IN VITRO DETERMINATION OF BICARBONATE DOSAGE TO ALKALINIZE LOCAL ANESTHETICS TO PHYSIOLOGIC pH

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IN VITRO DETERMINATION OF BICARBONATE DOSAGE TO ALKALINIZE LOCAL ANESTHETICS TO PHYSIOLOGIC pH

A Masters Thesis

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ABSTRACT

The addition of sodium bicarbonate to local anesthetic solutions immediately prior to their administration has been advocated as a method to reduce latency and prolong duration of regional blockade. The purpose of this study was to determine the appropriate dosages of sodium bicarbonate required to elevate the pH of local anesthetic solutions to physiologic pH (~7.4), while maximizing time to precipitation formation. This descriptive study investigated the alkalinization of four local anesthetic solutions (Lidocaine, Mepivacaine, Bupivacaine, and Chloroprocaine-HCL) before and after freshly added epinephrine. Final pH measurement and precipitation formation were recorded after the addition of incremental doses of sodium bicarbonate (8.4 % or 1 meq/ml). Mean final pH (+/- SD) and mean precipitation times (+/- SD) were calculated. Sodium bicarbonate doses required to achieve physiologic pH were identified. Pearson Product-Moment Correlation Coefficients were calculated to express the linear relationship between bicarbonate dose and mean onset time to precipitation formation. All of the local anesthetic solutions studied, with the exception of Mepivacaine (2%), with and without epinephrine, and all Bupivacaine solutions, were alkalinized to physiologic pH without the rapid formation of precipitate. Rapid precipitation terminated the buffering capacity of the sodium bicarbonate in the cases of Mepivacaine (2%), with and without epinephrine, and all Bupivacaine solutions; consequently, these solutions never reached physiologic pH. Although, freshly added epinephrine did not alter the dose of sodium bicarbonate required to achieve physiologic pH, epinephrine did influence precipitation onset time. Pearson Correlation Coefficients were significant ($p \leq .05$) for all solutions except Bupivacaine (0.25%) with epinephrine, and Bupivacaine (0.5%), with and without epinephrine. Mean onset times to precipitation vary with local anesthetic solution, concentration of the solution, the presence of freshly added epinephrine and dose of sodium bicarbonate added to the solution. Most local anesthetic solutions, regardless of the addition of epinephrine,

can be safely alkalinized to physiologic pH without rapid precipitate formation. Appropriate sodium bicarbonate doses for addition to each local anesthetic studied, mean final pH, and mean precipitation times can be utilized by anesthesia providers who choose to alkalinize local anesthetic solutions prior to their administration.

The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or the Uniformed Services University of the Health Sciences.

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DEDICATION

I dedicate this to the most important people in my life, my family and loved ones, especially Eron. The support and understanding you provided me during this endeavor allowed me to succeed. Thank you for your love and patience.

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Chapter One

Introduction

Background of the Problem

Pain, according to the International Association for the Study of Pain, may be defined as "an unpleasant sensory and emotional experience associated with actual damage or injury to a body tissue" (Mersky, 1986, p.S1). However, this definition does not adequately express the unique, mutable and subjective experience that those who suffer pain encounter. Milton alludes to the emotional experience of pain in Paradise Lost when he writes "Pain is perfect miserie, the worst of evils, and excessive, overturns all patience" (Milton, 1961, p.183). Furthermore, Albert Schweitzer articulates the intense impact of pain by stating "Pain is a more terrible lord of mankind than even death itself" (Schweitzer, 1931, p.62).

While the clinical practice of anesthesia is multifaceted, an integral component of practice is the alleviation and prevention of pain. Hippocrates stated "Divinum est opus sedare dolorum" which means "divine is the work to subdue pain." Although the debate regarding the advantages of general over regional anesthesia persists, the use of local anesthetics for regional blockade has received increasing support with the passage of time (Raj, 1985). Local anesthetics "block the conduction of impulses along nerves in a predictable and reversible manner" (Raj, 1985, p.127). The prominent feature distinguishing local anesthetics from general anesthetics lies in their selectivity. Local anesthetics anesthetize nerves innervating only chosen body parts, and depending upon their concentration, produce transient muscle paralysis and suppress somatic and visceral reflexes without inducing a loss of consciousness (de Jong, 1977, p.3).

Because local anesthetics penetrate tissues more readily in their uncharged form, onset of blockade is intimately linked to pH of the solution (Ritchie, Ritchie, Greengard, 1965). The proportion of a drug in the neutral and cationic forms is dependent upon the pH of solution and pK of the parent molecule so that when pH is equal to pK, half of the drug exists in the uncharged form and half in the charged form. The pK of amide local anesthetics lies between 7.5 and 8.1, which differs less that one logarithm from physiologic pH ~7.4 (Löfstrom & Sjöstrand, 1988). However, commercial preparations are supplied as salts where the addition of NaOH or HCL reduces their pH to a range of 3.2 to 6.5 (Astra, 1993). This provides stability to the solution, particularly in the presence of catecholamines, and it concurrently prolongs the shelf life (Astra, 1993).

The addition of sodium bicarbonate to local anesthetic solutions immediately prior to administration has been advocated as a method to reduce latency and prolong duration of regional blockade (DiFazio et al. 1986 ; Hilgier, 1985). However, the nonionized form is only slightly soluble in water, and therefore, precipitation of the free base limits the extent of alkalinization (Ikuta, Raza, Durrani, Vasireddy, Winnie & Masters, 1989). For this very reason anesthesia providers electing to alkalinize local anesthetics, do so immediately prior to administration to avoid injection of particulate free base along with the solution. According to an unpublished poll of practicing anesthesia providers at a Maryland hospital, depending upon the agent used and provider preference, various doses of bicarbonate ranging from 0.5 to 5 milliliters are added to the solution. Determination of optimal bicarbonate dosage and measurement of precipitation will guide providers in choosing an appropriate and safe alkalinized local anesthetic mixture for their patients.

Rationale and Significance of the Problem

Ritchie, Ritchie and Greengard (1965) were one of the first researchers to establish that the uncharged form of local anesthetics is that which traverses the membrane; yet, the cation is the active form responsible for blockade once inside the cell. Further studies of effects of the nerve sheath on local anesthetics confirmed this. In virtually all sheathed fibers, alkaline anesthetic solutions were found to be more effective (Ritchie et al. 1965). In 1983, Galindo established rapid neural blockade onset in patients receiving various local anesthetic - bicarbonate mixtures. Two years later, Hilgier (1985) found that the addition of bicarbonate to 0.5% Bupivacaine for brachial plexus blockade significantly reduced the onset by > 50% and prolonged duration of action as well. DiFazio et al. was one of the first large scale studies to demonstrate significant reduction of latency with alkalinized 1.5% Lidocaine with epinephrine solutions for epidural administration (1986).

While the benefits of alkalinization appear to be well established, the formation of precipitate remains a concern. The addition of bicarbonate to acidic local anesthetic solutions will inevitably precipitate at a given dose and time, thus altering stability of the solution and terminating its clinical usefulness (deJong, 1977, p.42). While precipitation not only decreases buffering capacity by reducing pH as much as 0.5, the lipid soluble precipitate may even induce tissue injury (Setniker, 1966).

Manufacturers intentionally acidify local anesthetic solutions, particularly those containing epinephrine, to provide stability and prolong shelf life by inhibiting the oxidation of the catecholamine. The pH of these solutions typically ranges between 3.5 and 4.0 (Moore, 1981). Application of the Henderson-Hasselbalch equation at such pH ranges, subsequently predicts that less than 1% of the drug will be available in its

nonionized form and thus capable of crossing the neuronal membrane (McMorland et al., 1988).

Purposeful addition of bicarbonate to local anesthetic solutions will optimally elevate pH to the parent compound's pK. However, addition of too much bicarbonate will likely result in premature precipitation. Measurement of pH before and after incremental dosing of bicarbonate, while simultaneously observing for the formation of precipitate, will identify the ideal required dosage of bicarbonate needed for safe and effective clinical practice.

