Reappraisal of Lytic Cocktail/Demerol, Phenergan, and Thorazine (DPT) for the Sedation of Children

Committee on Drugs

The importance of premedication for pediatric patients undergoing surgical procedures dates to the classic work of Waters, who believed that children were as entitled as adults to have premedication. The recommended premedication was morphine with scopolamine. Later, phenothiazines were believed to be useful as anesthetic premedications because of their sedative and vasodilator effects. These observations led to the combination of a narcotic with a phenothiazine, which induced deep sedation (sleeping) in the child and allowed easy separation from his or her parents before administration of the anesthetic. The narcotic provided a base of analgesia whereas the phenothiazine lowered the blood pressure and blunted the pressor responses to surgical stimulation.

The combination of meperidine (Demerol), promethazine (Phenergan), and chlorpromazine (Thorazine), commonly referred to as DPT, has been used for more than 20 years as a sedative and analgesic cocktail for pediatric patients. Although the combination of a narcotic with a phenothiazine was first developed to provide preanesthetic sedation for patients about to undergo general anesthesia, its primary use in children has been outside of the operating room. The DPT combination has been used as a primary sedative for infants and young children undergoing radiologic procedures (computed tomography, magnetic resonance imaging, and contrast studies). It has been used as a sedative/analgesic for invasive procedures (suturing, bone marrow aspirations, cardiac catheterization, and renal biopsy).

The precise mixture of constituents in the cocktail used for children varies somewhat from institution to institution. Original descriptions refer to a formulation including 25 mg/mL of meperidine, 6.5 mg/mL of promethazine, and 6.5 mg/mL of chlorpromazine, with a recommended dose of 0.1 mL/kg of body weight. Recent sources refer to a formulation consisting of a 2:1:1 mixture, with what amounts to a 1-mL/kg dosage recommendation. In fact, dosage recommendations may vary by a factor of 10. No proprietary mixtures are available, so the solution must be prepared locally. Intramuscular injection has been the most common route of administration; however, intravenous administration (without dosage modification) has been gaining in popularity. Few admonitions concerning dosage modification with respect to age or underlying disease have been published. Thus, despite the scarcity of data concerning its efficacy and safety in children, the DPT lytic cocktail has found widespread use in pediatrics.

PHARMACOLOGY OF THE CONSTITUENTS OF LYTIC COCKTAIL

Studies in adult patients have served as the basis for the use of this drug combination in children. Unless stated otherwise, the references cited contain data obtained with adult patients. No comparable pediatric studies exist.

Meperidine

Meperidine is a synthetic opioid with an analgesic potency about 10% of that of morphine. It has a more rapid onset and a shorter duration of action than morphine, but usual doses may be ineffective in up to 5% of patients. No rigorous studies have defined the pharmacokinetics or pharmacodynamics of meperidine in children. Common adverse reactions include dizziness, nausea, and vomiting. In comparative studies, meperidine was found to be more sedating and to have equivalent respiratory depressant effects when compared with equianalgesic doses of morphine.

Meperidine does not allay anxiety or induce retrograde amnesia. It is metabolized, at least in part, via N-demethylation, yielding normeperidine, which has a relatively long half-life. This active metabolite has been implicated as a cause of seizures in patients who receive meperidine in high doses or have renal functional impairment. It also has been found to accumulate in patients receiving concomitant chlorpromazine therapy.

Promethazine

Promethazine has moderate sedating properties and pronounced antihistaminic activity. It achieved widespread use in adults as a preanesthetic medication because its sedating properties were not associated with respiratory depressant effects. Some studies found this even when the drug was administered with morphine or meperidine. Another attractive attribute of promethazine is its modest, centrally mediated antiemetic activity.

In adult patients, the side effects of promethazine...
are limited. Sedation is prominent and extrapyramidal effects are uncommon. In contrast, significant concerns have been raised about the use of promethazine in infants and young children. Case reports have linked promethazine to apneic episodes in this age group. No systematic pharmacokinetic or pharmacodynamic studies of promethazine have been performed in infants and children.

Chlorpromazine
Chlorpromazine is a phenothiazine antipsychotic agent with relatively low potency. It has been used in adults and children to treat a variety of disorders from intractable hiccoughs to paranoia. Although this drug has a long history of efficacy, its clinical pharmacology in children is largely unknown. As a single agent, chlorpromazine has little if any sedative or analgesic properties.

The disposition of chlorpromazine is complex, with more than 150 metabolites identified. In addition, toxicity is common, with pronounced antidiurenergic and anticholinergic effects predominating early in therapy. The α-adrenergic blocking properties can result in profound hypotension if chlorpromazine is administered to individuals with a contracted vascular volume. Chlorpromazine may have deleterious effects in patients with congenital heart disease. In patients with cyanotic congenital heart disease, such as tetralogy of Fallot, the lower systemic vascular resistance from the α-blocking effect can cause profound obligatory right-to-left shunting through the ventricular septal defect and thereby precipitate a severe hypercyanotic spell. In patients with left ventricular outflow tract obstruction (eg, aortic stenosis at any site or hypertrophic cardiomyopathy), the α-blocking effect with hypotension can increase the left ventricular-aortic gradient, resulting in decreased coronary blood flow, shock, and even death. In patients with seizure disorders or a predisposition to seizures, chlorpromazine lowers the seizure threshold. Moreover, chlorpromazine is antianalgesic and commonly produces dystonic reactions.

