LEADING ARTICLE

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Use of Phenothiazines as Sedatives in Children

What are the Risks?

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Contents

Abstract

Phenothiazines have been widely used for their antiemetic, antipsychotic and sedative properties for many years. The introduction of alternative agents for paediatric sedation has led to the re-evaluation of phenothiazines as paediatric sedatives. Newer agents, such as fentanyl and midazolam, have short half-lives and reversal agents are available. Therefore these agents may offer comparable therapeutic efficacy with a better safety profile in young children. Reports of sudden infant death syndrome in children receiving a phenothiazine-containing syrup for symptoms of upper respiratory infection means that the outpatient use of these compounds in very young infants is not recommended.

Phenothiazine drugs have a variety of clinical uses as antipsychotics, antiemetics and hypnosedatives. They are also useful in combating vertigo, migraine headaches, hiccups, various movement disorders and for treating motion sickness. They have also been marketed for the treatment of nasopharyngitis in some European countries and have been included in some cough syrups. More recently, their usefulness as first-line hypnosedative drugs in children has been challenged by the advent of newer medications such as benzodiazepines, opioids and others. In this review we consider the pharmacotoxicology of phenothiazines within the context of paediatric sedation and the evidence upon which clinical decision-making should rest with regard to this paediatric indication.

1. Pharmacotherapy for Paediatric Sedation

1.1 Historical Context

The importance of effective paediatric sedation has long been recognised by physicians who need the child's passive cooperation for many tests, procedures, and therapies. Chloral hydrate, which was first synthesised in 1832 and used as a hypnotic agent in 1869 by Liebreich, has fulfilled this need for more than 130 years.[1] Chlorpromazine was the first phenothiazine discovered in 1952, and quickly became a commonly used drug for diseases other than schizophrenia when its antiemetic and sedative properties were realised. Barbiturates were also introduced as early hypnosedative agents for children, along with opioids. Such nonbarbiturate sedatives as glutethimide, methaqualone, methyprylon, meprobamate and ethchlorvynol became popular in the 1960s and 1970s; however the use of such agents in children was limited.

The introduction of chlordiazepoxide in 1961, with the subsequent addition of many drugs within the chemical class of benzodiazepines thereafter, has constituted a major advance in childhood sedation. The first US guidelines on paediatric sedation were published jointly in 1985 by the American Academy of Pediatric Dentistry and the American Academy of Pediatrics, and later revised in 1992.[2-4] An important component of these recommendations addresses the safety concerns in monitoring the cardiovascular and neurological status of the young child who is receiving drugs for sedation during medical or surgical procedures.

1.2 Pharmacological Alternatives for Paediatric Sedation

There are several drug classes besides phenothiazines that are available for sedating children (table I). The benzodiazepines are probably most commonly used for this indication. Newer agents, such as midazolam, have rapid onset, a short duration of action, a good safety profile and are readily reversible using the receptor antagonist flumazenil. Chloral hydrate has long been used for paediatric sedation and many clinicians are comfortable using this drug for outpatient paediatric procedures such as electroencephalography (EEGs), radiological studies and other tests that require a passive participant. Fentanyl combines sedative actions with analgesia and has been used for painful outpatient surgery and emergency department procedures.[5] In a comparative study of intranasal sufentanil and midazolam with intramuscular pethidine (meperidine), promethazine and chlorpromazine ('DPT'), Bates and colleagues[6] found that intranasal sufentanil-midazolam is as effective as pethidine-promethazine-chlorpromazine. In addition, time to discharge from the emergency department was longer in the group who received pethidine-promethazine-chlorpromazine.

