pharmacodynamics, applying different initial doses and different titration regimens taking into account the variability of in utero drug exposure of the newborn. Psychometric studies on sensitivity to change and responsiveness of different scoring systems would be useful as well. Given the risk of potential increased neuroapoptosis, long-term follow-up should focus on abnormalities in executive functions (15).

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Prolonged Propofol Infusions in Critically Ill Children: Are We Ready for a Large Controlled Study?*

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Sedation of PICU patients has been a challenge for critical care practitioners. As a result of our necessary compromise in choosing sedatives, intubated and mechanically ventilated children are at constant risk of suffering the consequences of either undersedation (i.e., migration of tubes or catheters, inadequate ventilation, and great discomfort) or significant side effects. In this context of imperfect options, propofol has emerged as a drug that could potentially shift the risk/benefit ratio in the right direction.

The pharmacological profile of propofol is very attractive for the purpose of sedation of critically ill children. It has an extremely short half-life of 2–3 minutes (1), and its predictable physiologic effect wears off shortly after the infusion is discontinued (2). These properties allow for ease of titration and are very useful for occasional and immediate awakening for neurological assessments and extubation readiness trials. In addition, propofol has potent anticonvulsive properties, is free of chemical dependence, and suppresses nausea (rather than causing it as do other sedatives). At the usual infusion doses, it has minimal effect on respiratory drive and hemodynamics. The more commonly used drugs in our arsenal for sedation in the PICU are fraught with these very issues of being more difficult to titrate, having slower onset of action and less predictable effect with significant risk of cardiorespiratory depression and withdrawal symptoms.

The initial excitement that propofol generated was muted by early reports of a potentially deadly complication later

***See also p. e66.**

Key Words: children; intensive care; propofol; rhabdomyolysis; sedation

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described by Bray (3) as the propofol infusion syndrome (PRIS). Reported primarily as isolated cases or small case series, the mere existence of this syndrome as well as its diagnostic criteria (which varied from report to report) have since been repeatedly questioned. Suggested theories potentially linking the phenomenon to impairment in the mitochondrial respiratory chain in patients with underlying stress, hypoxia, and glucose deprivation (4) have not been confirmed. A consistent thread throughout the reported cases linked side effects to both the hourly dose (usually above 4 mg/kg/hr) and the duration of infusion (usually greater than 48 or 72 hr).

In 1999, the manufacturer conducted a prospective multicenter trial (known as "Trial 0859IL-0068") in 327 PICU patients from 24 PICUs comparing 1% and 2% propofol emulsions to other sedatives. Propofol was initiated at a dose of 5.5 mg/kg/hr and titrated to a COMFORT score between 17 and 26. Unexpectedly, mortality by 28 days postinfusion in the propofol arm was higher than in the "other sedatives" arm (11% vs 4%, though not statistically significant). A number of important factors preclude clinically relevant conclusions from these results (5–7): 1) the study was not designed to detect differences in mortality and included patients with "do-not-resuscitate" orders; 2) half the deaths in the propofol arm were from one center. When excluded, mortality in the propofol arm was 3% versus 6% in the "other sedatives" arm; 3) more than half the deaths occurred more than 7 days after discontinuation of propofol; 4) plasma base excess increased rather than decreased during propofol infusions; and 5) the primary investigators did not attribute any of the deaths to propofol. Unfortunately, the results of that study have never been published, and only the results of the medical review by the Food and Drug Administration (FDA) are available (8).

Largely based on its interpretation of the mortality data analysis in Trial 0859IL-0068, the FDA instructed the manufacturer to issue a "Dear Doctor" letter indicating that propofol should not be used for PICU sedation in the United States. The current drug package insert states: "Diprivan injectable emulsion is not indicated for use in PICU sedation since the safety of this regimen has not been established."

Despite the potential liability of using a medication off-label and against a sternly stated warning, use of propofol infusions for sedation of critically ill children continued in most PICUs. Pediatric practitioners commonly use off-label medications in clinical practice, being forced to choose between an off-label drug with better pharmacological profile and FDA-approved drugs with an inferior profile. Although most PICUs have resorted to infusion duration less than 12 hours (largely for extubation readiness trials), there is significant variability in practice, with some centers using propofol infusions at high doses (up to over 10 mg/kg/hr) over several days (9, 10). Two case series from the United States and Sweden containing a combined total of 316 PICU patients reported the efficacy and safety of propofol infusions when used at infusion rates of less than 4 mg/kg/hr and infusion duration that is usually shorter than 48 hours (11, 12).

