

Reports of Death with Use of Propofol (Diprivan) for Nonprocedural (Long-term) Sedation and Literature Review

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PROPOFOL (Diprivan; AstraZeneca Pharmaceuticals, Wilmington, DE) has been marketed in the United States since November 1989. To date, there have been numerous case reports, case series, studies, and commentaries from researchers in various countries regarding adverse reactions and death in pediatric and adult patients to whom propofol was prescribed¹⁻⁶³ primarily for nonprocedural (long-term) sedation, although adverse events have been reported for anesthesia and procedural sedation as well. Many of the above have focused on "propofol infusion syndrome," a cardiovascular and metabolic derangement that has been described in both pediatric and adult patients sedated with propofol. Sedation with propofol in children has been controversial because of these reports and since the announcement in 2001 of a trend toward statistical significance of a concentration-dependent increase in 28-day mortality in propofol-treated patients in a randomized controlled clinical trial of 327 pediatric patients.⁶⁴ In this trial, the group who received standard sedation with lorazepam had 4% mortality, those treated with 1% propofol had 8% mortality, and those receiving 2% propofol (not approved in the United States) had 11% mortality despite a similarity in Pediatric Risk of Mortality scores for the three groups. These results led to a product labeling change that stated, "While causality has not been established, Diprivan injectable emulsion is not indicated for sedation in pediatric patients until further studies have been performed to document its safety in that population." Nevertheless, propofol has been used for sedation in children and adults because it has a rapid onset and a short duration of action once discontinued, although a slightly longer recovery has been reported after more than 12 h of infusion.⁶⁵

This article provides a review and analysis of US reports of death after pediatric and adult sedation with propofol that were submitted to the Food and Drug

Administration (FDA) and entered into its postmarketing drug safety database. Published reports and studies are also included for comparison with the postmarketing reports.

Materials and Methods

The FDA's Office of Surveillance and Epidemiology receives postmarketing reports of adverse drug events primarily from physicians, pharmacists, and consumers who submit them on a standardized form directly or indirectly through pharmaceutical companies. Each report is entered into a computerized database, the Adverse Event Reporting System, which uses a coding thesaurus of adverse reaction terms (MedDRA) for searching and retrieval purposes. From 1969 through 2002, more than 2.3 million case reports of adverse events for marketed drugs were entered.⁶⁶ The primary use of this database is the identification of drug-related adverse events with serious outcomes (death, life-threatening event, hospitalization, disability, congenital malformation, or event requiring medical intervention) that were not detected in premarketing studies. Fatal and other serious events that are not mentioned in the product labeling are priorities for analyses.

We reviewed and analyzed reports of death with propofol as the suspect drug in US pediatric patients (aged ≤ 16 yr) and adults (aged > 16 yr) for nonprocedural (long-term) sedation from marketing to April 2005. Initial and follow-up reports for the same patients were paired, and duplicates were excluded. The nature of the adverse event, demographics of patients, propofol indication, dose, and duration were noted and analyzed. Particular emphasis was placed on the identification of propofol infusion syndrome; for purposes of this review, it was defined as metabolic acidosis and/or rhabdomyolysis with progressive myocardial failure.⁴³ Although there have been many reports that have included such findings as hyperkalemia, lipemic serum, and kidney failure (a progression of rhabdomyolysis), we chose an accepted definition that included the most consistently reported serious clinical features of the syndrome.

The published literature was also reviewed by searching Medline's PubMed using terms such as *propofol toxicity* and *propofol infusion syndrome*; similarities were noted in results from studies and postmarketing reports.

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Results

US Pediatric Deaths for Nonprocedural Sedation Reported to the FDA

From the marketing of propofol in the United States in 1989 to April 2005, the Adverse Event Reporting System of the FDA contained unduplicated reports of 21 patients aged 16 yr or younger who died after administration of propofol for nonprocedural sedation. Seven reports of death in children who received propofol for indications other than sedation were excluded. Dates of death (or receipt date for one report with missing data) in the 21 patients ranged from 1993 to 2004. Thirteen (62%) were girls; 8 (38%) were boys. Ages ranged from 25 months to 16 yr (mean, 11 yr; median, 12 yr). Specific indications for propofol sedation were suppression of seizures in 5 patients, control of intracranial pressure in 5, sedation for respiratory failure in 1, and an unspecified indication in 10 (of whom 4 had head injuries). Of these 21 submitted reports, 4 stated that they were also published.^{5,8,15,44}

The mean peak propofol dose was $13.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($n = 18$; median, 9.5; range, 2.2–54). The mean duration of propofol use was reported as 2.4 days ($n = 20$; median, 2 days; range, 6 h to 6 days).

The most prominent adverse events were progressive cardiac dysfunction/failure (bradycardia, cardiac failure, “cardiovascular collapse,” arrhythmia, arrest) in 18 patients (86%), metabolic acidosis in 15 (71%), hypotension in 13 (62%), and rhabdomyolysis in 11 (52%). Fifteen (71%) of the 21 had disorders consistent with propofol infusion syndrome, 3 patients had cardiac failure without mention of acidosis or rhabdomyolysis, 2 had metabolic derangements without mention of cardiac dysfunction, and 1 had unstated adverse events.

