

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

# HIGH-DOSE PROPOFOL INFUSIONS FOR REFRACTORY INTRACRANIAL HYPERTENSION

## SUMMARY

Although propofol is often used safely for ICU sedation in doses up to 50 mcg/kg/minute, there are circumstances where higher doses are utilized in select critically ill patients. Recent reports have documented the development of a fatal syndrome associated with high-dose propofol infusion that is characterized by metabolic acidosis, rhabdomyolysis and refractory arrhythmias. This syndrome appears to be both dose and duration dependent. The largest series describing propofol infusion syndrome reports that it occurs at doses greater than 83 mcg/kg/minute for greater than 24 hours. High-dose propofol should therefore be utilized with caution and only in specific patient populations.

## RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **None**
- **Level 3**
  - **High-dose propofol should only be utilized if one of the following situations exists:**
    - **Patient has refractory intracranial hypertension**
    - **Patient has refractory status epilepticus**
  - **The following precautionary measures should be initiated/continued when propofol is infused at a dose >50 mcg/kg/minute:**
    - **Continuous electrocardiographic monitoring**
    - **Baseline and daily EKG**
    - **Baseline triglyceride level**
    - **Baseline and daily ionized calcium and creatine kinase levels**
    - **Calcium replacement protocol**

## INTRODUCTION

Propofol is utilized in many intensive care units for patient sedation despite its significant cost. For the majority of patients, benzodiazepines and haloperidol are as effective as propofol and significantly more cost effective. There are, however, specific populations in which propofol is a useful sedative when used with caution. For example, its favorable pharmacokinetic profile and beneficial effects on cerebral metabolic rate make it an effective agent for controlling intracranial hypertension following brain injury. However, doses exceeding those recommended for routine ICU sedation are often needed and reports

## EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

## LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

describing a potentially fatal syndrome associated with propofol infusion have been emerging over the past several years. Specifically, the development of metabolic acidosis, elevated creatine kinase levels and refractory arrhythmias have been reported in patients receiving high-dose propofol. Although the etiology remains unclear, consideration must be given to the lipid vehicle as well as the calcium-channel and beta-blocking properties of propofol as contributors to these adverse effects. Due to limited information on this syndrome in adults, a heightened awareness and consistent approach to monitoring is necessary.

## LITERATURE REVIEW

In a prospective, randomized, double-blind trial in moderate and severe head injury patients, Kelly et al. demonstrated that propofol was as effective as morphine in controlling intracranial hypertension (1). Long-term outcome and mortality were improved in the propofol group, although not significantly. While propofol infusions decreased the need for other sedating agents (including benzodiazepines and pentobarbital) and neuromuscular blocking agents, vasopressor agents were more likely to be necessary than when morphine was used alone for sedation.

Following five unexplained cardiac arrests in head-injured patients receiving propofol, Cremer et al. performed a three-year retrospective analysis of propofol use in their neurosurgical intensive care unit (2). "Propofol infusion syndrome" was defined by the presence of myocardial failure (requiring continuously increasing vasoactive medication support), metabolic acidosis, and rhabdomyolysis. Seven of 67 patients (10%) receiving propofol for control of intracranial hypertension died with symptoms consistent with propofol infusion syndrome. The odds ratio for occurrence of the syndrome was 1.93 for every mg/kg increase in mean propofol dose above 5 mg/kg/hr (83 mcg/kg/min). No patient who received less than 5 mg/kg/hr developed propofol infusion syndrome. Symptoms typically became evident 24-48 hours into the infusion. Cremer et al. recommended that propofol infusion at rates in excess of 5 mg/kg/hr should be discouraged until further data is available.

Tramer et al. performed a systematic literature review of 65 published articles and 187 reports to drug monitoring centers pertaining to propofol-induced bradycardia and asystole during anesthesia (3). Propofol significantly increased the risk of bradycardia compared to other anesthetic agents with an absolute risk of 15%. One-third of propofol-induced bradycardias were calculated to lead to asystole with one-third of these being fatal.

Perrier and colleagues reported the course of an adult trauma patient with a severe head injury who received high-dose propofol (4). In addition to metabolic acidosis and increased creatine kinase levels, the patient rapidly developed bradycardia and hypotension that did not respond to fluid, atropine or epinephrine administration. He progressed to pulseless electrical activity followed by asystole and death. Propofol had been infused for 98 hours at a rate of 530 to 700 mg/hr.

Cannon and colleagues reported the development of presumed propofol-infusion syndrome in a 13-year old patient with a severe head injury following the administration of propofol at 100 mcg/kg/minute for 4 days (5). Symptoms included metabolic acidosis (serum bicarbonate: 8 mEq/L), rhabdomyolysis (creatinine kinase: 389,000 U/L) and a right bundle branch block with wide QRS complexes. Despite escalating doses of vasoactive agents and aggressive attempts to correct the metabolic acidosis, the patient expired. In response to this report, several editorials were published describing similar cases (6,7). Kelly reported the development of metabolic acidosis, renal failure and cardiovascular collapse in a head-injured patient who received propofol (mean dose 126 mcg/kg/minute, range 10-200 mcg/kg/minute) for a total duration of 55 hours (6).

In addition to patients with head-injuries, several reports describe the development of symptoms associated with propofol-infusion symptoms in patients with other disease states including refractory status epilepticus and asthma (8,9).

## REFERENCES

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## High-Dose Propofol Infusion in Head Injury