Statement of the Problem

An in vitro determination of bicarbonate dosage will ascertain the appropriate amount of bicarbonate needed to safely diminish latency of regional blockade while simultaneously minimizing any risk to the patient. The purpose of this study is to determine the appropriate dosages of bicarbonate required to elevate the pH of local anesthetics close to physiologic pH while maximizing time to precipitate formation. Replication of in vitro alkalinization will substantiate previous study results and equip anesthesia providers with a dosing schedule for currently used agents while quantifying time to precipitate formation. It is hypothesized that a specific, reproducible amount of sodium bicarbonate can be added to local anesthetic solutions to raise the solution to physiologic pH (~7.4). Furthermore, it is hypothesized that the time to onset of precipitate formation in each solution is inversely related to the dose of sodium bicarbonate.

Major Research Questions

1) What dose (in milliequivalents) of sodium bicarbonate is required to raise the pH of Lidocaine (1%, 2%), Lidocaine with 1:200,000 epinephrine (1%, 2%), Mepivacaine (1%, 2%), Mepivacaine with 1:200,000 epinephrine (1%, 2%), Bupivacaine (0.25%,0.5%), Bupivacaine with 1:200,000 epinephrine (0.25%, 0.5%) Chloroprocaine-HCL (3%), and Chloroprocaine-HCL with 1:200,000 epinephrine (3%) to physiologic pH (~7.4)?

2) How much time can elapse, after the addition of a given dose of sodium bicarbonate to the above listed local anesthetic solutions, before the formation of precipitate?

Definition of Terms

pH: The potential of hydrogen, expresses the degree of acidity or alkalinity of a substance, expressed mathematically as the logarithm of the hydrogen ion concentration divided into one, i.e., (Log 1/(H+)).

pK: The negative logarithm of the ionization constant (K), when pH = pK 50% of the drug is ionized and 50% is nonionized.

Physiologic pH: Body pH of 7.35-7.45 or ~ 7.4.

Precipitation: Process of a substance being separated from a solution by action of a reagent so that a solid substance forms.

Local anesthetic: Any compound that blocks conduction of impulses along nerves in a predictable and reversible manner.

Summary and Overview

In practice, anesthesia providers elect to alkalinize local anesthetic solutions prior to administration to speed the onset of regional blockade and in some cases prolong its duration. By elevating pH of the solution closer to pK of the drug there is an increase in the amount of drug existing in the nonionized form that is subsequently available to cross the neuronal membrane and exert its effects intracellularly. This practice is limited by the formation of precipitate, and excessive bicarbonate doses only exacerbate this process. Determination of appropriate bicarbonate doses for alkalinization to physiologic pH, while minimizing the formation of precipitate or at least maximizing the time to formation of precipitate, will provide practitioners with a dosage schedule to standardize practice and ensure patient safety.

The focus of this study is to identify exact dosages of bicarbonate needed to elevated pH of local anesthetic solutions to physiologic pH while observing for the formation of precipitate and documenting the time interval elapsed.

Chapter Two

Review of Literature

Local anesthetics have been utilized in clinical practice for well over a century. The intent of this review of literature is fourfold: to summarize the historical development of local anesthetics, to delineate their various uses in clinical practice, to illustrate the pharmacologic mechanisms by which ester and amide local anesthetics exert their effects, and to elucidate the purpose, effects and limitations of alkalinization.

History of Local Anesthetics

The history of local anesthetics depicts the initial impetus and rational for research and development in the practice of anesthesia. Generally, human beings instinctively avoid or seek to reduce/relieve both physical and emotional pain by a variety of mechanisms. Local anesthetics provide a pharmacologic method of such relief. While it was not officially recognized and designated a "local anesthetic" until the 1800's, the ancient Incas chewed the leaves of the coca shrub, grown in the Andean foothills of Peru for its ability to alleviate fatigue and elevate mood (Koller, 1941). While the erythoxylin alkaloid was first extracted in 1855, it was not until 1860 that Albert Neiman successfully isolated cocaine from the erythoxylin extract and subsequently noted the crystals caused his tongue to be numb (Koller, 1941).

Nearly two decades elapsed before Carl Koller, a Vienna medical school graduate interested in ophthalmology and seeking an alternative to general anesthesia, capitalized on the local anesthetic properties of cocaine. After experimenting on animals, himself, and his colleagues, his preliminary reports were read to the

ophthalmology society in Heidleberg, Germany on 15 September 1884 (Koller, 1884). Word spread quickly extolling the virtues of the local anesthetic properties of cocaine, and within the year, its extensive use became global practice. Despite cocaine's beneficial effects, it was not long before its toxic and addictive properties were likewise identified. Many of the very pioneers responsible for cocaine's development and widespread use fell victim to its addictive traits (Koller, 1941).

The next truly significant advance came in 1904 with the development of procaine by Einhorn (deJong, 1970). Its low toxicity, lack of addiction, and relative stability made procaine synonymous with the term local anesthesia for over half a century (Wildsmith and Armitage, 1987). While procaine is more often used as a cardiac antiarrhythmic in clinical practice today, several of its derivatives (Tetracaine and Chloroprocaine for example) remain effective choices of local anesthetic agents (Stoelting, 1991).

Next, by departing from the ester configuration of cocaine and its analogs to investigate analine derivatives, the Swedish dentist Nils Löfgren successfully synthesized Lidocaine in 1948 (Löfgren,1948). Löfgren's contributions extend beyond the initial synthesis of Lidocaine; his systematic study of an extensive assortment of compounds laid the foundation for the subsequent study and development of alternative local anesthetics. The advent of Lidocaine marked a new era in local anesthesia due to its potency, stability, high tissue penetrance and low toxicity (deJong, 1970). Lidocaine and its derivatives (Mepivacaine, Bupivacaine, Etidocaine), to date, have stood the test of time and remain in extensive use today.

Use of Local Anesthetics

To effectively appreciate the comprehensive applications of local anesthetics in the treatment and relief of pain, an understanding of peripheral nerve impulse transmission and pain pathways is first required. Peripheral nerves have sensory, motor, and autonomic fibers, arranged in bundles called fasiculi. Depending upon their function, velocity of impulse transmission varies due to the presence of an insulating sheath known as myelin (Wildsmith and Armitage, 1987). The A-alpha fibers with the greatest diameter are highly myelinated, have the fastest transmission velocity due to saltatory conduction occurring only at the Nodes of Ranvier, and carry motor impulses. Conversely, the A-delta and C fibers are either lightly myelinated or lack myelin entirely, have the smallest diameter, and transmit pain impulses by sequential depolarization (deJong, 1970). Essentially, impulse conduction velocity is a function of, or more precisely, directly proportional to degree of myelinization and neural fiber diameter (Jack, 1975). Application of these principles is clinically relevant and is demonstrated by the requirement to block a minimum of three nodes of Ranvier to insure adequate anesthesia (Tasaki, 1953).

Beyond understanding impulse transmission and propagation, it is important to identify location of first, second and third order sensory neuron synaptic transmission, as these sites represent potential target areas of blockade. First order neurons represent the axon extensions of peripheral nerves with their cell bodies located in the dorsal root ganglia. A synapse occurs in the dorsal horn of the spinal cord known as Rexed's lamina or the substantia gelatinosa. This second order neuron then decussates in the anterior white commissure and ascends contralaterally in the anterolateral spinothalamic and spinoreticulothalamic tracts. The final synapse and third order

neuron originates in the thalamus which then projects to the post central gyrus or primary somatosensory area of the cortex (Wildsmith & Armitage,1987) (Raj, 1985).