2. Use of Phenothiazine Sedation in Children

2.1 Current Paediatric Indications for Phenothiazines

The phenothiazines were once the most important class of antipsychotic (neuroleptic) agents because of their actions on dopamine D_2 receptors and serotonin (5-hydroxytryptamine; 5-HT) receptors; both these neurotransmitters are thought to be related to the genesis of psychosis. Recently their

Table I. Drugs used in paediatric sedation

Drug	Class	Route	Adverse effects	Cost	Antidote
Chloral hydrate	Chloral derivative	Oral, rectal	Oversedation, respiratory depression, hypotension, sensitised myocardium, mutagenesis?	Low	No
Chlorpromazine	Phenothiazine	Intravenous, intramuscular, oral	Oversedation, extrapyramidal effects, acute dystonia, oculogyric crisis, anticholinergic effects, neuroleptic malignant syndrome, cardiotoxicity, sudden infant death syndrome	Low	No
Fentanyl	Opioid	Intravenous, transdermal, nasal	Oversedation, respiratory depression, rigid chest syndrome	High	Yes
Ketamine	Arylcyclohexylamine	Intravenous	Salivation, laryngospasm	High	No
Midazolam	Benzodiazepine	Intravenous, intramuscular, oral, nasal	Oversedation, respiratory depression, laryngospasm	Fairly high	Yes
Promethazine	Phenothiazine	Intravenous, intramuscular, oral	Oversedation, respiratory depression, extrapyramidal effects, acute dystonia, oculogyric crisis, anticholinergic effects, neuroleptic malignant syndrome, sudden infant death syndrome	Low	No

use for psychiatric disorders has been complemented by the introduction of 'atypical' antipsychotic agents, such as clozapine, olanzapine and risperidone, which have more specific actions on serotonergic receptors.

Besides sedation, phenothiazines may also be used in paediatric practice as antiemetic agents,[7] for migraine headaches,[8] in the treatment of movement disorders in autistic children,[9] and for behavioural disorders in children.[10] The use of chlorpromazine to relieve symptoms of withdrawal among neonates born to heroin-abusing mothers has also previously been described.[11] All of these indications for phenothiazines may take advantage of their other pharmacological actions (e.g. anticholinergic, antihistaminergic and α-adrenergic blocking properties).

The combination of pethidine, promethazine and chlorpromazine will be familiar to any clinician who has evaluated options for sedating a child for an emergency procedure such as suturing a laceration. In many paediatric emergency medicine centres, outpatient dental clinics, sleep and EEG laboratories, and radiology and imaging suites, sedation options more often include the use of short-acting opioids, chloral hydrate and/or benzodiazepines. In paediatric practice the introduction of promethazine-containing cough suppressants shed light on the use of phenothiazines in the very young child; unfortunately this uncovered induced sleep apnoea and, possibly, sudden infant death syndrome[12-16] which will be discussed in section 3.5.

2.2 Pharmacology

The phenothiazine class can be subdivided based on structure, and most of the structural divisions are related to the changing side chains on the tenth ring position. The phenothiazines are divided into aliphatic, piperazine and piperidine subclassifications (table II). Common members of the aliphatic group include chlorpromazine and promethazine; the piperazine group includes fluphenazine, perphenazine and prochloroperazine; the piperidine group includes mesoridazine and thioridazine. The different structural classes are associated with differential potencies of pharmacological effects, although there is great variability among the individual drugs in each class. For example, the piperidine group is associated with adverse cardiac effects, especially in the setting of overdose, and drugs in

Table II. Structural classes of phenothiazines

Aliphatic class
Chlorpromazine
Cyamemazine
Triflupromazine
Promethazine
Trimeprazine
Promazine
Methoxypromazine
Piperazine class
Acetophenazine
Fluphenazine
Perphenazine
Prochlorperazine
Trifluoperazine
Thiethylperazine
Thiopropazate
Piperidine class
Mesoridazine
Thioridazine
Pipamazine
Piperacetazine
Other related compounds
Butyrophenones
Haloperidol
Droperidol
Thioxanthenes
Chlorprothixene
Thiothixene
Zuclopenthixol

the piperazine group cause more extrapyramidal effects. Although drugs in the aliphatic group have lower antipsychotic potency than those in the piperazine class, they are associated with greater sedative and antiemetic effects. Both the aliphatic and piperidine classes of phenothiazines are more often associated with hypotensive effects, especially when taken in overdose.

