Drug Class Review

Sedative Hypnotic Barbiturates in Procedural Sedation

28:24.04 Barbiturates

Amobarbital (Amytal®)
Methohexital (Brevital® Sodium)
Secobarbital (Seconal®)
Thiopental (Pentothal®)

Final Report
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Executive Summary

Introduction: There are nine barbiturate agents currently available for use in the United States: amobarbital, butabarbital, butalbital, methohexital, pentobarbital, phenobarbital, primidone, secobarbital, and thiopental. Barbiturates are referred to as sedative-hypnotic agents and have a number of different therapeutic uses including treatment of: anxiety, headache, insomnia, seizure disorders, and for preoperative sedation or general anesthesia. This review focuses on barbiturate use in procedural sedation/anesthesia. Four of the nine available barbiturates are available in oral formulations and are approved for the treatment of insomnia: amobarbital, methohexital, secobarbital, and thiopental.

Procedural Sedation: Surgical procedures require a sedative agent or anesthetic which produces changes in the patient's perception resulting in an anesthetic state. Procedural anesthesia is usually carried out by a general anesthetic and adjunctive agents. General anesthetics are parental or inhaled and can produce anesthesia within a single circulation time. Anesthetic adjuncts augment anesthesia and allow for lower doses of the general anesthetic to reduce side effects. Barbiturates may be used for general anesthesia. The barbiturates most frequently used in the procedural sedation are thiopental and methohexital.

Clinical Efficacy: No comparative clinical trials evaluating the barbiturates in procedural sedation are available. Some placebo-controlled evidence is available. According to the data, barbiturate agents are more effective than placebo. Many trials comparing the barbiturates to propofol or benzodiazepines demonstrate similar sedative efficacy but higher rates of adverse events for the barbiturate treatment groups.

Special Populations: Clinical evidence evaluating the use of barbiturates in pediatrics, geriatric patients, or patients with a history of substance abuse is available. Barbiturate use in neonates, infants, and children requires special care because of the differences in pharmacokinetic and pharmacodynamic characteristics in these patient populations. Older adults are at increased risk of experiencing adverse events with barbiturate use as a result of the potentially reduced ability to metabolize and remove the drug. Patients with a history of substance abuse are also at an increased risk for inappropriate use of the drug. Overall, evidence suggests barbiturate use should be avoided in these patient populations.

Adverse Drug Reactions: The barbiturates are associated with many, potentially serious adverse events. The most common drug-related adverse event reported with barbiturate use is CNS depression. Short-term administration of barbiturates has little to no effect on the hepatic or renal systems. Barbiturate agents are highly toxic in acute overdose and may result in death. Many drug interactions are associated with the barbiturate agents because they can potentiate sedation of other agents, competitively inhibit the metabolism of some drugs, or increase the rate of hepatic clearance of some drugs. Barbiturates are contraindicated in patient with dyspnea or airway obstruction and porphyria and should be used with caution in patients with severe liver or renal disease.

Summary: The barbiturate agents are used as general anesthetics in procedural sedation. Barbiturates have narrow therapeutic indexes and their use is limited. The barbiturate agents indicated in procedural sedation/anesthesia include amobarbital, methohexital, secobarbital, and thiopental. No comparative clinical trials or meta-analyses evaluating the oral barbiturate agents in procedural sedation are available for evaluation. Some placebo-controlled evidence suggests barbiturate agents are more effective than placebo. Barbiturate use should be avoided in neonatal and geriatric patient populations. The barbiturate agents are associated with many, potentially serious adverse events, including CNS depression. Barbiturate agents are highly toxic in acute overdose and frequently result in death. Overall, clinical evidence is limited and use of barbiturate agents in procedural sedation is declining.

Introduction

A number of pharmacologic agents belong to the drug class referred to as sedative-hypnotic agents. Sedative-hypnotic agents work to induce a calming or sedating effect by depressing the central nervous system (CNS).[1] Sedative-hypnotic agents available in the United States include barbiturates, benzodiazepines, and some newer anti-insomnia agents with unique chemical structures. This review focuses on barbiturates. Nine oral and parenteral barbiturate agents are currently available for use in the United States: amobarbital, butabarbital, butalbital, methohexital, pentobarbital, phenobarbital, primidone, secobarbital, and thiopental.[2-4] Table 1 compares all of the barbiturate agents.