The gate control theory of Melzack and Wall attempts to define pain transmission as a "neural mechanism in the dorsal horn of the spinal cord that acts like a gate which can increase or decrease the flow of nerve impulses from peripheral fibers to the central nervous system" (Melzak and Wall, 1965, p.222). Furthermore, "the degree to which the gate increases or decreases sensory transmission is determined by the relative activity in large diameter (A-beta) and small diameter (A-delta and C) fibers and by descending influences from the brain" (Melzak and Wall, 1965, p.222).

Standard practice of regional anesthesia attempts to block transmission of pain impulses at various junctures along the pathway in a predictable and reversible manner, specifically at five well-defined sites of action. Local tissue infiltration blocks first order neurons and largely utilizes a volume dependent dilute solution of local anesthetic (Raj, 1985). Peripheral nerve blocks target specific nerves with first order neurons innervating select structures to be manipulated. These nerves are often superficial and readily accessible (Löfstrom and Sjöstrand, 1988). Proximal plexus nerve blocks involve anesthesia of a group of nerve fibers coursing together within a sheath. Their anesthetic solution administration site is located deeper and requires large volumes for efficacy (deJong, 1961). Epidural and subarachnoid blockade, commonly referred to as centroneuraxis anesthesia, affects the second order neurons, as both methods require proximity to or direct contact with the cerebrospinal fluid to produce their effects (Bromage, 1967). In summary, local anesthetics are used in a variety of applications clinically to impede pain impulse transmission at multiple locations along the pain pathway.

Pharmacologic Effects of Local Anesthetics

Just as with any medication administration, it is important to understand the pharmacokinetics and pharmacodynamics of local anesthetics if we are to successfully apply those actions in anesthetic practice. To fully understand the actions of local anesthetics requires knowledge of their structure, the physiochemical properties governed by those structures, and the ensuing membrane and action potential alterations produced by neural blockade.

The structure of local anesthetics can be classified into four distinct subunits: the aromatic benzene nuclear ring, an ester or amide linkage, the hydrocarbon chain, and the terminal tertiary amine (Winnie, Tay, LaValley, DeSosa, & Mazud, 1977). Each subunit serves a unique function influencing the effects of local anesthetic blockade.

The aromatic ring of the amino amide agents is a 2,6 dimethylanaline ring versus the p-araminobenzoic acid structure of the esters and has the greatest influence on lipid solubility (Raj, 1985). The ester or amide bond links the benzene nucleus to the hydrocarbon chain, and contributes to molecular stability with respect to hydrolysis while providing the basis for classification of local anesthetics (Raj, 1985). Stability of structure, in turn, influences metabolism with the amide local anesthetics exhibiting resistance to hydrolysis. Ester local anesthetics lack such resistance and are extensively and rapidly hydrolyzed by pseudocholinesterase (Kalow, 1952). Conversely, the amide local anesthetics are significantly metabolized by hepatic mixed function oxidase microsomal enzymes, entering primarily an oxidative dealkylation pathway (Tucker & Mather, 1979).

The hydrocarbon chain that influences physiochemical properties, may vary in length and connects the ester/amide linkage to the terminal amine. Elongation of the

chain enhances lipid solubility. Altering conformational structure, by addition of an alkyl group, may result in an increase or decrease in steric hindrance (Winnie et al., 1977). The final subunit is the tertiary terminal amine which governs the hydrophilicity of the compound (Raj, 1985). Hydrophilic properties affect not only how easily a molecule may become charged, but also the hydrophilic-hydrophobic balance plays an important role in membrane permeability and affinity for plasma and tissue proteins (deJong, 1977).

Lipophilicity and hydrophilicity are important applied concepts in local anesthetic administration as they determine ability to traverse the lipid bilayer neuronal membrane. While it is the uncharged base form of the drug that is capable of crossing the membrane (Butterworth & Strichartz, 1990), the charged cationic form is responsible for impulse blockade from within the cell by its influence on sodium conduction (Narahashi & Frazier, 1971).

Since local anesthetics directly affect impulse generation, it is necessary to understand the electrophysiology of nerve transmission. Resting membrane electrochemical potential is determined by intracellular potassium concentration. Potassium concentrations are high intracellularly and low extracellularly and the converse is true for sodium. At rest, the membrane's semipermeable nature to potassium only, allows for a slow, continual intracellular to extracellular leak of potassium ions. Arrival of an electrical stimulus at the polarized membrane, causes activation of voltage gated sodium channels allowing rapid intracellular influx of sodium ions and an increase in membrane potential. If threshold is reached, depolarization occurs and an action potential is generated. Inactivation of sodium channels, along with gated potassium efflux, is responsible for repolarization of the cell. The continual active transport by the sodium/potassium/ATPase pump assists in

re-establishment and maintenance of resting membrane potential gradients (Em) (deJong, 1978; Butterworth & Strichartz, 1990).

It is well established that local anesthetics exert their effects by their influence on sodium conductance; specifically, they "block impulses by inhibiting individual sodium channels thereby reducing the aggregate inward sodium current of the nerve fiber" (Butterworth & Strichartz, 1990, p.29). As previously noted, the rapid sodium influx is responsible for impulse generation. By binding to both activated and inactivated channels, local anesthetics "prevent the conformational changes of activation and antagonize the binding of activator agents that poise channels in activated, open states" (Butterworth & Strichartz, 1990, p.29).

Conceptual Framework

Most local anesthetics used in clinical practice today are tertiary amines and can exist as neutral molecules or positively charged ammonium ions depending upon pH of the solution and pK of the anesthetic (Ritchie, Ritchie & Greengard, 1965). The Henderson-Hasselbalch equation describes this proportional relationship and provides the scientific framework upon which the practice of local anesthetic alkalinization is based (Stewart, 1981). Mathematical application of this principle illustrates that when pH of solution is equal to pK of the drug, 50% of the drug exists in the uncharged free base form and 50% in the cationic charged form (Kamaya, 1983; Moore,1981). The further away from pK of the drug that solution pH proceeds, the less drug available in the nonionized form. Ritchie and Greengard (1961) established that local anesthetics penetrate the membrane in their free base uncharged form only. However, local anesthetics are usually supplied as a salt between hydrochloric acid and a weak base which then dissociate in the presence of water (Kamaya et al., 1983). In addition to

prolonging shelf life, this acidification provides greater solution stability, especially in the presence of commercially added catecholamines, by preventing their oxidation (DiFazio et al., 1986, Astra, 1993). Consequently, while pK's of local anesthetics range from 7.6 to 8.9, their commercial solutions are supplied with pH's ranging from 2.7 to 6.8 (Raj, 1985; Astra, 1993).

Administration of the local anesthetic solution at manufacture pH yields less than 1% of the drug in the nonionized free base form (McMorland et al., 1988). However, if the solution is made less acidic, "upon injection, more of the nonionized form will be available and the onset of anesthesia will be facilitated" (Ikuta, 1989, p.229). Numerous studies have demonstrated that alkalinization of local anesthetics prior to administration reduces onset of blockade and may prolong duration (Mcmorland et. al., 1988; Landriscana, 1992; Fernando and Jones, 1991; Chestnut et al., 1989; Mcmorland et al., 1986; Difazio et al., 1986; Hilgier, 1985). Unfortunately, precipitation of the free base in aqueous solution limits the extent to which pH can be adjusted and may induce tissue injury (Ikuta et al., 1989; Setniker,1966).

According to an unpublished poll of Maryland anesthesia providers, those electing to alkalinize local anesthetics prior to administration, do so empirically. Upon review of the literature over the last three decades, only two previous studies were located that attempted to determine bicarbonate dosage necessary to alkalinize local anesthetic solutions while maximizing time to precipitate formation. Peterfreund, Datta, and Ostheimer in 1989 alkalinized Lidocaine, Mepivacaine, Bupivacaine, Eidocaine and Chloroprocaine and published their results as a suggested alkalinization table. While their study observed for the formation of precipitation, reported dosing recommendations included only pH achieved at given bicarbonate dosages. Ikuta et al. performed a similar study in 1989 of the same agents reporting their results as titration

curves. This study observed a significant variance in precipitate formation of solutions containing freshly added epinephrine versus commercially added epinephrine. Replication of in vitro alkalinization will substantiate previous study results and equip anesthesia providers with a dosing schedule for currently used agents while quantifying time to precipitate formation.