HISTORY OF THE ATARACTIC MIXTURE
An ataractic mixture is a combination of drugs that creates a feeling of “serenity” when administered to patients. Several developments in pharmacology and anesthesiology contributed to the formulation of the lytic cocktail and its use as a sedative/analgesic. In the late 1940s, antihistaminic agents were demonstrated to potentiate the sedative effects of the barbiturates. This work was extended during the 1950s, when chlorpromazine also was shown to potentiate the hypnotic effects of barbiturates. These animal studies provided the preliminary data necessary to support the initiation of clinical trials in these areas. A series of articles reported the adjuvant effects of chlorpromazine in the treatment of moderate to severe pain when combined with opioids. These observations were confirmed by other investigators who demonstrated that chlorpromazine, while having little intrinsic analgesic activity, markedly augmented the analgesic activity of both morphine and meperidine. This allowed one to obtain a desired analgesic effect with lower doses of opioid. Therefore, either morphine or meperidine could be used in doses that were not associated with respiratory depression but could, in the presence of chlorpromazine, result in “optimal” analgesia.

The toxicity of the combination of meperidine and chlorpromazine was also studied. Profound lethargy that persisted long after the clearance of meperidine was noted. This lethargy was accompanied by a decrease in respiratory rate (63% ± 11%), a decrease in systolic blood pressure (9% ± 2% supine and 28% ± 5% standing), and severe mental debilitation. Side-effect profiles were not evaluated systematically using the three-drug combination, although there was ample evidence that combining either promethazine or chlorpromazine with an opioid leads to enhanced toxicity as well as enhanced hypnosis and analgesia. Early studies showed that promethazine increased agitation and hyperventilation when administered before anesthesia. It was concluded that there was “no significant advantage to the combination of promethazine with an opiate.” In one study, a more profound respiratory depression was reported when promethazine was administered with meperidine.

In another report in which complete lytic cocktail (DPT) was used in the treatment of eclampsia, seizures recurred because of both a lowering of the seizure threshold and a reduction of cerebral blood flow attributed to phenothiazines.

While all of this work on preanesthetic medications was proceeding, the techniques of neuroleptanalgesia were also being developed. Neuroleptanalgesia describes a state of “apparent indifference to pain induced by the combination of a potent analgesic with a neurolept or major tranquilizing drug.” The approach grew out of the work of Laborit and Huguenard, who first described the lytic cocktail to produce a state of “artificial hibernation.” Even in this first description of the use of lytic cocktail, the state of artificial hibernation was associated with considerable cardiovascular instability and prolonged depression of consciousness.

Pediatric Experience With Lytic Cocktail
Early experience with the combination of phenothiazine and a narcotic revealed a high incidence of extrapyramidal movements and seizures, resulting from excessive doses of phenothiazine. The classic lytic DPT cocktail was formulated in response to the need of pediatric cardiologists for a sedated and narcotized patient. Previous attempts at preparing appropriate sedatives using combinations of barbiturates and narcotics had proven unsatisfactory. In 1958, Smith et al examined three DPT combinations (Cardiac Mixtures 1–3) and found the most satisfactory to be the 2:1:1 ratio described above (0.1 mg/kg intramuscularly; a maximum of 1.5 mL, with lower doses in cyanotic children). It is interesting that in their series of 670 children, “only 17 patients appeared shocked,” whereas “three subjects developed serious respiratory depression” and one subject died “twenty minutes after returning to the ward.” Despite these complications, this drug combination fulfilled an important need at the time.
The next citation of DPT in the pediatric literature appeared in 1967 in a study of the effects of sedation on acid-base balance during cardiac catheterization.22 The authors of the study stated that "all patients received the widely used sedative mixture of 50 mg (1 cc) meperidine, 12.5 mg (0.5 cc) chlorpromazine and 12.5 mg (0.5 cc) promethazine." These doses, however, are twice as high as those previously reported.

In an effort to compare the relative efficacy and safety of DPT with other potential sedative modalities, investigators in the late 1970s reported a randomized study comparing rectal thiopental with intramuscular DPT as sedation for computed tomographic scanning.23 The lytic cocktail failed to produce adequate sedation at standard doses in 14% of the children, compared with a 3% failure rate using thiopental.

Two years later, the Pediatric Drug Surveillance Program in Boston reported the risks of premedication for computed tomographic scanning in children.24 Major adverse events were seen only with "Demerol Compound," which was the Boston Children's Hospital formulation of DPT lytic cocktail. The incidence of life-threatening adverse events was 4%, which was four times that seen with other patients monitored by the Pediatric Drug Surveillance Program. Similar results were reported by another group of investigators, who used the DPT cocktail for a variety of procedures.