This differential activity of the phenothiazines is related to the individual affinity of each drug for the various receptors on which they act: histaminergic, α-adrenergic, muscarinic, serotonergic and dopaminergic.[17] All the agents in the phenothiazine class differ in affinity for the dopamine D_2 receptor as well as in their adrenergic, muscarinic and serotonergic receptor affinity. Antagonism of the dopamine receptor in the postrema at the chemoreceptor trigger zone gives these agents their antiemetic properties. Peripheral α-adrenergic blockade may result in hypotension. Quinidine-like effects on the cardiac conduction system are associated with negative inotropism and conduction delays. Most of the phenothiazines are H_1 histamine antagonists and possess considerable antimuscarinic affinity. Drugs that are antagonists for the histamine receptors are associated with sedation; those that show antagonism for the muscarinic receptors are associated with anticholinergic effects.

2.3 Pharmacokinetics

Most of the extensive kinetic studies have been carried out on the prototypical phenothiazine, chlorpromazine. For brevity some generalisations will be made. Phenothiazines as a class are well absorbed drugs, although they generally have poor bioavailability with extensive tissue binding to gastrointestinal receptors and a large first-pass effect through the liver. As a class they are characterised by extensive plasma protein binding and complex hepatic metabolism, with up to 100 identified metabolites. High lipid solubility contributes to the parent drug and its metabolites being distributed into many peripheral compartments, including the brain, so that its apparent volume of distribution is large.[18] In a child with a proportionally lower amount of body fat this may be a factor in distribution of the drug. Phenothiazines will also cross the placenta and potentially pose a risk to the fetus.[8] The typical elimination half-life of these drugs is of the order of 20 to 40 hours.[18] Although most of the kinetic studies on this class of drugs has been in adults, in the neonatal population distribution and metabolism may be affected by immature hepatic metabolism, especially in the premature neonate.[19]

3. Adverse Effects

3.1 Drug Interactions

Phenothiazines may act to enhance the sedative effects of such drugs as antihistamines, tricyclic

antidepressants, opioids or other drugs with sedating characteristics. This may result in effects ranging from excessive sleepiness to respiratory depression. Drugs with anticholinergic effects, such as antihistamines and tricyclic antidepressants, may also have additive effects on the phenothiazines. Anticholinergic drugs may delay the absorption of phenothiazines as well as producing more anticholinergic symptoms. Tricyclic antidepressants, which are utilised in the treatment of many paediatric disorders such as enuresis, attention deficit hyperactivity disorder, depression and chronic pain, may enhance the cardiotoxicity of phenothiazines such as thioridazine, resulting in cardiac dysrhythmias. The coadministration of lithium with a phenothiazine agent may predispose the patient to neuroleptic malignant syndrome. Phenothiazines, like all drugs with extensive hepatic metabolism, can compete with the sites of metabolism for other drugs such as anticonvulsants. Barbiturates, conversely, may lower blood phenothiazine concentrations by virtue of their induction of the cytochrome P450 enzyme complex.

3.2 Neuroleptic Malignant Syndrome

Although this potentially fatal complication of phenothiazines is rare, its lethality and the difficulty in diagnosing neuroleptic malignant syndrome warrant the clinician's close attention. The incidence of this complication of antipsychotic therapy is estimated at approximately 0.2%, although the diagnosis can be missed and attributed to other aetiologies such as infection.[20,21] When phenothiazines are used in lower dosages in a controlled psychiatric setting, the incidence of neuroleptic malignant syndrome may be as low as 0.07%.[22]

Neuroleptic malignant syndrome can develop over the course of days and is characterised by extreme muscle rigidity, fever, autonomic instability and change in consciousness. Patients on long-acting phenothiazines may be at greater risk.[23] Other risk factors for neuroleptic malignant syndrome include male gender, dehydration, psychomotor agitation or exhaustion, higher phenothiazine dosages and parenteral administration. Although seen at all stages of phenothiazine use, neuroleptic malignant syndrome is most common in the first 2 weeks of therapy.[24] Laboratory analysis of blood demonstrates an elevated creatinine kinase in the majority of patients.[25]

Neuroleptic malignant syndrome has been described with all the phenothiazines. Several proposed mechanisms have been put forward as to its aetiology. The effects of dopamine blockade on the hypothalamus and substantia nigra have been implicated in the production of rigidity and fever seen in neuroleptic malignant syndrome.