Summary

The development of local anesthetics and their application in the practice of regional anesthesia has provided a method of pain relief in a variety of settings to include surgery, childbirth, and alleviation of acute and chronic pain. Our further study and understanding of neural impulse generation and transmission, along with identification of pain pathways, advanced our ability to effectively relieve pain. Therapeutic application of local anesthetics progressed with a better understanding of structure and pharmacochemical properties. The subsequent manipulation of those properties, such as alkalinization to speed onset of local anesthetic blockade, allows for even greater benefits in clinical practice by improving both quality and safety of therapy.

Chapter Three

Methodology

This descriptive study investigated *in vitro* determination of sodium bicarbonate dosage required to alkalinize local anesthetic solutions to physiologic pH. Data were obtained by use of a pH meter and visual inspection of solution for precipitate formation against both light and dark backgrounds at various time intervals.

Introduction and Overview

This study was conducted in a multidisciplinary laboratory of a northeastern United States graduate education university. The local anesthetic and sodium bicarbonate solutions were purchased from a regional health care facility pharmacy. Commercial preparations studied included Lidocaine, Bupivacaine, Mepivacaine and Chloroprocaine-HCL, in various concentrations and solutions both with and without freshly added epinephrine (Table 1). Initial pH readings of solution were measured for comparison to manufacturer-reported pH. The solution pH was then remeasured after addition and mixing of bicarbonate with the solution. Time to visual precipitate formation was recorded in minutes; all measurements were taken at room temperature.

Materials and Methods

Five milliliter aliquots of the local anesthetic solutions, listed in Table 1, were withdrawn from vials by needle and syringe and placed in plain glass beakers at room temperature. Initial pH was measured before the addition of sodium bicarbonate.

Table 1.

Local Anesthetic Solutions Studied

Lidocaine 1%
Lidocaine 2 %
Lidocaine 1% with epinephrine (1:200,000) **
Lidocaine 2% with epinephrine (1:200,000) **
Mepivacaine 1%
Mepivacaine 2%
Mepivacaine 1% with epinephrine (1:200,000) **
Mepivacaine 2% with epinephrine (1:200,000) **
Bupivacaine 0.25%
Bupivacaine 0.5%
Bupivacaine 0.25% with epinephrine (1:200,000)**
Bupivacaine 0.5% with epinephrine (1:200,000) **
Chloroprocaine-HCL 3%
Chloroprocaine-HCL 3% with epinephrine (1:200,000)**

** Note: Epinephrine solutions were freshly added.
Note: All samples were 5 mls except 10 mls were used for the Bupivacaine(0.5%) and Bupivacaine (0.5%) with epinephrine solutions.

Sodium bicarbonate 8.4% (1mEq/ml) was added with a pipette in increments to the local anesthetic solutions and thoroughly mixed by manual agitation. Solution pH was then remeasured, within five minutes of addition and mixing, with a Corning pH meter 125 calibrated to pH 4.00, 7.00, and 10.00 with certified buffer solutions. Solutions were visually inspected for precipitate formation against both black and white backgrounds at five minute intervals. Observation periods terminated at three hours or formation of precipitate, whichever occurred first. All measurements were repeated on three samples, and the mean of those three was analyzed.

Instrumentation

The pH meter used was the Corning 125 manufactured by Corning Medical and Scientific Instruments. The model 125 covers pH ranges of 0 to 14 with resolution to 0.001. Relative accuracy is +/- 0.002 within a temperature span of 0 to 100 degrees Celsius. The Corning pH meter 125 employs an automatic temperature compensator (ATC) that adjusts for the slope versus temperature characteristics of electrodes. Additionally, a slope control compensates for deviations from theoretical values of Nernst slope electrodes. Two point calibration and sloping was completed prior to data collection utilizing certified buffer solutions of pH 4.0, 7.0 and 10.0 and in accordance with manufacturer guidelines.

Data Collection

The following information was recorded for each solution studied:

1. Local anesthetic solution
2. Concentration of solution
3. Presence of epinephrine
4. Starting pH
5. pH after the addition of incremental sodium bicarbonate dose
6. Time to formation of precipitate

Procedure/Consent

Permission was obtained from the University and the multidisciplinary laboratory for use of equipment and facilities prior to the gathering of research data. Institutional review board approval was likewise obtained after proposal submission and prior to data collection. No human subjects were involved in the study eliminating the need for consent forms.

Data Analysis

Data were reported as the pooled average or mean pH ($\pm$ standard deviation) of samples of all experiments. Precipitate data were reported as the mean time in minutes from alkalinization to the first observation of precipitation. A Pearson Product-Moment Correlation Coefficient was computed to express the direction and magnitude

of the relationship between bicarbonate dosage and time to precipitate formation. Data were analyzed using SPSS/PC+, Version 7.2 (SPSS Inc., Chicago, Il.) and were reported in tabular and graphic form. Sodium bicarbonate dose required to reach physiologic pH was then identified for each local anesthetic solution. To facilitate clinical application for alkalinization, data was transformed to represent volume of bicarbonate solution added to 20 milliliter vials of local anesthetic solutions.

Summary

The methodology for this quasi-experimental in vitro study of local anesthetic alkalinization included baseline solution preparation and measurements, an intervention constituting manipulation of the independent variable (bicarbonate dosage), and repeated measurements and observation. The local anesthetic solutions listed in Table 1 were withdrawn from vials and initial solution pH measured. Sodium bicarbonate was added in incremental doses, according to the local anesthetic solution being studied. After thorough mixing, solution pH was then remeasured and each sample was observed against light and dark backgrounds for the formation of precipitate, up to a maximum of three hours. The optimal bicarbonate dosage to elevate pH of local anesthetic solutions while maximizing time to precipitate formation was determined.

Chapter Four

Results

Restatement of the Hypotheses

Hypothesis I: It is hypothesized that a specific, reproducible amount of sodium bicarbonate can be added to local anesthetic solutions to raise the solution to physiologic pH (~7.4).

Hypothesis II: It is hypothesized that the time to onset of precipitate formation in each solution is inversely related to the dose of sodium bicarbonate.

Presentation of the Research Questions

1) What dose (in milliequivalents) of sodium bicarbonate is required to raise the pH of local anesthetic solutions with and without the addition of epinephrine, to physiologic pH (~7.4) (Table 1)?

2) How much time can elapse, after the addition of a given dose of sodium bicarbonate to local anesthetic solutions, before the formation of precipitate?

Results

The first hypothesis was accepted for the Lidocaine (1%, 2%) solutions with and without epinephrine, Mepivacaine (1%) solutions with and without epinephrine, and Chloroprocaine (3%) solutions with and without epinephrine. Local anesthetic solution percentage, presence of epinephrine, sodium bicarbonate doses, mean final

pH, and mean time to precipitate formation with standard deviations are listed in Tables 2-15 (Appendix A). The first hypothesis was rejected for the Bupivacaine solutions (0.25%, 0.5%) with and without the addition of epinephrine, and Mepivacaine (2%) with and without the addition of epinephrine. The solutions formed precipitates before the local anesthetics could be alkalinized to physiologic pH.

The second hypothesis was accepted for the local anesthetic solutions, with the exception of Bupivacaine (0.25%) with epinephrine and Bupivacaine (0.5%) with and without epinephrine. There was a negative degree of linear relationship between sodium bicarbonate and all of these Bupivacaine solutions. However, the relationships were not statistically significant ($r = -.894$, $p \leq .10$, $r = -.733$, $p \leq .20$, and $r = -.835$, $p \leq .10$) respectively. The degree of linear relationship between sodium bicarbonate dose and mean precipitation time is expressed for each solution in Table 16 as Pearson Product-Moment Correlation Coefficients. Lidocaine (2%) did not demonstrate any formation of precipitate at any bicarbonate dose within the three hour time limit. A correlation coefficient, therefore, could not be calculated.