In this issue of *Pediatric Critical Care Medicine*, Koriyama et al (13) add to this body of evidence by describing their experience with propofol sedation in 210 PICU patients (220 infusions). The patient population was typical for a multidisciplinary PICU. Their practice was to limit the maximum infusion rate to 4 mg/kg/hr plus up to 1 mg/kg/hr of bolus doses and the infusion duration to 24 hours. With an 87% compliance with those guidelines, the median propofol dose including boluses was 2.7 mg/kg/hr (maximum 7.8 mg/kg/hr) and the mean duration was 10.3 hours (maximum 41.3 hr). Duration of the majority of infusions was under 24 hours. None of the patients developed any of the components of PRIS. The study is limited by a relatively short infusion duration (< 24 hr) and by its retrospective nature where tests monitoring for the development of rhabdomyolysis, hyperlipemia, or electrocardiogram (ECG) changes were at the discretion of the clinical team.

With this encouraging but incomplete information, what is the pediatric intensivist to do? First, until better data become available, and despite the remaining doubts as to the importance or even mere existence of PRIS, propofol infusion for a duration greater than 12 hours should probably be reserved for cases where other sedatives have failed, are contraindicated, or wherein the treating clinician's opinion about the benefit of using it outweighs the potential risks. Effort should be made to reduce the risk of PRIS by restricting the dose (< 4 mg/kg/hr) and duration (< 48 hr) of the infusion. Other sedatives can be added to allow the lowest possible propofol dose. The idea of "propofol holiday" may be explored, that is, holding the infusion after 48 hours for a day or two and then restarting it if necessary for another infusion course. The proposed pathophysiological mechanisms (4) suggest that discontinuation of other IV lipid sources and provision of adequate carbohydrate sources could be helpful. Careful monitoring of hemodynamics, ECG changes (specifically looking for ST changes and the Brugada-like pattern), acid-base balance, serum lactic acid, and creatine kinase is advisable.

With cumulative data showing the safe use of prolonged propofol infusions in more than 500 PICU patients, we may have reached a potential equipoise that would allow for a large multicenter prospective study. Ackerman (14) has provided an excellent summary of the ethical considerations that would go into the design of such study. Prolonged propofol infusions are already being used in many centers or not used at all in others, with wide variation in practice. This could potentially place some patients at risk while denying others a great benefit. A well-designed study could determine variables for safe use of the drug, providing patients with the advantages of both efficacy and safety of a drug with a remarkable pharmacological profile.

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Anticoagulation Monitoring During Extracorporeal Membrane Oxygenation: Is Anti-Factor Xa Assay (Heparin Level) a Better Test?*

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Bembea et al (1) recently published an informative survey on anticoagulation practices among extracorporeal membrane oxygenation (ECMO) centers within the Extracorporeal Life Support Organization. This study revealed that the anticoagulation practices varied widely among these centers, but activated clotting time (ACT) was the most common test used to monitor anticoagulation as reported by 113 of 116 respondents (97%). ACT assay has been around since the 1960s and was first applied in patients undergoing cardiopulmonary bypass in the 1970s (2, 3). Over time, ACT became a common tool for intensivists/perfusionists to monitor ECMO anticoagulation because of its ease-of-use by the bedside and cost-effectiveness. ACT assesses the time of whole blood to form a clot after the addition of various coagulation activators, such as kaolin and glass beads. With advancements in the fields of thrombosis and hemostasis, laboratory medicine, and critical care medicine, other coagulation assays are now becoming readily available and could be used to monitor ECMO anticoagulation in "real time." In particular, anti-Factor Xa assay seems to have a better correlation with heparin dosing during ECMO as reported in small case series (4, 5). The survey by Bembea et al (1) reported that 75 of 115 respondents (65%) routinely or occasionally use anti-Factor Xa assay, mostly as an adjunct to ACT. In this issue of *Pediatric Critical Care Medicine*, Liveris et al (6) reported in a small case series ($n = 17$ patients) that anti-Factor Xa level had a better correlation to heparin dosing compared with ACT and activated partial thromboplastin time (aPTT) during ECMO.

However, the important question remains unanswered as to whether any single test used to monitor ECMO anticoagulation is better than another in terms of lowering the morbidity or mortality associated with ECMO. It makes biologic sense that anti-Factor Xa assay is more specific to the dosing of heparin. In the test tube, the anti-Factor Xa assay measures the ability of a patient's plasma (presumably containing heparin-antithrombin complex) to inhibit exogenously added factor Xa hydrolyzing its synthetic substrate. Thus, the anti-Factor Xa assay evaluates only one chemical reaction. However, unfractionated heparin has other mechanism of actions including 1)

***See also p. e72.**

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