Intensive supportive care in preventing the complications of the condition such as airway compromise and renal failure have assisted in decreasing the lethality of this condition. Such supportive care includes vigorous external cooling methods and iced lavage of the stomach, bladder or rectum, with serial monitoring of core body temperature. Other interventions that have been utilised including dantrolene sodium, a phenytoin derivative that inhibits calcium release from the sarcoplasm and thereby interferes with the muscular contractions thought to be involved in the genesis of the elevated body temperature. Centrally acting dopamine agonists, such as bromocriptine, amantadine and levodopa/carbidopa, have also reportedly been successful in reversing the hyperthermia associated with this syndrome.[26]

3.3 Dystonic Reactions and Extrapyramidal Dyskinesias

Acute dystonic reactions and other extrapyramidal effects are seen with all antipsychotics, although more frequently with those containing a piperazine moiety substitution on the basic ring structure. Akathisias or hypokinesias are uncommon extrapyramidal effects in paediatric patients receiving a phenothiazine in therapeutic dosages. Dystonic reactions are very distressing to the patient, but the rare fatalities are typically associated with pharyngeal muscle spasm. The typical presentation of a patient with dystonia is a young person with spasmodic contractions of the upper trunk and

head with a sustained severe torticollis. Eye movements can also be affected separately, causing the so-called 'oculogyric crisis'. Gupta and Lovejoy[27] described in a paediatric population that acute dystonic reactions occurred between 5 and 50 hours of the first dose of phenothiazine. Those with a family history of dystonia appear to be at increased risk. The balance of dopamine and acetylcholine when disrupted appears to cause an excess of cholinergic activity and predispose to dystonias.[28] It has also been postulated that adaptation of the nervous system to post-synaptic dopaminergic blockade results in overcompensation and increased amounts of synaptic dopamine.[29,30] Clinically, 5 different types of dystonic reactions have been described: oculogyric (superiorly directed gaze and eye rotation), buccolingual (tongue protrusion, grimacing, trismus), opisthotonic (arched back, rigid posturing), torticollic (contraction of sternocleidomastoid muscle), and tortipelvic (abdominal wall spasm, abnormal gait).[31]

Acute dystonias are treated with an anticholinergic agent such as diphenhydramine or benzatropine. Respiratory monitoring is necessary because of the possibility of laryngeal spasm requiring airway support. In some children with autism, as pointed out by Meiselas et al.,[9] there is the potential for diagnostic confusion between what constitutes stereotypies secondary to the underlying developmental disorder and what may be the manifestations of an antipsychotic-induced dyskinesia. Good supportive care and close monitoring are other aspects of the management of dystonia, which may recur without prolonged antidote administration.[31]

3.4 Other Adverse Reactions

The adverse effect profile of an individual phenothiazine agent may relate to its relative affinities for the different neurotransmitter receptors responsible for its pharmacological actions.[17] Individuals would be expected to demonstrate a range of these affinities which, along with varying pharmacokinetics and hepatic enzyme induction patterns,[32] are thought to account for variable sensitivity to adverse effects and are probably under genetic control. All phenothiazines have associated anticholinergic adverse effects because of their binding at muscarinic receptor sites. Anticholinergic signs and symptoms include sedation, dry mouth, mydriasis, urinary retention, ileus, delirium and hallucinations. Phenothiazines all lower the seizure threshold in a dose-related fashion. In all patients, including adults and those patients with psychiatric indications, phenothiazine use is associated with seizures at an incidence of 1.2%.[33-36]

The preparation of pethidine, promethazine and chlorpromazine is frequently used for the sedation of children undergoing painful procedures. Terndrup et al.,[37] in a prospective analysis of 63 paediatric emergency patients receiving sedation for procedures such as laceration repair, found minor but statistically significant changes in respiratory rate, oxygen saturation and heart rate. None of these patient required resuscitation. Nahata et al.,[38] in a larger prospective sample of 95 paediatric patients, found 4 patients who developed respiratory depression, 1 requiring therapy with naloxone. None of the children in this series had been administered more than the recommended dose of this combination. In a survey of paediatric emergency medicine programmes on the issue of sedation, Cook et al.[39] found chloral hydrate as the most commonly used drug and the combination of pethidine, promethazine and chlorpromazine as the second most commonly utilised sedative. They reported 2 paediatric deaths in infants undergoing cardiac catheterisation with pethidine-promethazine-chlorpromazine sedation. Both infants had congenital heart disease. However this study is hampered by the low (31%) return rate of their questionnaire.