For each of the local anesthetic solutions, the sodium bicarbonate dose required to reach physiologic pH was identified (Tables 2-15, Appendix A). A 0.3 and 0.4 milliliter dose of sodium bicarbonate raised the final pH of the Lidocaine (1%), with and without epinephrine, and Lidocaine (2%) with and without epinephrine solutions respectively, to physiologic pH. A slightly higher dose of 0.5 milliliters of sodium bicarbonate raised the pH of Mepivacaine (1%) to physiologic pH, irrespective of the presence of epinephrine. Only 0.2 milliliters of bicarbonate alkalinized Chloroprocaine-HCL (3%), both with and without epinephrine, to physiologic pH. The Mepivacaine (2%) with and without epinephrine, and all of the Bupivacaine solutions, were not able to be alkalinized to physiologic pH before the reactions were limited by precipitation. Bupivacaine (0.5%), at the lowest dose measured, only

Table 16.

Correlation between sodium bicarbonate dose and precipitation time

Local Anesthetic Solution	Pearsons Coefficient	Significance (2 - tailed)
Lidocaine 1%	**- .905**	**$p \leq .05$**
Lidocaine 1% with epinephrine	**- .837**	**$p \leq .05$**
Lidocaine 2%	***	***
Lidocaine 2% with epinephrine	***	***
Mepivacaine 1%	**- .944**	**$p \leq .05$**
Mepivacaine 1% with epinephrine	**- .976**	**$p \leq .05$**
Mepivacaine 2%	**- .876**	**$p \leq .05$**
Mepivacaine 2% with epinephrine	**- .971**	**$p \leq .05$**
Chloroprocaine-HCL 3%	**- .903**	**$p \leq .05$**
Chloroprocaine-HCL 3% with epinephrine	**- .883**	**$p \leq .05$**
Bupivacaine 0.25%	**- .875**	**$p \leq .05$**
Bupivacaine 0.25% with epinephrine	**- .894**	**$p \leq 0.1$**
Bupivacaine 0.5%	**- .733**	**$p \leq 0.2$**
Bupivacaine 0.5% with epinephrine	**- .835**	**$p \leq 0.1$**

reached a pH of 5.6 in the plain solution and 6.6 in the epinephrine solution. The latter did not precipitate, but the former demonstrated an oily film at a mean time of 16 minutes. The high end dosing of Bupivacaine (0.5%), while precipitating immediately, still only achieved pH's of 7.16 in the plain solution and 6.93 in the epinephrine added solution (Tables 2-15, Appendix A). For each solution, the bicarbonate dose and resultant pH are graphically represented in Figures 1-5.

Mean precipitation times varied with solution and concentration (Tables 2-15, Appendix A). Lidocaine (1%) did not precipitate when the solution was alkalinized to a pH of 7.43. However, when the Lidocaine (1%) with epinephrine solution was alkalinized to a pH of 7.41, the sample precipitated at a mean time of 80 minutes. The Lidocaine (2%) solutions did not precipitate regardless of epinephrine addition. At a pH of 7.42, the Mepivacaine (1%) solution precipitated at a mean time of 37 minutes. As with Lidocaine, the addition of epinephrine to Mepivacaine (1%) decreased precipitation time to 23 and 27 minutes at pH's of 7.37 and 7.43 respectively. Mepivacaine (2%) precipitated at 7 minutes in the plain solution and 3 minutes in the epinephrine solution while only achieving pH's of 7.35 and 7.17 before the reaction was limited by precipitation. Both Chloroprocaine-HCL (3%) solutions did not precipitate at physiologic pH. However, rapid precipitation occurred within 35 minutes or less when a pH of 7.5 or greater was reached. Bupivacaine (0.25%) did not precipitate as long as pH remained at 6.73 or less which was reached at bicarbonate doses of .005 and .006 milliliters. However, at higher doses the maximum pH achieved was 7.08 with precipitation formation in less than 11 minutes. The epinephrine solution attained an average pH of 6.97 at a .008 dose of bicarbonate without precipitating until a mean of 75 minutes.

Figure 1.

Lidocaine : Bicarbonate Dose vs. pH

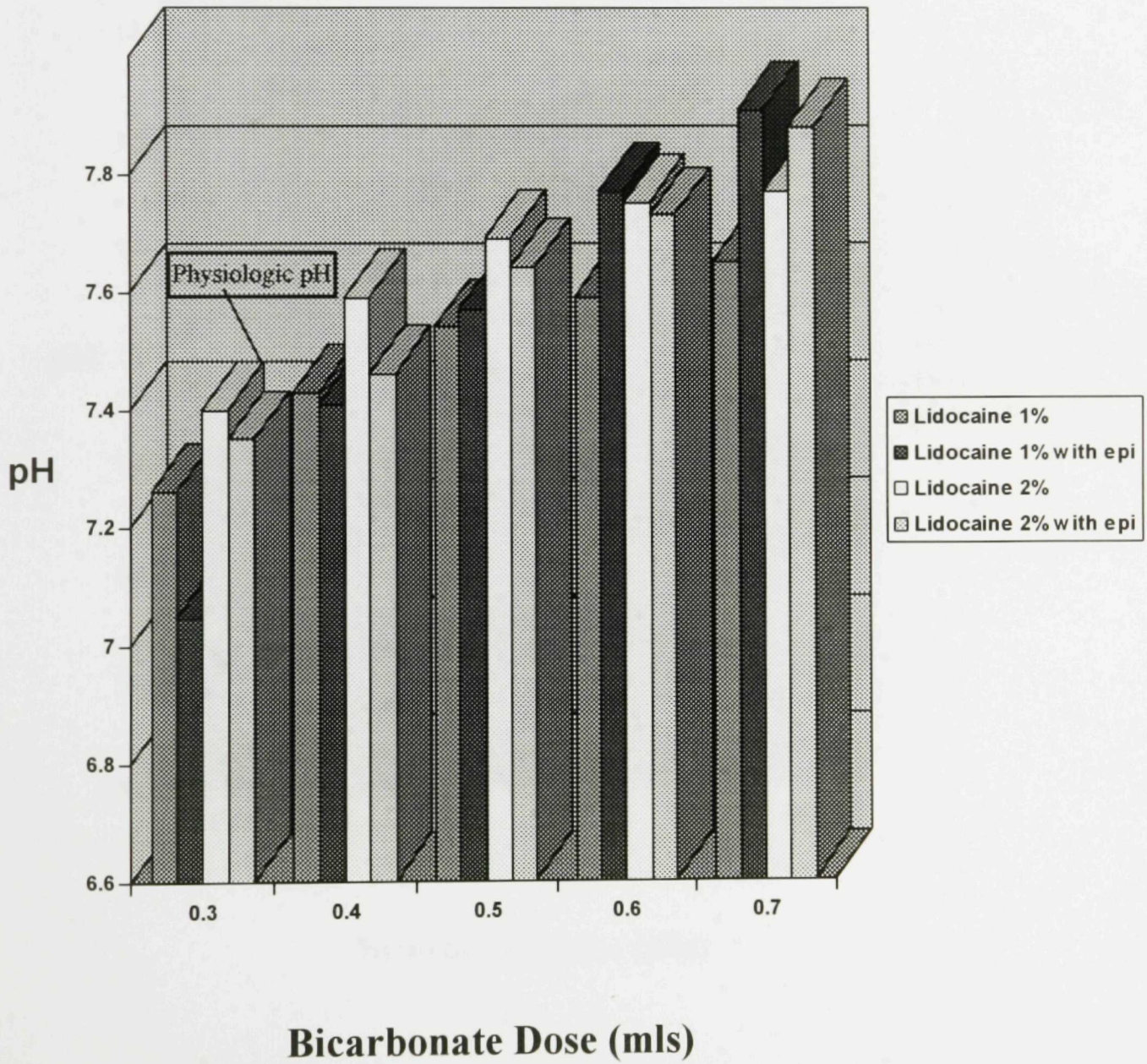


Figure 2.

