Propanidid, an intravenous anesthetic agent
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The author discusses the ultra-short acting eugenol-derivative propanidid, its anesthetic applications and possible side effects. Propanidid, currently unavailable in the United States, was first brought to the attention of the author during a visit to South America, where she observed its use in procedures of short duration.

Propanidid, an ultra-short acting nonbarbiturate, is an eugenol ester which may be used as an intravenous induction agent or as a total anesthetic for short, minor operations. Even though the onset of action of propanidid is rapid, the induction may be stormy due to excitatory side-effects. Recovery from propanidid is also rapid as the drug is broken down by pseudocholinesterase. Propanidid possesses characteristic side effects and sequelae that may negate any potential advantage the drug has to offer.¹

Propanidid is not available for use in the United States. Its major drawback, venous irritation, has apparently delayed its introduction into this country. Also, further investigation of this drug is required, as several conflicting studies exist regarding propanidid's specific properties and the mechanisms of action. Perhaps in the future, as a result of ongoing research, another derivative of the eugenols or a less irritating form of propanidid itself may emerge and be marketed in this country.

A review of past and present literature proved to be a formidable undertaking due to the extensive studies in publication. The purpose of this article is to provide the anesthetist with background information and reference sources concerning propanidid and the eugenols, with an eye to the possibility that the same or similar agents could become available in the United States.

Historical background
The chief constituent of oil of cloves and cinnamon leaf oil is eugenol which is used in the production of vanillin. In the 1950s, anesthetic properties were discovered in several derivatives of eugenol; however, these properties differed from those of previously used intravenous agents. Eugenol derivatives stimulated respiration; they did not induce respiratory depression. In addition, recovery was rapid due to the enzymatic breakdown of the eugenol derivatives.¹

In 1957, Prey and associates in Germany first reported the clinical use of G-29,505, a derivative of eugenol.² In England in 1961, Swerdlow published an account of G-29,505 as a useful anesthetic agent for brief operations.² That G-29,505 provided analgesia was reported by Dundee in the same year.³ One year later, researchers in London concluded that the hypotension and pulmonary edema seen with G-29,505 was due to the solvent in which the drug was dissolved and was not due to the drug itself.⁴ A high incidence of venous thrombosis eventually forced the complete abandonment of G-29,505.¹
In 1964, FBA-1420, another eugenol derivative, was reported in the literature by Dundee and Clark. This drug was later officially named propanidid, and it is currently the only eugenol used for anesthesia.\(^5\) (Figure 1.) It was soon discovered that small, subanesthetic doses of propanidid provided some analgesia.\(^6\) That propanidid could be substituted for thiopental (Pentothal\(^8\)) as an induction agent was the conclusion of research by Dundee, Clark and associates in 1967. They noted that brevity of action was an advantage of propanidid while its emetic sequelae were a deterrent to its use.\(^7\)

**Chemistry.** Propanidid is 3-methoxy-4 (N,N diethyl-carbamoylmethoxy)-phenylacetic acid n-propylester. It can be dissolved to form a 5% aqueous solution by the use of a solubilizing agent such as cremopher EL.\(^1\)

**Metabolism.** Propanidid is rapidly distributed to all well perfused tissues, and 40% of it is protein bound. Pseudocholinesterase is responsible for the rapid biotransformation of the drug. There are two important metabolic pathways for propanidid. The primary pathway involves splitting the ester linkage; this terminates anesthesia. The secondary pathway involves splitting of the diethylamino group. Excretion of propanidid is rapid, as 90% of the drug appears as a urinary metabolite within two hours. Six percent of the drug may be excreted in the feces, and 0.1% is excreted in the expired air as carbon dioxide.\(^1\)

**Onset and duration.** The onset of action of propanidid is comparable to that of thiopental and methohexital\(^8\) and is 8-11 seconds.\(^1\) Awakening occurs in 4-8 minutes with rational conversation possible 2-3 minutes later.\(^9\) Propanidid is considered slightly less potent than thiopental.\(^1\)

The amount of propanidid required per minute to maintain anesthesia changes little over the course of an hour; therefore, it may be concluded that there is minimal cumulation of propanidid. In a 1965 study of dental patients, it was discovered that awakening time from propanidid is the same as that from methohexital. However, the patient was able to return home sooner after propanidid anesthesia than after methohexital. Another study done in the same year concluded that both propanidid and methohexital have a more rapid recovery time than thiopental.\(^1\)

As the dose of propanidid is raised, the increase in sleep duration is not completely linear. A higher initial blood level induces a more rapid destruction of the drug. The longest duration of sleep is six minutes when only a single safe dose is given.\(^1\) Since propanidid’s effects are brief, either the dose of the drug must be repeated or other agents must be administered to prolong anesthesia.\(^9\) It has also been noted in the literature that the duration of propanidid is shorter in men than in women, while the effects of the drug may last longer in patients who are older than 40 years of age.\(^10\)