Gupta and Lovejoy[27] described drowsiness, irritability, ataxia, thick speech, drooling, torticollis, trismus, oculogyric crisis, convulsions, dystonia, hyper-reflexia, rigidity, and/or tremors in 20 different children, 13 of whom experienced these toxic reactions after therapeutic doses of prochlorperazine, chlorpromazine, trifluoperazine or promazine. Dystonic reactions were reported in 4 children after

therapeutic doses of thiethylperazine used as an antiemetic.[7]

Phenothiazines have quinidine-like effects on the cardiac conduction system, causing nodal conduction delays through and delayed ventricular repolarisation, which is manifest as prolonged PR intervals, prolonged QTc intervals, flattened or biphasic T waves, and attendant dysrhythmias in patients who have overdosed on these medications. Postural hypotension is frequently seen as a adverse effect of phenothiazine use. More serious life-threatening cardiotoxicity associated with phenothiazine use includes ventricular arrhythmias. Thioridazine in particular has been associated with arrhythmias, which may degenerate into the polymorphic ventricular tachycardia known as torsade de pointes.

Other less common adverse effects of phenothiazines in susceptible individuals include photosensitivity reactions (dermatitis, urticaria, purple-grey discolouration of the skin) and other rashes. Hepatitis with cholestasis, bile duct damage and fibrosis has been described; other gastrointestinal symptoms including nausea, vomiting and gastritis are sometimes seen.[40] Marrow suppression with severe but reversible neutropenia and blood dyscrasias have also been observed. Galactorrhoea, menstrual difficulties and bodyweight gain have been reported. Priapism in an adult taking fluphenazine was reversed using intravenous diphenhydramine.[41] Pigmentary retinopathy has been described in patients on thioridazine, and lenticular deposits were associated in rare cases with aliphatic phenothiazine use.[40] A case of a lupus-like syndrome also has been reported after aliphatic phenothiazine use.[40]

3.5 Phenothiazines, Sleep Apnoea and Sudden Infant Death Syndrome

Kahn and Blum[13] described their experience with the death of 4 male children (mean age 14 weeks) receiving a syrup containing the phenothiazine alimenazine (3 children received the medication for nasopharyngitis, 1 as a somnolent). All children had no obvious cause of death. The same investigators followed this observation with a prospective study of 52 cases of sudden infant death syndrome, 36 'near-miss' infants and 176 control children. They found that although the incidence of nasopharyngitis was similar in all groups the use of phenothiazines was more common in the sudden infant death syndrome group (23%) and the 'near-miss' group (22%) as compared with control individuals (2%).[12]

A study of healthy infants without personal or family history of sudden infant death syndrome who received promethazine while monitored found on the second of 6 nights of observation an increase in the number of episodes of central apnoea in addition to several episodes of obstruction apnoea.[14] Several possible mechanisms have been postulated. These include: (i) worsening of central apnoea from central nervous system depression with pre-existing nasopharyngitis; (ii) enhancement of REM sleep; (iii) muscle hypotonia;[14] (iv) impairment of thermoregulation from the anticholinergic actions of phenothiazines;[15] and (v) enhancement by phenothiazine of peripheral and central endorphin levels.[42] In light of the above considerations, the use of phenothiazine-containing cough and cold preparations in children under 2 years of age should be discouraged.

4. Phenothiazine Overdose

4.1 Epidemiology

One of the risks with any sedative is the potential for poisoning, either by iatrogenic errors in the hospital setting or unintentional or intentional poisonings occurring at home. Phenothiazines have a sufficiently narrow therapeutic : toxic dose ratio to make the potential for severe, life-threatening overdoses a valid concern, especially among young children who may have an exaggerated toxic response to these compounds.