Barbiturates have been around since the early 1900s and were once used extensively as sedative-hypnotic drugs.[5] In the late 1950's, the introduction of the new, safer benzodiazepine agents led to a steep decline in barbiturate use.[5] Today, except for a few specialized uses (neonatal seizure disorder or anesthesia), the barbiturates are rarely used.[3-5] Barbiturates are available in oral, intravenous (IV) and intramuscular (IM) formulations and have a number of different therapeutic uses including treatment of: anxiety disorders, headache, insomnia, seizure disorders, and for preoperative sedation or general anesthesia.[3, 4] This review will focus on barbiturate use in procedural sedation/anesthesia. Four of the nine available barbiturates are approved for the treatment of insomnia: amobarbital, methohexital, secobarbital, and thiopental.

Disease Overview

Surgical procedures usually require an immobilized patient who experience amnesia for the procedure.[6] Amnesia for a surgical procedure is accomplished by a sedative agent or anesthetic which produces changes in the patient's behavior or perception resulting in an anesthetic state. These changes in behavior may include amnesia, absence of psychological or autonomic responses to noxious stimulation, analgesia, and/or unconsciousness. General anesthetics are usually parental or inhaled and can produce anesthesia within a single circulation time. Blood concentration levels then fall rapidly as the drug is redistributed out of the CNS and back into the blood. The characteristics of a successful anesthetic include one which produces a state of anesthesia, minimizes any indirect/adverse effects, maintains physiological homeostasis, and improves postoperative outcomes.[6]

Procedural anesthesia is usually carried out by a general anesthetic and adjunctive agents.[6] General anesthetic agents include: barbiturates, propofol, etomidate, ketamine, and a number of inhalation anesthetics.[3, 4] A general anesthetic is usually accompanied by an anesthetic adjunct to augment anesthesia and allow for lower doses of the general anesthetic to reduce side effects. Adjunct agents include: benzodiazepines, alpha-2 adrenergic receptor agonists, analgesics, and neuromuscular blocking agents.[3, 4] Barbiturates are not frequently used anesthetics because of their adverse event profiles.[7] Barbiturates have slow elimination and large volumes of distribution which can result in unconsciousness lasting several days.[6] When used, the barbiturates most frequently used in procedural sedation are thiopental and methohexital.[6, 7] Amobarbital and secobarbital may also be used but much less frequently.[6]

Table 1. Comparison of Barbiturate Agents[3, 4]

Product	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	$t_{½}$, hours	Active Metabolite(s)	Generic Available
Amobarbital (Amytal®)	IM, IV	Injection solution: 0.5 g	Short-term treatment of insomnia, anxiety, and to provide preoperative sedation.	Use in therapeutic or diagnostic "Amytal® Interviewing" or Wada test	30-200 mg 1-3 times/day (max dose: 1000 mg)	15-40	Yes	No
Butabarbital (Butisol Sodium®)	Oral	Oral elixir: 30 mg/5 mL (480 mL) Oral tablets: 30 mg, 50 mg	For use as a sedative or hypnotic.	N/A	15-30 mg 1-4 times/day	~100		No
Butalbital, Acetaminophen, and Caffeine (Fioricet®, others)	Oral	Oral capsule: 50mg/325mg/40mg, 50mg/500mg/40mg, 50mg/300mg/40mg Oral liquid: 50mg/325mg/40mg per 15 mL (480 mL) Oral tablet: 50 mg/325 mg/40 mg, 50mg/500mg/40mg, 50mg/750mg/40mg	Treatment of tension or muscle contraction headache.	N/A	1-2 doses every 4 hours	35	Yes	Yes: tablet
Butalbital, Acetaminophen, Caffeine, and Codeine (Fioricet® with Codeine)	Oral	Oral capsule: 50mg/325mg/40mg/30mg	Treatment of tension or muscle contraction headache.	N/A	1-2 capsules every 4 hours	35	Yes	Yes
Butalbital and Acetaminophen (Sedapap®, others)	Oral	Oral tablet: 50mg/325mg Oral capsule: 50mg/650mg	Treatment of tension or muscle contraction headache.	N/A	1-2 doses every 4 hours	35	Yes	Yes: tablet
Butalbital, Aspirin, and Caffeine (Fiorinal®)	Oral	Oral capsule: 50mg/325mg/40mg Oral tablet: 50mg/325mg/40mg	Treatment of tension or muscle contraction headache.	N/A	1-2 doses every 4 hours	35	Yes	Yes
Butalbital, Aspirin, Caffeine, and Codeine (Fiorinal® with Codeine)	Oral	Oral capsule: 50mg/325mg/40mg/30mg	Treatment of tension or muscle contraction headache.	N/A	1-2 capsules every 4 hours	35	Yes	Yes
Methohexital (Brevital® Sodium)	IV	Injection solution: 500 mg, 2.5 g	For use in induction of anesthesia or procedural sedation.	For use in Wada test.	0.5-1 mg/kg; may every 2-5 minutes	2-6		No

