion. If unexplained increases of CPK ≥ 5000 U/L or lactate ≥ 4.0 mmol/L occur, propofol is discontinued and an alternate sedation regimen is instituted. The values for CPK and lactate for screening were chosen above the normal range, but not high enough for negative clinical sequelae to allow early detection of PIS.

Statistical methods

Continuous variables were compared using Wilcoxon Ranked Sums test and categorical variables were compared using χ^2 test or Fisher's exact test where appropriate. All statistical analysis was done with SAS version 9.2 (SAS Institute, Cary, NC). A *p* value of less than 0.05 was considered significant.

Study design

A before-and-after observational study design was selected to demonstrate the effectiveness of the screening protocol.

Results

A total of 7,852 patients were admitted to the TICU at between 1st January, 2005 and 31st December, 2011. During Phase I (1082 TICU admissions), 207 patients (19.1%) received continuous infusions of propofol. 81% were male with a median age of 32 years. This cohort was severely injured with a median ISS of 26, GCS of 9, and head AIS of 4. The mechanism of injury was predominantly blunt trauma (90%) with motor vehicle collisions accounting for the largest percentage (48%). The majority of patients had TBI (75%). Mortality for the entire cohort was 13%.

Of the 207 Phase I patients, 6 (2.9%) developed PIS. The PIS cohort had a similar median age, gender, and mechanism of injury to the other patients (Table 1). Median injury severity was higher in patients who developed PIS. Although admission GCS was similar between the groups, mortality was nearly five times higher in the patients that developed PIS (50% vs. 11%, *p* = 0.054). PIS patients had higher median CPK and higher median creatinine, but no difference was detected in median lactate.

Table 1
Demographics and injury severity comparing PIS and No PIS during Phase I.

	Total (n = 207)	PIS (n = 6)	No PIS (n = 201)	<i>p</i>
Age (years)	32 (24)	32 (5)	32 (24)	0.57
Male	167 (81%)	4 (67%)	163 (81%)	0.66
Blunt	186 (90%)	6 (100%)	180 (90%)	1.0
ISS	26 (20)	44 (20)	26 (18)	0.04
GCS	9 (9)	7 (3)	9 (8)	0.30
Head AIS	4 (3)	5 (0)	4 (3)	0.003
ICP > 25 mmHg	56 (27%)	5 (83%)	51 (25%)	0.012
Mortality	26 (13%)	3 (50%)	23 (11%)	0.054

Continuous variables expressed as median (IQR). Categorical variables expressed as percentage. PIS, propofol infusion syndrome; ISS, injury severity score; GCS, Glasgow Coma Scale; AIS, abbreviated injury score; ICP, intracranial pressure.

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