The American Association of Poison Control Centers (AAPCC) reported 11 065 toxic exposures to phenothiazine sedatives in 1997, 1965 of which involved preschoolers <6 years of age and 1622 involved children 6 to 19 years old. Of the total

poisonings (adults + children), 7274 events were treated at a healthcare facility, 2116 poisonings resulted in moderate-to-major toxicity, and 14 resulted in death.[43] The data set from the AAPCC in 1996 included 1 death from promethazine in a 7-month-old reportedly caused by a therapeutic error.[44]

4.2 Clinical Toxicology

The clinical syndromes described in section 3 of this review (neuroleptic malignant syndrome, dystonic reactions, oculogyric crisis) can all be seen in the phenothiazine-poisoned patient. Most commonly, symptoms include depressed consciousness to the point of coma and other neurological abnormalities. Disturbances of body temperature (either fever or hypothermia) are common. The triad of coma, prolonged QTc interval and pupillary meiosis (due to adrenergic blockade) should raise the clinician's suspicion of phenothiazine poisoning. Extrapyramidal effects are seen commonly, including akathisias, acute dystonic reactions, tardive dyskinesias and parkinsonian syndromes (less common in children than adults). In 1 series of 30 children with an acute overdose of phenothiazines, 20 exhibited oculogyric crisis, 23 had torticollis, 22 had athetoid movements, 19 had opisthotonic posturing and 18 had facial grimacing.[45] In the series of Gupta and Lovejoy,[27] 7 children had accidentally ingested a phenothiazine and experienced neurological toxicity including tremors, ataxia, irritability, hyper-reflexia, opisthotonus, rigidity and/or drowsiness.

4.3 Diagnosis

Most often the diagnosis of phenothiazine poisoning is made in a patient who presents with symptoms referrable to the neurological system and a known history of access to phenothiazine medications. Therapeutic misadventures must be entertained in the circumstance of the patient who develops a dystonia while hospitalised or being treated by several different specialists who unintentionally 'stack' different phenothiazine compounds for differing indications in the same patient: 1 service may be treating pain, another the patient's symptoms of nausea and vomiting, and a third their psychiatric disorder.

Some phenothiazine tablets (e.g. chlorpromazine) can be seen radiographically in a scout film of the abdomen.[46] The diagnosis can be confirmed by laboratory methods. Phenothiazines can be detected in the urine using colourimetric techniques – the 'Forrest' reaction uses ferric chloride, perchloric acid and nitric acid which turns urine containing phenothiazines a pinkish to purple colour.[47] Quantitative blood concentrations can be obtained by high performance liquid chromatography in patients whose screening urine test is positive.

4.4 Management

The patient with a recent phenothiazine ingestion in overdose can be given activated charcoal as a decontamination measure. Charcoal binds to all of the phenothiazine compounds with good avidity, so that the complexed drug is eliminated in the stool rather than absorbed into the blood stream.

A patient who presents to the emergency department with an unknown poisoning, in which the clinical signs resemble an acute dystonic reaction or oculogyric crisis, can be given a diagnostic trial of intravenous diphenhydramine, benzatropine or trihexyphenidyl. These antidotes will promptly reverse the reaction and thereby help confirm the diagnosis of poisoning.

The patient known to be exposed to phenothiazines who develops dysautonomia, changed consciousness, muscle tremors and rigidity, elevated creatine kinase and altered consciousness should be administered dantrolene to counteract the neuroleptic malignant syndrome and should be managed using the supportive measures for neuroleptic malignant syndrome described in section 3.2.

5. Conclusions

Phenothiazine compounds are characterised by their common core ring structure, but contain different side chains and substituted chemical structures that influence their pharmacological actions.

Selected phenothiazine drugs, such as chlorpromazine or promethazine, may be used by clinicians for their desired sedative properties in children. They do have advantageous efficacy and cost characteristics and are not known to have latent toxicities such as mutagenesis or carcinogenesis. However, the pharmacokinetics of these agents mean that the induced sedation can be prolonged.