US Adult Deaths for Nonprocedural Sedation Reported to the FDA

From the marketing of propofol in the United States to April 2005, the Adverse Event Reporting System contained unduplicated reports of 68 patients aged older than 16 yr who died after administration of propofol for nonprocedural sedation. Ninety reports of death with propofol as the suspect drug were excluded; 89 concerned administrations for anesthesia and procedural sedation, and 1 concerned a medical error/overdose.

Dates of death (or receipt dates for 12 reports with missing data) for the 68 patients ranged from 1989 to 2004. Twenty-two (33%) were women, 45 (66%) were men, and 1 (1%) had unspecified sex. Ages ranged from 19 to 86 yr (mean, 51 yr; median, 55 yr). For the 34 patients with weight recorded, the mean weight was 201 lb (median, 180 lb; range, 110–420 lb). Specific indications for propofol sedation were respiratory disorders in 21 (31%), prevention/suppression of seizures in 9 (13%), head trauma and control of intracranial pressure

in 9 (13%), postsurgery sedation in 7 (10%), agitation in 5 (7%), unspecified indication in 4 (6%), and delirium/tremors in 1 (2%). Three reports were also published.^{10,20,49}

The mean peak propofol dose was $7.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($n = 44$; median, 5.4; range, 0.6–25). A few patients received bolus doses that were not readily calculable in terms of $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The mean duration of propofol use was reported as 7.3 days ($n = 61$; median, 4.4 days; range, < 1 h to 42 days).

The most prominent adverse events in the adult deaths were progressive cardiac dysfunction/failure (bradycardia, cardiac failure, arrhythmia, arrest) in 31 patients, metabolic acidosis in 21, hypotension in 20, rhabdomyolysis in 13, renal failure in 16, respiratory failure/adult respiratory distress syndrome in 7, persistent sedation in 7, hyperthermia/fever in 6, hypertriglyceridemia in 6, multiorgan failure in 5, liver dysfunction in 5, tremors/weakness/polyneuropathy/movement disorders in 5, sepsis in 5, hepatic failure in 4, and hyperkalemia in 4.

Twenty-one (31%) of the 68 patients had disorders consistent with propofol infusion syndrome, 6 more (9%) had disorders probably or possibly related to it, 29 (43%) had disorders not consistent with the syndrome, and for 12 (18%), consistency with it was unknown.

Published Literature

During 1992 through 2004, at least 12 publications with adverse event data on 33 children from six countries that concerned use of propofol for pediatric nonprocedural (long-term) sedation were identified.^{1–4,6–9,12,18,21,22} Most were individual case reports; two were case series of 5 and 18 children.^{1,4} Outcomes were primarily manifestations of propofol infusion syndrome (e.g., combinations of bradycardia, cardiac failure, arrhythmia, arrest, metabolic acidosis, rhabdomyolysis, and lipemic serum). Twenty-four (73%) of the 33 children died. Common features included high doses and long durations of propofol administration. For the 14 patients with available individual dose data in the case reports and case series of 5 children, the average peak dose was $9.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (range, 5.1–15; median, 9.7). In the case series of 18 children, the average dose was reported as $8.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.⁴ For the 15 patients with individual data, the average duration of propofol was 2.8 days (range, 0.75–4.8 days; median, 3 days). The average duration of propofol for the 18 children in the case series was also 2.8 days.⁴

At least five published reports of patients in the United States^{13,30–33} and two from other countries^{34,35} have documented the occurrence of propofol infusion syndrome in adults. As in the children, the syndrome occurred with high doses of propofol (sometimes with 2% concentrations) usually administered over extended periods. In most cases, propofol was administered for long-

term sedation, but there are also reports of its occurrence or of its prodromal symptoms (primarily lactic acidosis) in children²³ and adults when administered short term for anesthesia.³⁷⁻⁴¹

Similar to the trial in which increased mortality was found in children sedated with propofol,⁶⁴ researchers have reported increased mortality in a study of adults to whom propofol was administered for sedation. In 2001, Prasad *et al.*⁴⁹ reported that overall mortality was higher with propofol (8 of 14 patients, 57%) compared with midazolam (1 of 6 patients, 17%) ($P = 0.16$) in a retrospective chart review of consecutive patients (aged 17 yr or older) treated for refractory status epilepticus at the University of Virginia Hospital. The investigators noted that in this small study, although propofol and midazolam were comparable in seizure suppression, refractory status epilepticus patients with APACHE II scores of 20 or higher had statistically significant better survival ($P = 0.05$) with midazolam than with propofol. However, reclassifying the one patient treated with both agents to the midazolam group eliminated this statistically significant difference ($P = 0.22$). Two patients who developed hemodynamic compromise with propofol died, whereas no patients with midazolam developed hemodynamic compromise.