**Pharmacological properties**

**Tremors.** An induction dose of propanidid, 4 mg/kg, may cause tremors, muscle movements, or hiccups in 11% of patients; there is only a 9% incidence with equipotent doses of thiopental. Opiate premedications decrease these side effects, while the incidence increases as the dose of propanidid is raised.\(^1\)

**Analgesia.** Studies concerned with the analgesic properties of propanidid have conflicting results, and analgesia with subanesthetic doses of propanidid has not been demonstrated. Even though there may be transient analgesia in only some patients, there is no evidence of anti-analgesia. The clinical value of propanidid analgesia has not yet been demonstrated.\(^1\)

**Cardiovascular.** Hypotension is not significant with low doses of propanidid, and the incidence of hypotension (10%) is the same with equipotent doses of thiopental, methohexital and propanidid.
The incidence and the severity of hypotension increase as the dose is raised. In a 1975 study of 18 dogs, it was found that propanidid increased the heart rate, increased left ventricle preload, the central venous pressure, and the pulmonary artery pressure. Therefore, propanidid increases the myocardial oxygen consumption. This is compensated for when propanidid increases the coronary perfusion by decreasing coronary vascular resistance. The authors of this study have concluded that the circulatory effects of propanidid are more pronounced but shorter in duration than the effects of thiopental when the two drugs are given in equipotent doses.

In a 1978 study of eight patients who received 6 mg/kg propanidid as a bolus during bypass surgery, it was concluded that the hypotensive effects resulted from direct action at the arteriolar level—a peripheral vascular effect. In contrast, Dundee believes that the hypotension after induction with propanidid is cardiac in origin and is unrelated to peripheral vasodilation. Propanidid consistently increases the pulse; this change may be secondary to the decrease in blood pressure.

Arrhythmias. When propanidid is used for induction, arrhythmias from laryngoscopy and intubation are rarely seen. Dundee believes that this drug also abolishes ventricular arrhythmias under light halothane anesthesia. Further investigation is required before any anti-arrhythmic properties of propanidid are firmly established, even though it has been suggested that propanidid depresses the conducting system of the heart in a manner similar to that of quinidine and procaine.

One study found that propanidid converted arrhythmias to sinus rhythm in four out of nine cases without the use of cardioversion. In contrast, a second study of 258 patients observed no anti-arrhythmic effects of propanidid. That propanidid may demonstrate anti-arrhythmic properties for specific rhythm disturbances is feasible. If propanidid does prove to be anti-arrhythmic, its auxiliary use with cardioversion is apparent.

Respiratory. Propanidid produces a bi-phasic ventilatory response. Initially, respiration is stimulated. This is followed by a period of hypventilation that may proceed to apnea, which may last for 90 seconds. For healthy patients, the gas exchange is adequate during the period of hypventilation; however, oxygenation is impaired after opiate premedication.

Neuromuscular. Since pseudocholinesterase breaks down propanidid, high doses of this drug may prolong the action of succinylcholine. Propanidid may also increase the requirement of d-Tubocurarine. The effect of propanidid on neuromuscular transmission is complex; both an anticholinesterase action as well as an inhibition of muscle contraction must be considered.

Toxicity. The change in liver function tests after prolonged administration of large doses of propanidid is only of statistical significance. Renal function is normal even when 750 mg of propanidid are administered.

Since 40% of propanidid is protein bound, debilitated patients with a decreased protein content may have prolonged anesthesia and increased toxic effects.

Patients with low levels of pseudocholinesterase sleep longer after propanidid is administered, as this drug is broken down by pseudocholinesterase. This delay in breakdown is usually not clinically apparent except after prolonged intermittent administrations of propanidid.

Since propanidid possesses moderate anticholinesterase activity, the danger of using this drug concomitantly with another anticholinesterase agent, such as echlothiopate iodine, is the prolongation of action of propanidid.

One of propanidid's breakdown pathways is the splitting of the ester linkage. This occurs quickly in the liver and at a slower rate in the blood by pseudocholinesterase. It may be assumed theoretically that patients with liver disease have a delayed metabolism of propanidid; however, the author was unable to locate any studies that dealt with the clinical implications of this problem. A reduction in the dose of propanidid appears to be advisable for these patients.

Nausea and vomiting. Emetic sequelae are more frequent with propanidid anesthesia than with any other currently used intravenous agent.

Venous sequelae. Inadvertent administration of propanidid intra-arterially leads to a sensation of warmth and numbness in the extremity but causes no vascular damage. However, the incidence of tissue irritation and venous damage is greater with propanidid than with either thiopental or with methohexitol. The overall incidence of venous sequelae may be reduced from 15% to 6% when propanidid is diluted with saline from a 5% solution to a 3.5% solution.

