Etidocaine - A Long-Acting Anesthestic Agent

Review of the Literature

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In recent years, emphasis has been placed on the development of newer local anesthetic agents which can produce prolonged duration of analgesia. Prior to 1957, the longest acting local anesthetic agent available was tetracaine. At that time, a new long-acting agent, bupivacaine, was described by Ekenstam et al (1957). In 1971, a summary of the clinical experience with this agent was presented by Moore et al. Adams et al (1972) described another new local anesthetic agent with prolonged duration of action, etidocaine. This report presents the results of studies in patients of the anesthetic, pharmacologic, and pharmacokinetic properties of this agent.

Small alterations of structure in a local anesthetic molecule may produce large changes in physiochemical properties and clinical performance. Etidocaine (DURANEST®), is a xylidide derivative structurally similar to lidocaine but with two small modifications to convert it to (±)-2-(N-ethylpropylamino)-2′, 6′-butyroxylidide hydrochloride. It is a colorless crystalline salt, easily soluble in water, with a melting point of 203°C. This agent has a high organic solvent/aqueous partition coefficient indicating that it is very lipid soluble in the base form. It is also highly bound to proteins.

These relatively slight alterations in the lidocaine molecule confer a 50 percent increase in its protein binding power, and a 50-fold increase in lipid solubility; producing a local anesthetic agent with the unusual properties of rapid onset combined with a very long duration. Studies in animals and man have shown etidocaine to be neither irritating nor prone to produce methemoglobinemia. The drug is rapidly taken up and redistributed in body tissues, and blood concentrations fall rapidly. Its toxicity is reported to be less than bupivacaine and about four to four-and-a-half times that of lidocaine.

Animal studies with etidocaine by numerous investigators have indicated a rapid onset of action and high frequency combined with a very prolonged duration of action which is completely reversible. The comparative anesthetic potency and acute toxicity of lidocaine, etidocaine, bupivacaine and tetracaine in animals according to Adams et al (1972) (Table 1) indicated that etidocaine, bupivacaine, and tetracaine were equipotent but had four times the anesthetic potency of lidocaine. However, when administered by rapid intravenous injection etidocaine and bupivacaine were four times and tetracaine six times as toxic as lidocaine, whereas, when administered subcutaneously in mice, bupivacaine and tetracaine were five to seven times as toxic as lidocaine, while etidocaine was only twice as toxic as lidocaine.

Table 1

COMPARATIVE ANESTHETIC POTENCY AND ACUTE TOXICITY

Local agents	Lidocaine	Etidocaine	Bupivacaine	Tetracaine
Concentration for peridural	2.0%	0.5%	0.5%	0.5%
Anesthetic potency (comparative)	1	4	4	4
Acute toxicity, rapid I.V. injection (comparative)	1	4	4	6
Acute toxicity subcutaneous	1	2	5	7

Data derived from studies of Adams et al (1972)

The systemic toxicity of a local anesthetic agent is directly related to its concentration in blood and organs such as brain and heart. The blood levels and, thus, the potential toxicities of these agents are affected by site of injection, total dosage administered, the presence of a vasoconstrictor agent in the anesthetic solution, and the pharmacologic characteristics of the drug itself. Lund et al (1975) studies revealed that the highest blood levels were obtained following caudal injection, and that venous plasma levels of etidocaine following lumbar peridural and brachial plexus administration were similar. This result differs from previous studies which have reported that the greatest absorption of lidocaine occurs after intercostal nerve blockade, followed, in order, by caudal, lumbar peridural, brachial plexus, sciatic femoral, and subcutaneous administration. The unusually low blood level of etidocaine observed following lumbar peridural administration may be related to its high lipid solubility. Since the peridural space contains considerable fat, it is conceivable that etidocaine may be sequestered in the peridural fat compartment, so that less of the agent is available for vascular absorption.

No sign of central toxicity was observed with either lidocaine or etidocaine, although subjects re-

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ceiving lidocaine tended to sleep, which was not the case with etidocaine. Hematologic screening, blood chemistries, and urinalyses performed 24 hours before and after each study showed no abnormality. (Stanton-Hicks et al (1973).)