Studies of propofol exposure in children and adults have identified hypotension as the most frequent and serious acute adverse event.^{28,46,49,57} Propofol infusion syndrome has been rarely identified in studies because investigators have restricted propofol to lower doses than those documented in case reports, and when doses have not been restricted, studies have been limited by small sample size and lack of controls. However, the syndrome was found in a retrospective cohort study of the discharge diagnoses and medical records of 227 head-injured adults aged 16-55 yr admitted to a neurologic intensive care unit in The Netherlands between 1996 and 1999.¹⁴ Seven (3.1%) of the 67 patients who met the inclusion criteria were judged to have died from propofol infusion syndrome (all 7 had cardiac arrhythmia and metabolic acidosis or rhabdomyolysis). The mean propofol dose in the cases was $6.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, compared with $4.8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the 60 noncases. Five patients received 2% propofol, and 2 received 1% propofol. All patients had received the drug at rates higher than $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for more than 58 h (2.4 days). All died after a median duration of 91 h (3.8 days). By logistic regression analysis, the crude odds ratio for occurrence of the syndrome was 1.93 (95% CI, 1.12-3.32; $P = 0.018$) per unit ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) increase in mean propofol dose. The authors concluded that propofol infusion at rates higher than $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ should be discouraged for long-term sedation in the intensive care unit.

In a study conducted in the United States in which 1% propofol was used, the investigators recommended that

continuous infusion for extended periods of time not exceed $67 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Their recommendation was based on data from a retrospective uncontrolled study²⁶ of 142 children (age range, 2 months to 18 yr) given continuous intravenous propofol for a median duration of 16.5 h at a dose that did not exceed $50 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) plus an additional bolus dose of propofol that did not exceed $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. In this study, 10 children developed metabolic acidosis that was attributed to the primary diagnosis in all 10 patients. Blood pressure declined slightly. Based on this relatively small uncontrolled study, the investigators concluded that propofol could be administered safely and effectively to children in the pediatric intensive care unit, provided that prospectively established dosing guidelines are followed explicitly. Their study and recommendations have been criticized^{64,67} because of small sample size and lack of controls.

In a pharmacokinetic study of 21 critically ill ventilated children in the United Kingdom, aged 1 week to 12 yr and sedated with $4\text{-}6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol, 2% (strength not approved in the United States), combined with a constant morphine infusion for up to 28 h,²⁹ 2 of 17 children who reached target sedation scores of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ required a reduction in the infusion rate of propofol because of hypotension. One child developed persistent hypotension and metabolic acidosis after 5 h of propofol infusion at a constant infusion rate of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The child had undergone mitral valve repair surgery, and metabolic acidosis was apparent at the start of the propofol infusion and after it was discontinued. Midazolam was substituted; the hypotension and acidosis responded over the following 8 h to intravenous fluid and vasoconstrictors. The investigators concluded that increased peripheral distribution volume and reduced metabolic clearance after surgery caused prolonged elimination of propofol in very small infants and in children recovering from cardiac surgery.

Discussion

A review of deaths reported to the FDA regarding propofol for nonprocedural sedation found that at least 70% of pediatric deaths and 30% of adult deaths were similar to case reports in the medical literature in which children and adults developed propofol infusion syndrome after its use at high doses and for long durations. Although interpretation of safety signals derived from reports in the FDA's safety database of voluntarily submitted adverse drug reactions is limited by underreporting, possible differential reporting by drug, missing data on reports submitted, and inability to control for confounders, data can be compared for consistency with published information. In this situation, we determined

that some adult deaths and a high frequency of pediatric deaths in particular seem similar in clinical characteristics, course of illness, and propofol dose and duration to published literature reports and studies of propofol infusion syndrome.

The biologic mechanism underlying this syndrome may be related to the cardiovascular depressant effects of propofol.⁶⁸ The drug acts in a dose-dependent manner to antagonize β adrenoreceptors in rat myocardial membranes.⁶⁹ It has been shown to impair oxygen utilization or inhibit electron flow in the guinea pig cardiomyocyte and to significantly depress ventricular performance in the isolated perfused heart.⁷⁰ These effects correlated linearly with the propofol infusion concentration. Wolf *et al.*⁷¹ have stated that abnormalities in propofol infusion syndrome are consistent with specific disruption of fatty acid oxidation caused by impaired entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain.

Our analysis of US deaths with propofol along with case reports, case series, and studies reported in the medical literature indicate that propofol administered in higher doses, in higher concentrations, and usually for longer durations seems to increase the risk of propofol infusion syndrome in both children and adults. Doses of propofol should be kept as low as effectively possible, and patients who are required to be sedated with propofol should have monitoring of blood pressure, electrocardiograms, and arterial blood gases for unexplained metabolic acidosis and arrhythmias. As recommended by the American College of Critical Care Medicine,⁶⁵ alternative sedative agents should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during high-dose propofol infusions. Additional studies may be warranted to compare the risks and benefits of propofol with other sedative agents in pediatric and adult patients.

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