Hypersensitivity. A true hypersensitivity, either inborn or acquired, to propanidid may exist. This hypersensitivity may not be apparent until a patient receives his second propanidid anesthetic. Histamine release is the direct cause of the hypersensitivity reaction. Flushing, cutaneous edema,
and bronchospasm may be observed. A case has been reported of an anesthetist who developed an allergic reaction characterized by pruritus and swelling of the eyelids and face on four separate occasions after contact with propanidid. In another case, an anaphylactic arrest occurred in a mother who received 500 mg of propanidid as an induction dose for an elective cesarean section. The mother had an increase in IgE antibody levels that lasted for five months. However, the newborn had no IgE antibodies. The placenta may prevent the maternal IgE antibodies as well as maternal histamine and other amines released during anaphylaxis from crossing to the fetus.

Anesthetic applications

In addition to its use as an induction agent, propanidid may be the sole agent for short, minor operations. In a study of women who were admitted for induced abortions on an outpatient basis, it was found that the group who received thiopental and nitrous oxide regained the ability to stand steadily 20 minutes after the termination of anesthesia. In contrast, the propanidid and nitrous oxide group regained the same ability 10 minutes after the anesthesia was terminated.

In a 1975 study, driving performance was found to be significantly worse than the control group for six hours after thiopental anesthesia. However, propanidid produced no impairment in driving skills two hours after its termination. Since recovery is more rapid and complete with propanidid than after any other intravenous agent, its usefulness as an anesthetic for outpatients is obvious.

Even though recovery from dental surgery is more rapid with propanidid, it is only to be preferred to thiopental and methohexital for its mental clarity. Postoperative vomiting is a distinct disadvantage of using propanidid in dentistry.

Since the duration of anesthesia required for cardioversion is limited, very small doses of propanidid are practical.

The role of propanidid in obstetrics is controversial. Even though propanidid crosses the placenta, the concentration in the umbilical venous blood is less than the concentration in the maternal blood due to cholinesterase in the placenta. In a study done in 1971, the Apgar scores of the neonate whose mother had received propanidid for cesarean section were better than the Apgar scores of the infant whose mother had received thiopental. However, in a 1976 study, propanidid was associated with marked maternal tachycardia, a high degree of biochemical and drug-induced fetal asphyxia, and a 6% incidence of painful factual recall by the mother. The conclusion was that propanidid offered no particular advantage over thiopental as an induction agent for cesarean section.

Advantages. To state briefly, the principal advantages of propanidid are brevity of action and rapid recovery, availability in solution, and use for patients with porphyria.

Disadvantages. In contrast, numerous disadvantages of propanidid exist. The brevity of action from propanidid may result in accidental overdose from repeated administrations. There are distinct cardiovascular and excitatory side effects associated with the use of propanidid, and induction with it may not be smooth because tremors, muscle movements and hiccups may occur. The incidence of emetic effects and phlebitis from propanidid is higher than it is from any other intravenous agent or from thiopental, respectively. It is noted again that propanidid prolongs the action of succinylcholine.

Patient considerations

The use of propanidid warrants these particular considerations:

1. The initial hyperventilation seen with propanidid increases the uptake of inhalation agents.
2. The induction dose of propanidid is decreased if the patient is debilitated, as more propanidid is unbound and active when the patient's protein concentration is decreased.
3. Since propanidid is broken down by pseudocholinesterase, the patient with a low pseudocholinesterase level may have delayed recovery after propanidid anesthesia.
4. The incidence of excitatory phenomena with propanidid is increased with hyoscine (scopolamine) and promethazine premedications, but opiate premedications decrease these side effects.
5. The administration of propanidid to a patient who is in shock may negatively affect an already depressed myocardial performance.

Conclusion

Propanidid may be a useful addition to the anesthetist's armamentarium, especially if it is employed for short operations. However, this drug has characteristic side effects and sequelae that are not benign and warrant consideration. Research into propanidid is extensive but incomplete; thus, the conclusions of various studies are conflicting at times. As with the use of any anesthetic agent,
the potential benefits of propanidid must be weighed against its potential hazards.

REFERENCES

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Donna Jean Diaz, CRNA, BSN, was graduated summa cum laude with a Bachelor's degree in nursing from the University of Bridgeport in Bridgeport, Connecticut in 1976. She was employed for two years in the Pediatric Intensive Care Unit at Yale-New Haven Hospital in Connecticut before entering anesthesia training. Mrs. Diaz is a 1980 graduate of St. Raphael's School of Nurse Anesthesia in New Haven. She is currently working as a staff anesthetist at St. Francis Hospital and Medical Center in Hartford, Connecticut.

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