Mepivacaine: Bicarbonate Dose vs. pH

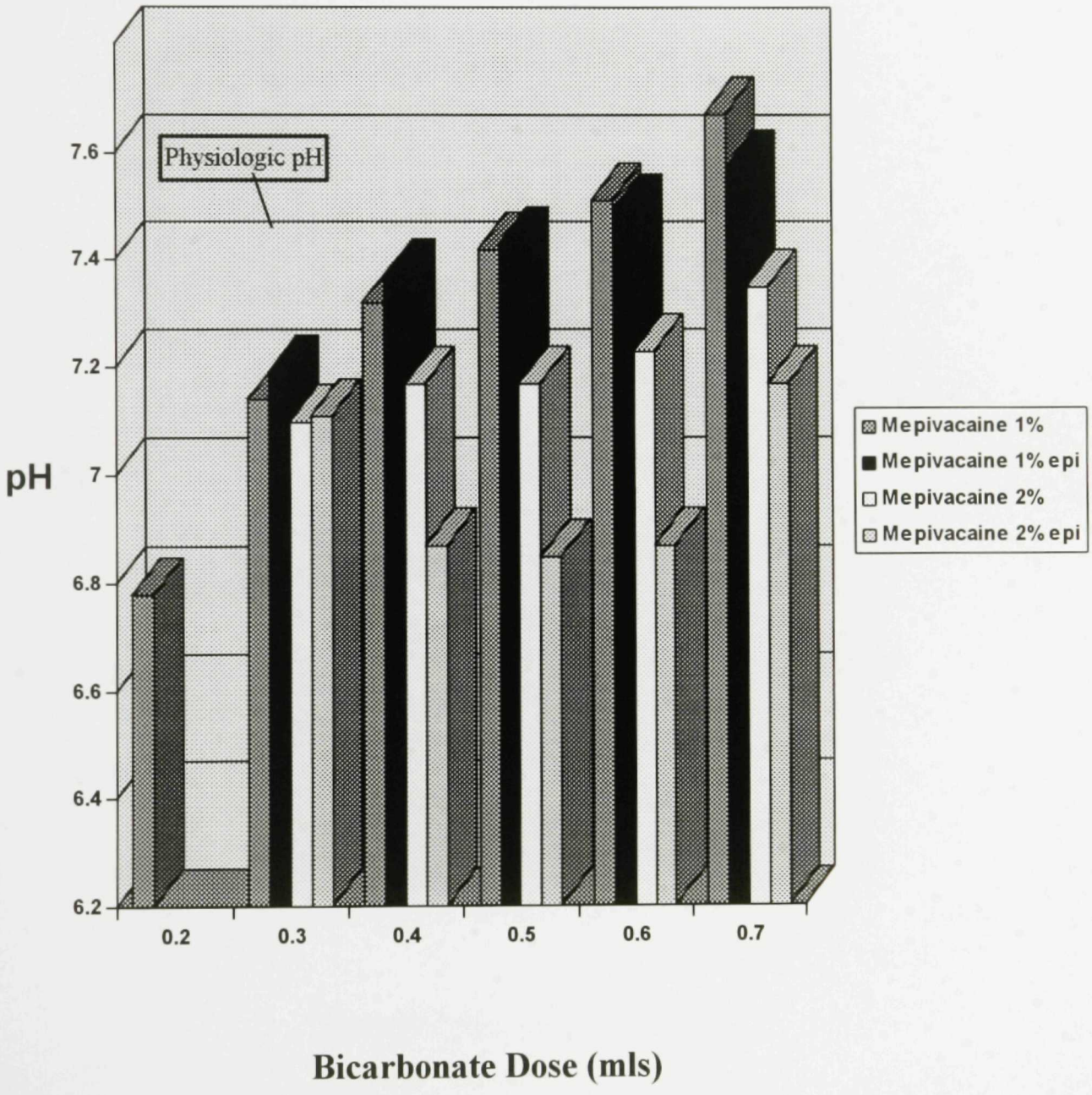


Figure 3.

Chloroprocaine-HCL: Bicarbonate Dose vs. pH

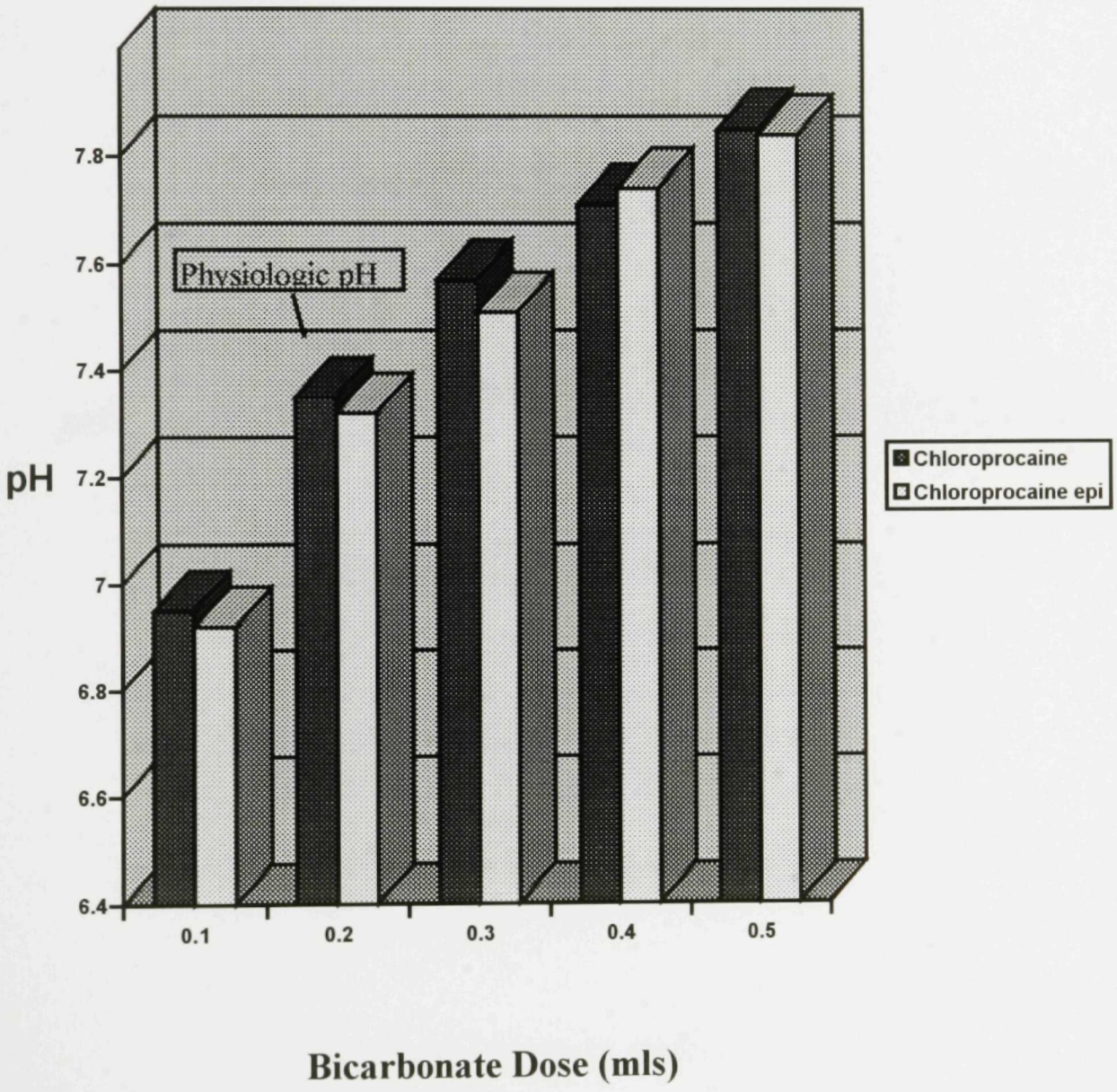


Figure 4.