Because of the multiple pharmacological effects of the phenothiazines on several broad classes of neurotransmitters, their use is attended by a high frequency of short-term adverse effects. Several specific syndromes of acute toxicity, notably extrapyramidal adverse effects (particularly dystonic reactions), the neuroleptic malignant syndrome and the potential for cardiotoxicity, may occur even at therapeutic dosages. Several of these toxicities, including neuroleptic malignant syndrome, sleep apnoea and cardiac conduction problems, can be life-threatening. Moreover, phenothiazines do not have a specific antidote capable of reversing such adverse effects as over-sedation or cardiotoxicity, although neuroleptic malignant syndrome may respond to dantrolene and acute dystonic reactions usually resolve with diphenhydramine.

Newer choices for sedation, such as synthetic opioid compounds (e.g. fentanyl) or benzodiazepines (e.g. midazolam), and even some of the older agents, such as chloral hydrate or the barbiturates, may offer comparable therapeutic efficacy with a better safety profile in young children. The outpatient use of phenothiazine-based drugs in very young infants is not recommended because of the association of these compounds with sudden infant death syndrome.

References

1. Sing K, Erickson T, Amitai Y, et al. Chloral hydrate toxicity from oral and intravenous administration. J Toxicol Clin Toxicol 1996; 34: 101-6
2. Committee on Drugs, American Academy of Pediatrics. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 1985; 76: 317-21
3. Committee on Drugs, American Academy of Pediatrics. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 1992; 89: 1110-5
4. Wilson S, Creedon RL, George M, et al. A history of sedation guidelines: where we are headed in the future? Pediatr Dent 1996; 18: 194-9
5. Chudnofsky CR, Wright SW, Dronen SC, et al. The safety of fentanyl use in the emergency department. Ann Emerg Med 1989; 18: 635-9
6. Bates BA, Schutzman SA, Fleisher GR. A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. Ann Emerg Med 1994; 24: 646-51
7. Lacouture PG, Mitchell AA, Lovejoy FH. Thiethylperazine (Torecan)-associated dystonic reactions in children. Pediatrics 1979; 64: 954-5
8. Graf WD, Riback PS. Pharmacologic treatment of recurrent pediatric headache. Pediatr Ann 1995; 24 (9): 477-84
9. Meiselas KD, Spencer EK, Oberfield R, et al. Differentiation of stereotypies from neuroleptic-related dyskinesias in autistic children. J Clin Psychopharmacol 1989; 9: 207-9
10. Weizman A, Weitz R, Szekely GA, et al. Combination of neuroleptic and stimulant treatment in attention deficit disorder with hyperactivity. J Am Acad Child Psychiatr 1984; 23 (3): 295-8
11. Kahn EJ, Neumann LL, Polk GA. The course of the heroin withdrawal syndrome in newborn infants treated with phenobarbital or chlorpromazine. J Pediatr 1969; 75: 495-500
12. Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. Pediatrics 1982; 70 (1): 75-8
13. Kahn A, Blum D. Possible role of phenothiazines in sudden infant death [letter]. Lancet 1979 Aug; 18: 364
14. Kahn A, Blum D. Phenothiazine-induced sleep apneas in normal infants. Pediatrics 1985; 75 (5): 844-7
15. Stanton AN. Sudden infant death syndrome and phenothiazines [letter]. Pediatrics 1983; 71 (6): 986
16. Buck ML, Blumer JL. Phenothiazine-associated apnea in two siblings. DICP 1991; 25: 244-7
17. Richelson E. Neuroleptic affinities for human brain receptors and their use in predicting adverse effects. J Clin Psychiatr 1984; 45: 331-6
18. Wampler G. The pharmacology and clinical effectiveness of phenothiazines and related drugs for managing chemotherapy-induced emesis. Drugs 1993; 25 Suppl. 1: 35-51
19. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. Clin Pharmacokinet 1996; 31 (6): 423-43
20. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am 1993; 77 (1): 185-202
21. Caroff SN, Mann SC, Lazarus A, et al. Neuroleptic malignant syndrome: diagnostic issues. Psychiatr Ann 1991; 21: 130-47
22. Gelenberg AJ, Bellinghausen B, Wojcik JD, et al. A prospective survey of neuroleptic malignant syndrome in a short-term psychiatric hospital. Am J Psychiatr 1988; 145: 517-8
23. Legras A, Hurel D, Dabrowski G, et al. Protracted neuroleptic malignant syndrome complicating long-acting neuroleptic administration. Am J Med 1988; 85: 875-8
24. Addonizio G, Susman UL, Roth SD. Neuroleptic malignant syndrome: a review and analysis of 115 cases. Biol Psychiatr 1987; 22: 1004-20
25. Heiman-Patterson TD. Neuroleptic malignant syndrome and malignant hyperthermia - important issues for the medical consultant. Med Clin North Am 1993; 77: 477-91
26. Martin ML, Lucid EJ, Walker RW, et al. Neuroleptic malignant syndrome. Ann Emerg Med 1985; 14: 354-8
27. Gupta JM, Lovejoy FH. Acute phenothiazine toxicity in childhood: a five-year survey. Pediatrics 1967; 39: 771-4