These experiences, as well as the anecdotal evidence of others, culminated in the 1989 admonition against the use of lytic cocktail in children.26 Nevertheless, in 1990 a survey of emergency departments of member institutions of the National Association of Children's Hospitals and Related Institutions revealed that DPT lytic cocktail remains the most commonly used form of sedation for suturing in pediatric emergency departments. These results are surprising given that only 22% of respondents reported the cocktail to be effective more than 90% of the time.3 These deficiencies have been highlighted by recent retrospective and prospective studies of DPT lytic cocktail from the pediatric emergency center in Syracuse, New York.27,28 Although the retrospective study did not directly report efficacy, only 8 of 487 patients required repeated sedation, whereas the prospective study demonstrated a 29% failure rate. Adverse events were rare in the two studies; however, patients required $19 \pm 15$ hours to return to normal behavior.

CONSIDERATIONS FOR THE RATIONAL AND SAFE SEDATION OF INFANTS AND CHILDREN

Whenever it is considered necessary to sedate a pediatric patient, one must consider the type of procedure planned (painful or nonpainful), the duration of the procedure (important in choosing the appropriate sedative), the underlying medical condition of the patient (whether the patient has properly fasted, whether the blood volume is contracted, whether the patient is taking other medications that may interact with the sedative, and whether the patient is able to eliminate the drug), the need for anxiolysis or narcosis, and experience with alternative techniques or routes of administration.

The drugs used for the sedation of infants and children should be selected from among those for which rational pediatric dosing guidelines are available. Sedative effects should be titratable and controllable so that the duration of the effect of the dose does not exceed greatly the duration of the procedure.

Opioid medications should be reserved for painful procedures (eg, angiography, cardiac catheterization, very large lacerations) and should not be administered merely to sedate the child (eg, before undergoing computed tomography). Even when faced with painful procedures (eg, bone marrow aspiration), children may prefer the anxiolysis and amnesia produced by a benzodiazepine (midazolam) to the narcosis produced by a narcotic (fentanyl).29 The appropriate use of local anesthetics is mandatory.

The duration of the planned procedure is also an important consideration. It is not generally desirable to have the child sedated for much longer than the duration of the procedure. The reported $19 \pm 15$ hours before return to normal after DPT administration28 is obviously excessive. Such prolonged sedation unnecessarily ties up nursing personnel and complicates following the recommended guidelines for monitoring sedated children.30 The clinician can never be certain how long any given procedure will last, but most routine procedures can be predicted within a reasonable time range, allowing a choice of the appropriate drug or drug combination.

Children are less likely to have a problem with sedative-associated respiratory depression during a painful procedure because discomfort stimulates respiration. However, once the procedure is terminated or before a procedure is begun, the child is at greatest risk for becoming more deeply sedated because there is no painful stimulus. Even when the child does not appear to be sedated at the end of the procedure, late sedation may develop from a variety of causes, such as continued drug uptake, delayed excretion, pharmacodynamics, or the lack of external stimulation. It is essential that the child be observed in an appropriate recovery facility for a sufficient period before discharge.30

ALTERNATIVE AGENTS

Fortunately, a number of newer drugs are available that may provide safe and effective sedation and analgesia for children. These drugs include midazolam, a short-acting, water-soluble benzodiazepine; fentanyl, a short-acting, potent synthetic opioid; ketamine, a dissociative anesthetic agent; and propofol, a short-acting intravenous anesthetic. Detailed discussion of these drugs is beyond the scope of this commentary. Practitioners who wish to use these agents should become familiar with their respective risks and benefits and, with their colleagues in anesthesiology or clinical pharmacology, should develop safe protocols for their use.
CONCLUSIONS

The DPT lytic cocktail remains a widely used sedative and analgesic for pediatric patients. Neither the combination itself nor its dosage is based on sound pharmacologic data. There is a high rate of therapeutic failure as well as a high rate of serious adverse reactions, including respiratory depression and death, associated with its use.

Even when it is effective, DPT appears to lack many of the desirable characteristics of a sedative for children. Specifically, the dose cannot be titrated easily and individually, the onset of action is significantly delayed (20 to 30 minutes), the duration of sedation is protracted (5 to 20 hours), the duration of analgesia is much shorter (1 to 3 hours), and no anxiolytic or amnestic properties exist.

RECOMMENDATIONS

In light of the available information, the American Academy of Pediatrics recommends the following.

1. The risks and potential benefits of DPT lytic cocktail for each patient must be evaluated carefully before it is used. Alternative sedatives/analgesics should be considered.

2. If DPT lytic cocktail is used, all of the guidelines pertaining to deep sedation for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures should be followed.

3. Careful monitoring of blood pressure and ventilation should accompany the standard monitoring of oxygen saturation.

4. Additional caution should be exercised when using lytic cocktail in children with seizure disorders, other central nervous system abnormalities, or congenital heart disease consisting of tetralogy of Fallot-type anatomy or of left ventricular outflow obstruction, such as any type of aortic stenosis.

5. Criteria for discharge from the sedation-monitoring area must be established with full recognition of the "trance-like" state produced by this neuroleptanalgesic technique.

REFERENCES

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