Bupivacaine 0.25%: Bicarbonate Dose vs. pH

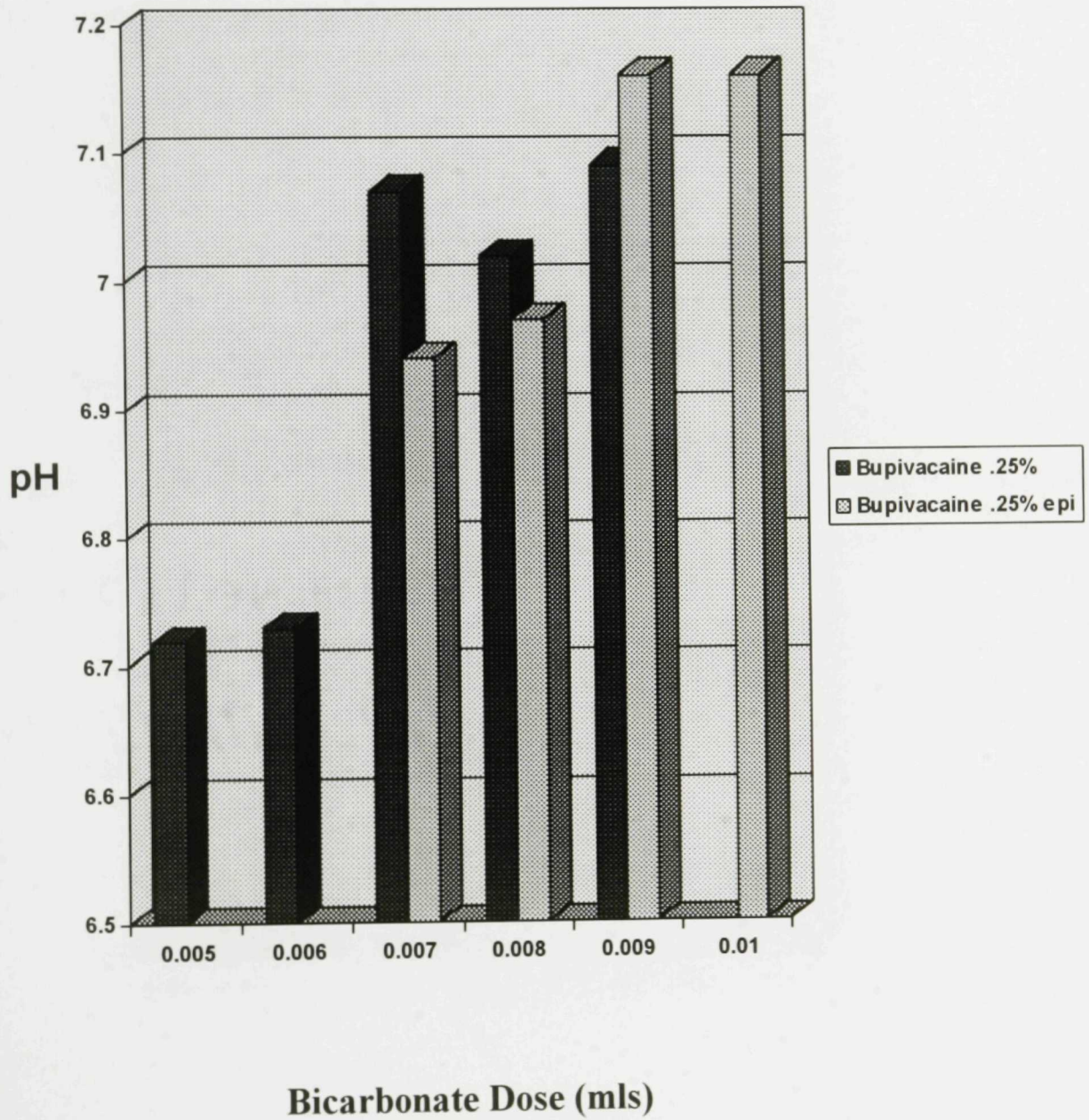
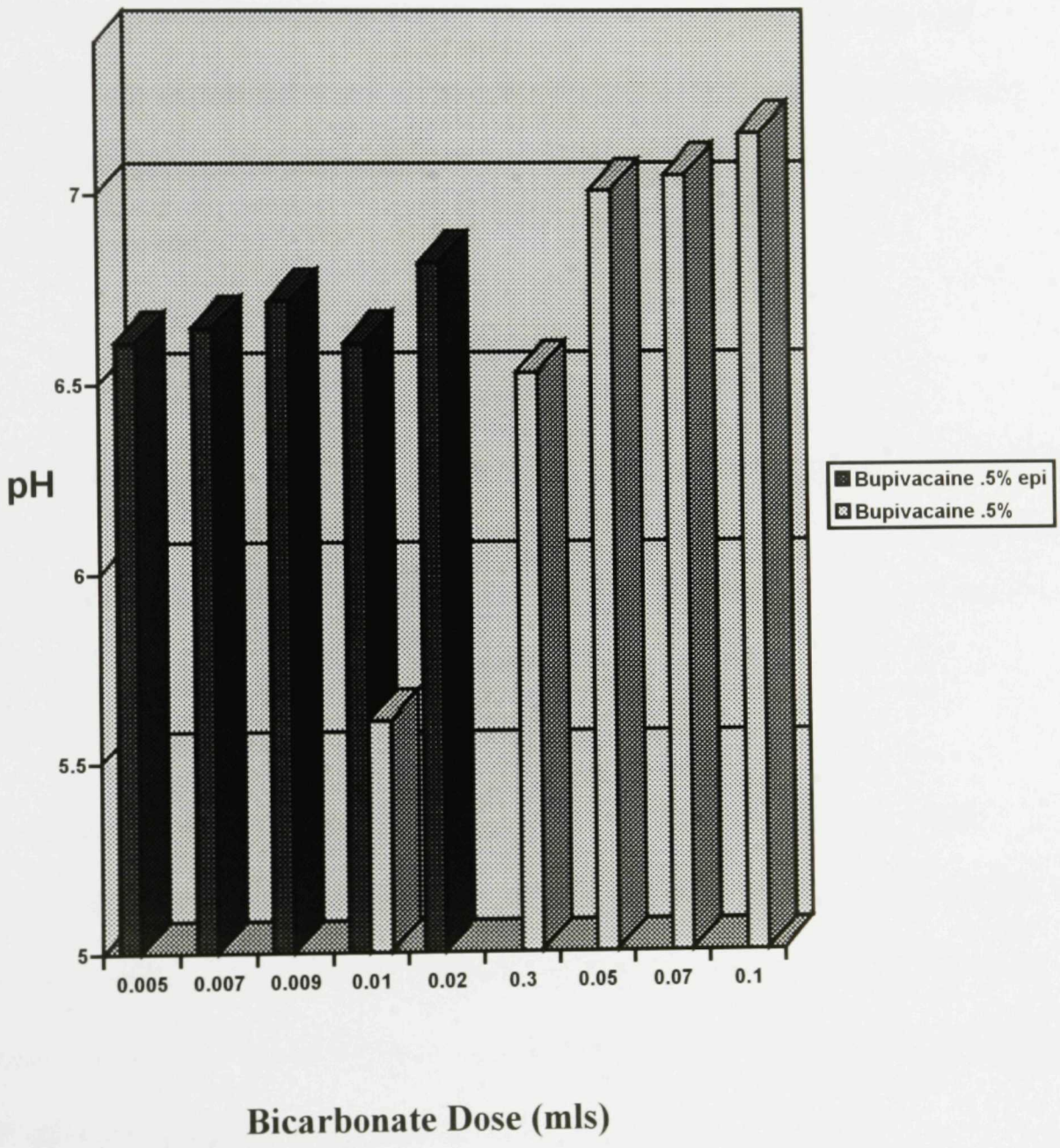


Figure 5.