Pentobarbital (Nembutal®)	IM, IV	Injection solution: 50 mg/mL (20 mL, 50 mL)	For use as a sedative/hypnotic or treatment of refractory status epilepticus.	For use in a barbiturate-induced coma or treatment of increased intracranial pressure.	Hypnotic/sedative: 100-200 mg Status epilepticus: loading: 5-15 mg/kg; maintenance: 0.5-1 mg/kg/hour	15-50		No
Phenobarbital (Luminal®)	IM, IV, Oral	Oral elixir: 20 mg/5 mL (7.5 mL, 15 mL, 473 mL) Injection solution: 65 mg/mL (1 mL); 130 mg/mL (1 mL) Oral tablet: 15 mg, 30 mg, 60 mg, 100 mg	Treatment of generalized tonic-clonic, status epilepticus, and partial seizures OR for use as a sedative/hypnotic.	Treatment of neonatal hyperbilirubinemia, chronic cholestasis, and neonatal seizures.	30-200 mg/day divided Anticonvulsant: loading: 10-20 mg/kg; maintenance: 1-3 mg/kg/day divided	37-140	No	Yes
Primidone (Mysoline®)	Oral	Oral tablet: 50 mg, 250 mg	Treatment of grand mal, psychomotor, and focal seizures.	Treatment of benign familial tremor.	100-125 mg at bedtime and gradually increase to maintenance dose; usual dose: 750-1500 mg/day divided	5-15	Yes	Yes
Secobarbital (Seconal®)	Oral	Oral capsule: 100 mg	For use as a preanesthetic agent or in the short-term treatment of insomnia	N/A	100-200 mg at bedtime	15-40	Yes	No
Thiopental (Pentothal®)	IV	Injection solution: 250 mg, 400 mg, 500 mg, 1 g	For induction of anesthesia or treatment of convulsive states or elevated intracranial pressure	N/A	Anesthesia: induction: 3-5 mg/kg; maintenance: 25-100 mg Intracranial pressure: 1.5-5 mg/kg/dose Seizures: 75-250 mg/dose	3-11.5	Yes	No (no longer available)

Pharmacology

The barbiturate agents work by enhancing gamma-aminobutyric acid (GABA) activity, the major inhibitory neurotransmitter in the CNS, by binding to the barbiturate site at the GABA-receptor complex.[3, 4] This binding interferes with transmission of impulses from the thalamus to the cortex of the brain resulting in depressed CNS activity. All barbiturate agents exert similar clinical effects but differences in their pharmacokinetic profiles result in variations in therapeutic uses and indications.[3, 4]

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2012), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 4/2012, evaluating efficacy of barbiturate agents in procedural sedation. Trials evaluating the barbiturates as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as Wada (language/memory) tests[8-11], anxiety management[12], seizure control[13], product formulations[14, 15] or behavior criteria.[16]
- Individual trials comparing barbiturates in dose-finding studies or in healthy volunteers.
- Individual clinical trials evaluating barbiturate agents or formulations not currently available in the US or clinical trials without access to the full article.

Clinical Efficacy

No comparative clinical trials or meta-analyses evaluating the oral barbiturate agents in procedural sedation/anesthesia are available for evaluation. Lack of comparative clinical data for barbiturates may stem from their approval for use came before 1962 when the Kefauver-Harris Drug Control Act required all drugs be proven both efficacious as well as safe. Some placebo-controlled trials evaluating the barbiturate agents in procedural sedation are available. According to the data, barbiturate agents are more effective than placebo.[15, 17-19] Many clinical trials comparing barbiturates to propofol, etomidate, chloral hydrate, or a benzodiazepine are available. According to these data, the barbiturate agents have similar efficacy when compared to other sedative agents but may also be associated with higher rates of adverse events.[20-28]

- **Are there patient subgroups based on demographics (e.g., age, racial groups, gender) or comorbidities for which one of the barbiturates is more effective or associated with fewer adverse effects?**

Neonates

There is limited evidence available comparing the barbiturates in the pediatric population. Barbiturate use in neonates, infants, and children requires special care because of the differences in pharmacokinetic and pharmacodynamic characteristics in these patient populations. For example, the phenobarbital half-life elimination is 53-140 hours in adults but is 45-500 hours in neonates.[3, 4] This means it takes much longer for the drug to be removed from the body in neonates and can result in increased adverse events. Dosing barbiturates in neonates, infants, and children should be based on weight, gestational age, and blood concentration levels. In addition, infants of mothers physically dependent on barbiturates are at high risk for developing dependency and subsequent withdrawal of the barbiturate resulting in vomiting, tremors, and, potentially, seizures after birth.[29, 30] Barbiturate withdrawal in a new infant is usually treated by administering and gradually decreasing doses of phenobarbital.