It has been reported that the preseizure EEG and behavior effects of lidocaine and etidocaine differ in monkeys. On infusion of equipotent doses, preseizure activity was preceded by drowsiness with lidocaine but not with etidocaine. Munson et al (1975) findings indicate that these agents affect CNS toxicity before depressing either ventilation or circulation. The use of a single dose of diazepam (0.1 mg/kg) was effective in terminating seizure activity and allowed resumption of rhythmic ventilatory activity. In supine animals this dosage of diazepam had no hypotensive effect.

Etidocaine seizure dosage was significantly higher than the seizure dosage of either bupivacaine or lidocaine as reported by Munson et al (1975). This can be explained by the fact that one of the cyclic metabolites of etidocaine is a hydantoin which represents only 10 percent of the administered dose. The local anesthetics are toxic substances with a low therapeutic ration, the main symptom of toxicity being convulsions (Scott, 1975). The presence of the hydantoin metabolite following administration of etidocaine could possibly contribute to the lower toxicity of etidocaine when compared with bupivacaine. Minor metabolites of etidocaine are of the imidazoline type. Five-membered ring structures of the imidazoline type have been shown to possess potent alpha-receptor blocking properties, as well as histaminergic, cholinergic, and sympatho mimetic properties (Burger, 1970). It is possible, therefore, that the imidazoline type metabolites could cause autonomic side effects, in particular peripheral vasodilatation and hypotension.

Morgan et al (1977) studied etidocaine route of elimination, it was found that the principal route of elimination of etidocaine by the neonate is by metabolism. As in the adult the hepatic extraction ratio of etidocaine is high in the neonate. These results suggest that although the ability of the neonate to metabolize drugs is less than that of the adult, the extent to which this affects the elimination of drugs by the neonate may depend on the hepatic extraction characteristics of the particular drug in question.

Roe and Cohn (1973) demonstrated, in fact, that the autonomic blockade as measured by changes in limb temperature subsided significantly earlier than the somatic block when using etidocaine. Ramanathan et al (1978) reported two cases of prolonged spinal nerve involvement after epidural anesthesia with etidocaine.

Etidocaine is remarkable for three qualities: rapid onset, long duration, and intense motor block. The simultaneous properties of short latency and long duration represent a welcome and unexpected departure from other long-acting agents. Visceral pain is not always blocked in the classical fashion but is easily obtunded with light general anesthesia.

REFERENCES

Adams J Kronberg G Takman B (1972) Local anesthetic activity and acute toxicity of (±)-2-(N-ethylpropylamino)-2',6'-butyroxylidide A new long acting agent J Pharm Sci Vol 61 1829.

Burger A (1970) *Medicinal Chemistry* p 1050 New York Wiley Interscience.

Ekenstam Egner & Pettersson (1957) N-alkylpiperidine carboxylic acid amides Acta Chemica Scandinavian II: 1183.

Lund P Bush D and Covino B (1975) Determinants of Etidocaine Concentration in the Blood Anesth 42: 497.

Lund P Civik J Pagdanganan R (1973) Etidocaine — a new long-acting local anesthetic agent: A clinical evaluation Anesth and Analg 52: 482.

Moore D Bridenbaugh L Bridenbaugh P Thompson G (1971) Bupivacaine hydrochloride: A summary of investigational use in 3274 cases Anesth and Analg Current Research 50: 856.

Morgan D McQuillan D Thomas J (1978) Pharmacokinetics and metabolism of the anilide local anesthetics in neonates-etidocaine EurJClin Pharm 13: 365.

Morgan D Smyth M Thomas J Vine J (1977) Cyclic metabolites of etidocaine in humans Xenobiotica 7: 635.

Munson E Tucker W Ausinch B Malagodi M (1975) Etidocaine, bupivacaine, and lidocaine seizure thresholds in Monkeys Anesth 42: 471.

Ramathan S Chalon J Richards M Patel C Turndorf H (1978) Prolonged spinal nerve involvement after epidural anesthesia with etidocaine Anesth and Analg 57: 361.

Roe C Cohn F (1973) Sympathetic blockade during spinal anesthesia surgical Gyne and Obs 136: 265.

Scott B (1975) Acta Anesthesioligica Scandinavica Suppl 60 p 117.

Stanton-Hicks M Murphy T Bonica J Berges P Mather 1 Tucker G (1975) Effects of peridural block: vascular properties, circulatory effects, and blood levels of etidocaine and lidocaine Anesth 42: 398.