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Chloral Hydrate Sedation for Infant Pulmonary Function Testing

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To the Editor:

In the November 2013 issue of *Pediatric Pulmonology*,¹ Dr. Hegde highlighted recent problems with the use of chloral hydrate (CH) as sedation for infant pulmonary function tests (PFTs) in the United States (US). The joint American Thoracic Society/European Respiratory Society (ATS/ERS) Working Group on Infant Respiratory Function Testing has been working to address this problem over the past year.

As background, CH has been used to provide moderate sedation for infant PFTs and other procedures for decades. However, CH never went through the formal drug approval process with the US Food and Drug Administration (FDA). In 2006, when the FDA conducted a comprehensive review of unapproved drugs, including CH, they enforced regulatory action against manufacturers of CH for unapproved marketing of the drug. In response, manufacturers decided to discontinue its production, rather than expend the cost required to obtain FDA approval. Currently no commercially manufactured preparations of CH capsules, suppositories, or syrup are now available in the US. Importation of CH manufactured outside of the US is problematic due to its categorization as a controlled substance by the Drug Enforcement Administration. This also complicates sharing of CH between hospitals, as almost no hospital pharmacies have a controlled substances distribution license.

The options for CH use for infant PFTs in the US depend upon its intended use. For clinical use, physicians can still prescribe CH in an unapproved, off-label fashion. Commercial compounding pharmacies will prepare CH liquid, but may charge a large membership fee. Another option is for hospital pharmacies to purchase bulk CH powder and compound it themselves. There are a few manufacturers who are continuing to manufacture bulk CH powder.

The position for research use has recently been clarified after communication with the FDA regarding use of CH for infant PFTs performed in the Prematurity and Respiratory Outcomes Program study (NCT01435187). The FDA regards CH as standard of care for infant PFTs. Therefore an investigational new drug (IND) application for compounded CH is not required if the following conditions are met: the CH being used is manufactured in the US; CH is compounded in compliance with state and local regulations regarding compounded drugs; the purpose of the research project is not to study CH itself; and the research protocol has been reviewed and approved by the local institutional review board. This FDA response suggests that other researchers using infant PFTs in studies would also not be required to submit an IND application. However, there may be specific aspects of a research study involving CH sedation for infant PFTs that would trigger a need for an IND application, and in situations where doubt exists about the need for an IND application, the FDA should be consulted to advise on this aspect.

CH has been the preferred medication for infant PFT sedation for over 25 years at multiple sites in the US and around the world for several reasons.² It is an oral medication and thus avoids the need for an intravenous catheter. Its duration of action matches well with the duration of the infant PFT, and it provides the appropriate level of sedation. This is not the case for other alternate sedatives, such as midazolam or propofol which either provide inadequate sedation or excessive sedation, respectively. The use of an alternate sedative also has potential implications for available reference data, as all existing healthy infant PFT reference data, that we are aware of, have been derived from studies using CH. Choice of sedation can potentially affect breathing patterns and respiratory mechanics, and reference data may not be transferable between all sedative choices. The clinical importance of appropriate reference data for infant PFT has been recently outlined,³ and reinforces the importance of contemporaneously collected healthy control data for infant PFT interpretation, especially if alternate sedatives are being considered.

Although CH did not undergo the normal FDA drug approval process, data on pharmacology, toxicity and safety in infants do exist.^{2,4,5} Toxicity is rare and associated with multiple dosing. However, multiple dosing is rarely used for PFTs infants and if given, the first dose is typically moderate (50–75 mg/kg) and followed by a smaller second dose (25 mg/kg) if inadequate sedation is achieved. CH is considered moderate sedation, and as such hospital policies require the presence of a physician trained in pediatric advanced life support and availability of appropriate resuscitation equipment. The safety of CH sedation for infant PFTs has been prospectively evaluated in a large multicenter clinical study of 100 infants with cystic fibrosis (CF).⁶ Out of a total of 342 infant PFTs, the most common adverse event was vomiting, which occurred in 8% of infants. Only one serious adverse event was reported, and in retrospect that infant had an early upper respiratory infection. CH has also been used in several other large infant PFT studies with enrollments of 100–150 infants.^{7–10} Although recording of safety data was not a specific study goal, none of these studies reported any adverse events with the use of CH for infant PFTs.

In summary, CH remains the preferred mode of sedation for infant PFTs for several reasons outlined above. There is an ample track record of its safety provided patients are appropriately monitored. Although commercial manufacture has ceased in the US, options

exist to clinicians and researchers wishing to perform infant PFTs using CH sedation. Objective measures of respiratory function are critical for the treatment and study of pediatric lung disease. Through the diligent efforts of multiple members of the international pediatric pulmonology community over many years, we now have technology and protocols for accurate and reproducible assessment of respiratory function in infants. The ATS/ERS Working Group will continue to work with pediatric pulmonologists to ensure access to this important medication for infant PFTs and to overcome any local barriers to its use for both clinical care and research.

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