

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.

## **PROTOCOL FOR ACUTE SEDATION AND PAIN MANAGEMENT OF NEUROTRAUMA PATIENTS (AGE $\geq 16$ )**

**\*\*PROTOCOL IS FOR 48 HOURS FOLLOWING ADMISSION ONLY\*\***

### OVERVIEW

The goal of sedative therapy in patients with traumatic brain injury is to prevent secondary neuronal damage due to increases in intracranial pressure or inadequate cerebral perfusion pressure (1). Additionally, sedatives must not interfere with performance of the clinical neurological examination. Selection of drug therapy in this population is challenging as there is no one agent that is considered ideal. Unfortunately, the literature addressing sedation of the neurotrauma patient is limited. Most trials evaluating the effects of sedatives on cerebral physiology were performed in healthy volunteers or patients undergoing elective neurosurgical cases. Therefore, in addition to the usual considerations regarding selection of sedative therapy, special consideration must be given to a drug's metabolic and elimination pathways as well as its effects on the cerebral and systemic vasculature.

Propofol is a sedative-hypnotic agent that has a favorable pharmacokinetic profile and beneficial effects on cerebral metabolic rate, making it an effective drug for routine sedation as well as controlling intracranial hypertension following brain injury. Its short half-life not only allows for easy titration, but also for rapid awakening when neurological evaluation is necessary. Propofol is eliminated by hepatic conjugation to inactive metabolites and its pharmacokinetics are not altered in the presence of renal or hepatic disease. Its beneficial effects on the cerebrovasculature are mediated via dose-dependent decreases in cerebral blood flow and metabolic rate.

Although propofol is an effective sedative in the neurotrauma population, consideration must be given to several adverse effects. First, due to potent respiratory depressant effects, patients must be mechanically ventilated prior to administration. Second, cardiovascular depressant effects occur due to reductions in preload, contractility and systemic vascular resistance which result in a decreased mean arterial pressure. This, in turn, can lead to a decreased cerebral perfusion pressure. Finally, 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. 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. The largest series describing propofol infusion syndrome reports that it occurs at doses greater than 83 mcg/kg/minute for greater than 24 hours (2). High-dose propofol should therefore be utilized with caution. Due to limited information on this syndrome in adults, a heightened awareness and consistent approach to monitoring is necessary.

As this protocol includes the use of propofol for patients age  $\geq 16$ , it is important to note that the Food and Drug Administration (FDA) has determined that there may be important safety concerns when this agent is used for pediatric ICU sedation (3). A "Dear Health Care Provider" letter from AstraZeneca, the manufacturer of Diprivan<sup>®</sup>, states that propofol is not approved in the US for pediatric ICU sedation and should not be used for this purpose (3). The FDA's recommendation is based on data from a randomized, controlled, clinical trial that evaluated the safety and efficacy of Diprivan<sup>®</sup> versus standard sedative agents in pediatric ICU patients ranging in age from newborn to 16 years (4). The study revealed an increase in the number of deaths in patients treated with Diprivan<sup>®</sup> as compared to standard sedative agents. However, all deaths were assessed as not related to treatment by the clinician caring for the patient. Additionally, only one of the patients who died was in the 16 to 17 year age group. Due to limited data supporting an increased rate of death associated with propofol in pediatric patients age  $\geq 16$  years, as well as the relative lack of alternative agents available for neurotrauma sedation, the use of short-term propofol for this population should be considered an acceptable practice.

## CRITERIA

- Age  $\geq$ 16 years
- Initial Glasgow Coma Score < 8 AND suspected/documentated intracranial bleed

## ACTIONS

- **For patients NOT mechanically ventilated**
  - Sedative
    - Midazolam 2mg IV x 1 dose for agitation
  - Analgesic
    - Fentanyl 12.5mcg IV x 1 dose for pain
  - Subsequent orders for anxiolytic and/or analgesic therapy to be determined based on patient response
- **For patients mechanically ventilated**
  - Sedative
    - Initiate propofol 5 mcg/kg/minute and titrate by 10 mcg/kg/minute increments up to 50 mcg/kg/minute to achieve a Sedation-Agitation Scale (SAS) of 2 to 3
      - 1. Propofol Infusion Protocol for Neurotrauma Patients (Age  $\geq$ 16) is available on SWIFT
    - If propofol doses exceeding 50 mcg/kg/minute are needed to control elevated intracranial pressure, the following precautionary measures are to be initiated/continued:
      - 1. Baseline and daily EKG
      - 2. Baseline triglyceride level
      - 3. Baseline and daily ionized calcium and creatine kinase levels
      - 4. Calcium chloride replacement protocol if central intravenous access is available
  - Analgesic
    - Fentanyl 25 – 50mcg IV Q1HR PRN PAIN

## REFERENCES

1. Rhoney DH. Neurotrauma. *In*: Pharamcotherapy Self-Assessment Program, Book 6,
2. Critical Care/Urgent Care. Fourth Edition. American College of Clinical Pharmacy, 2002, pp 181-224.
3. Cremer OL, Moons KGM, Bouman EAC, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117-118.
4. AstraZeneca Pharmaceuticals. Dear Health Care Provider letter.
5. [www.fda.gov/medwatch/safety/2001/diprivan\\_deardoc.pdf](http://www.fda.gov/medwatch/safety/2001/diprivan_deardoc.pdf) (2006 March 3).
6. Data on File, AstraZeneca, Diprivan Trial 0068 Abstract, April 27, 2001.