28. Rupniak NMJ, Jenner P, Marsden CD. Acute dystonia induced by neuroleptic drugs. Psychopharmacol 1986; 88: 403-19
29. Koble H, Clow A, Jenner P, et al. Neuroleptic-induced acute dystonic reactions may be due to enhanced dopamine release on to supersensitive postsynaptic receptors. Neurology 1981; 31: 434-9
30. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side-effects of neuroleptic drugs. Psychol Med 1980; 10: 55-72
31. Corre KA, Niemann JT, Bessen HA. Extended therapy for acute dystonic reactions. Ann Emerg Med 1984; 13: 194-7
32. Wright JH, Whitaker SB, Welch CB, et al. Hepatic enzyme induction patterns and phenothiazine side effects. Clin Pharmacol Ther 1983; 34: 533-8
33. Cold JA, Wells BG, Froemming JH. Seizure activity associated with antipsychotic therapy. DICP 1990; 24: 601
34. Logothetis J. Spontaneous epileptic seizures and electroencephalographic changes in the course of phenothiazine therapy. Neurology 1967; 17: 869-77
35. Marks RC, Luchins DJ. Antipsychotic medications and seizures. Psychiatr Med 1991; 9: 37-52
36. Shaw EB, Dermott RV, Lee R, et al. Phenothiazine tranquilizers as a cause of severe seizures. Pediatrics 1959; 23: 485-491
37. Terndrup TE, Dire DJ, Madden CM, et al. A prospective analysis of intramuscular meperidine, promethazine, and chlorpromazine in pediatric emergency department patients. Ann Emerg Med 1991; 20 (1): 31-5
38. Nahata MC, Clotz MA, Krogg EA. Adverse effects of meperidine, promethazine, and chlorpromazine for sedation in pediatric patients. Clin Pediatrics 1985; 24 (10): 558-60
39. Cook BA, Bass JW, Nomizu S, et al. Sedation of children for technical procedures: current standard of practice. Clin Pediatr 1992; Mar: 137-42
40. Anonymous. Med Lett Drugs Ther 1991; 33: 43-50
41. Fishbain DA. Priapism resulting from fluphenazine hydrochloride treatment reversed by diphenhydramine. Ann Emerg Med 1985; 14: 600-2
42. Sandyk R. Phenothiazine-Induced sleep apneas and the opioid system [letter]. Pediatrics 1986; 77 (22): 261
43. Litovitz TL, Klein-Schwartz W, Dyer KS, et al. 1997 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1998; 16: 443-97
44. Litovitz TL, Smilkstein M, Felberg L, et al. 1996 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1997; 15: 447-500
45. Duffy B. Acute phenothiazine intoxication in children. Med J Aust 1971; 676-8
46. Barry D, Meyskens FL, Becker CE. Phenothiazine poisoning – a review of 48 cases. Calif Med 1973; 118: 1-5
47. Forrest IS, Forrest FM. Urine color test for the detection of phenothiazine compounds. Clin Chem 1960; 6: 11-5

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