Geriatrics

There is limited evidence available comparing barbiturate use in the geriatric population. Older adults are at increased risk of experiencing adverse events with barbiturate use as a result of the potentially reduced ability to metabolize the drug.[3, 4] In addition, barbiturates are potent CNS depressants, have a low therapeutic index, are highly addictive, and are implicated in many drug interactions which can increase the risk of adverse events in this patient population.[31] Data from two large clinical trials demonstrate an increased risk for hip fracture in older patients taking barbiturates.[32, 33] As a result, barbiturates are not recommended for use in the geriatric population unless used for control of seizures.

Patients with a History of Drug/Alcohol Abuse

There is limited evidence available comparing the barbiturates in patients with a history of drug/alcohol abuse. Because these agents are associated with high risk of addiction and overdose can be lethal, these agents should not be used in patients with a history of or high risk for substance abuse.[3, 4]

Adverse Drug Reactions

- **How does the safety of the barbiturates compare with each other?**

The barbiturates are associated with many, potentially serious adverse events. The most common drug-related adverse events reported with barbiturate use are related to CNS depression. CNS effects may include drowsiness, confusion, dizziness, and

headache. Barbiturates can also produce dose-dependent decreases in blood pressure and respiratory depression.[6] Short-term administration of barbiturates has little to no effect on the hepatic or renal systems.[6] Barbiturate agents are highly toxic in acute overdose. Symptoms of an overdose may include sluggishness, incoordination, difficulty in thinking, slowness of speech, impaired judgment, staggering, respiratory depression, coma, and death. Patients who survive barbiturate toxicity may develop renal failure secondary to anoxia. Tolerance to barbiturates can develop quickly (< 2 weeks) and withdrawal occurs in patients who have become physically dependant on the agent. Other adverse events reported with the barbiturates include vertigo, nausea, vomiting, diarrhea, irritability, and paradoxical excitement.

Comparative clinical evidence evaluating the safety of the barbiturates is limited. One study evaluated the frequency of reported adverse reactions to various sedative hypnotic agents in a 1000-bed teaching hospital over a three year period.[34] During this time, no adverse events were reported with pentobarbital use (546 doses dispensed) and only one adverse event (hypersensitivity skin reaction) was reported with phenobarbital use (21,531 doses dispensed). A second study of adverse sedation events reported in pediatric patients found a relatively even distribution of adverse events across the major drug classes (opioids, benzodiazepines, barbiturates, and other sedative/hypnotics).[35] In addition, there are many case reports and review articles documenting the risks associated with long-term use (tolerance, dependence, withdrawal) and overdose (CNS and respiratory depression).

Many drug interactions are associated with the barbiturate agents.[3, 4] Barbiturates can potentiate sedation by other agents, particularly ethanol and benzodiazepines. Barbiturates can also competitively inhibit the metabolism of some drugs (via the P450 system; e.g. CYP 3A4) or increase the rate of hepatic clearance of some drugs with chronic barbiturate use. Barbiturates are contraindicated in patients with dyspnea or airway obstruction and porphyria and should be used with caution in patients with severe liver or renal disease.

Summary

The barbiturate agents are used as general anesthetics in procedural sedation. Barbiturates have narrow therapeutic indexes and their use is limited. The barbiturate agents indicated in procedural sedation/anesthesia include amobarbital, methohexital, secobarbital, and thiopental. No comparative clinical trials or meta-analyses evaluating the oral barbiturate agents in procedural sedation are available for evaluation. Some placebo-controlled evidence suggests barbiturate agents are more effective than placebo, although they maybe associated with higher rates of side effects when compared to other drug classes, such as benzodiazepines or propofol. High rates of tolerance and adverse events are reported in the literature with barbiturate use in mental health disorders. Clinical evidence evaluating the use of barbiturates in neonates, geriatric patients, or patients with a history of substance abuse suggests barbiturate use should be avoided in these patient populations. The barbiturate agents are associated with many, potentially

serious adverse events with long-term use. The most common drug-related adverse events reported with barbiturate use are related to CNS depression. Barbiturate agents are highly toxic in acute overdose and may result in death.

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