Bupivacaine 0.5%: Bicarbonate Dose vs. pH



Bupivacaine (0.5%) precipitated in under 20 minutes for even the lowest dose of bicarbonate addition, and only a maximum pH of 7.16 was achieved at higher doses with concurrent immediate precipitation. The Bupivacaine (0.5%) solution with epinephrine was alkalinized to a maximum pH of 6.72 without any precipitation at a dose of .009 milliliters of bicarbonate. Figures 6-9 illustrate the various types of precipitate observed.

Summary

A reproducible amount of sodium bicarbonate can be added to most local anesthetic solutions to alkalinize the solutions to physiologic pH. The exceptions are Mepivacaine (2%) with and without epinephrine and all of the Bupivacaine solutions. This amount of sodium bicarbonate and mean final pH's achieved are listed in Tables 2-15 (Appendix A), and presented graphically in Figures 1-5.

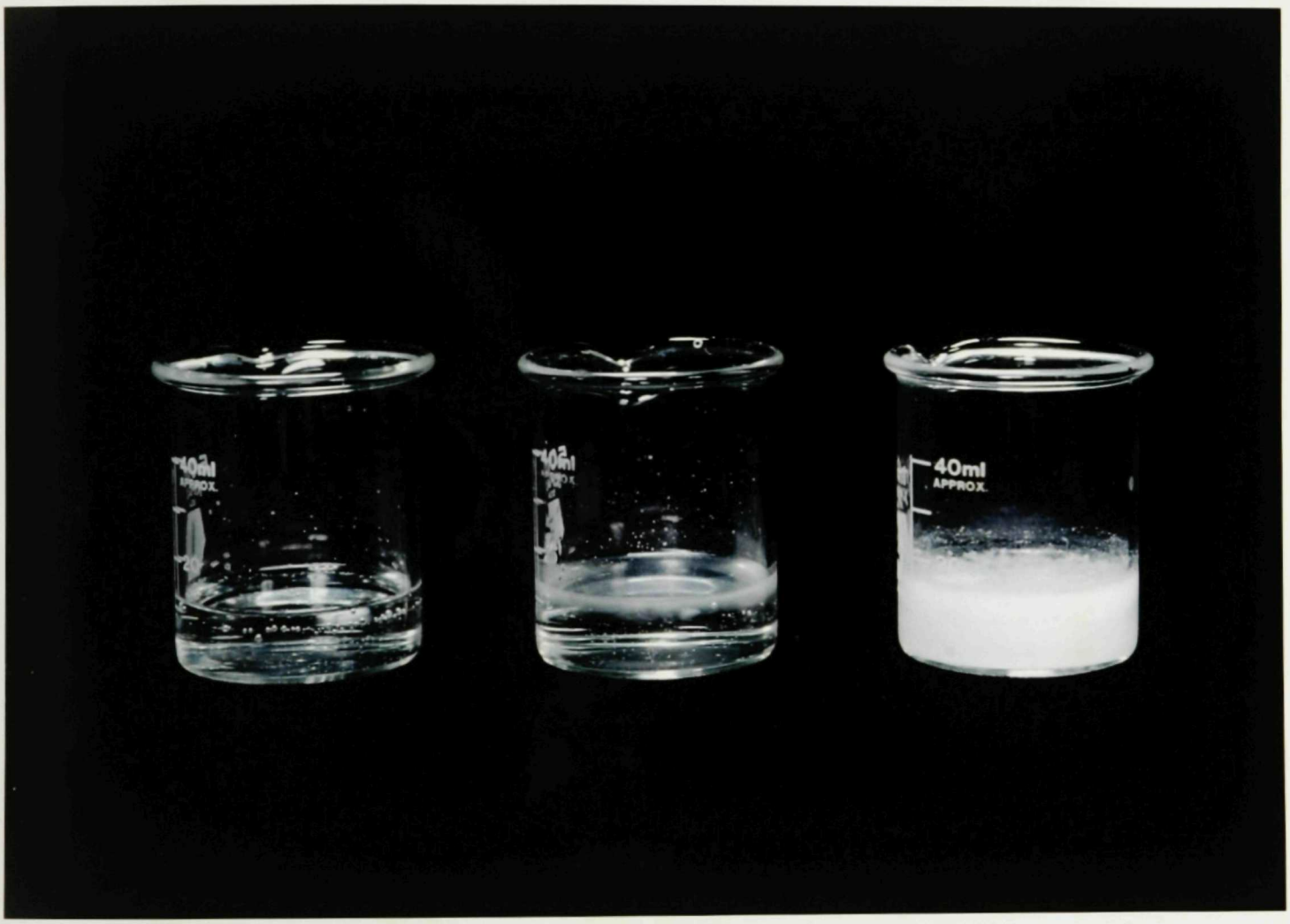
Precipitation time varies considerably with type of local anesthetic agent, concentration of the agent, the presence of freshly added epinephrine, and dosage of bicarbonate added to the solution. Table 16 presents the degree of linear relationship between sodium bicarbonate dose and mean precipitation time for each solution studied, and Figures 6-9 illustrate the types of precipitate formed.

Figure 6.

Figure 7.

Figure 8.

Figure 9.



Chapter V

Discussion and Conclusions

Overview of the Study

Alkalinization of local anesthetic solutions prior to their administration has been advocated as a method to reduce latency and prolong duration of regional blockade. However, the nonionized form is only slightly soluble in water and thus precipitation of the free base limits the extent of alkalinization. The purpose of this study was to determine the appropriate dosages of sodium bicarbonate required to elevate the pH of local anesthetics to physiologic pH while maximizing time to precipitate formation. The local anesthetic solutions listed in Table 1 were withdrawn from vials and initial solution pH was measured. Sodium bicarbonate (8.4%) was then added in incremental doses and the solution was manually agitated. The pH was then remeasured and solutions were observed for the formation of precipitate. Observation terminated at a maximum of three hours. Optimal sodium bicarbonate dosage to elevate the five milliliter samples of local anesthetic solutions to physiologic pH, while maximizing time to precipitate formation, was determined. The adjusted bicarbonate doses for 20 milliliter vials of local anesthetics are listed in Table 17.

Overview of the Results

Nearly all local anesthetic solutions studied were able to be alkalinized to physiologic pH with the exception of Mepivacaine (2%) with and without epinephrine and all of the Bupivacaine solutions. The rapid formation of precipitate in these solutions limited the extent of alkalinization. For all other local anesthetic solutions, as their concentration increased, the amount of sodium bicarbonate required to raise the

solution to physiologic pH was reduced. While the addition of freshly added epinephrine did not alter the necessary dose of bicarbonate required to reach physiologic pH, epinephrine did reduce initial solution pH and also decreased mean time to initial formation of precipitate. However, initial formation of precipitate was *prolonged* by the addition of epinephrine to Bupivacaine (0.25%) and the solution also reached a higher pH before precipitation occurred.

All of the Lidocaine solutions could be alkalinized to physiologic pH without the formation of precipitate. An oily film was observed with the Lidocaine (1%) solutions, with and without epinephrine, when pH exceeded 7.5. While the film dissipated with agitation of the beaker, for the purpose of this study, time at initial observation was documented as precipitate formation time. However, Lidocaine (2%), with and without epinephrine, did not demonstrate any formation of precipitate within the three hour time period, regardless of sodium bicarbonate dose. While starting pH of Lidocaine solutions fell between manufacturer stated ranges of 5.0 - 7.0, differences did exist between manufacturers. The Lidocaine (2%) solutions, manufactured by Astra, had starting mean pH's of 6.67 and 6.58 in the plain and freshly added epinephrine solutions respectively. The Lidocaine (1%) solutions, manufactured by Elkins-Sinn Incorporated (ESI), had mean starting pH's of 6.04 and 6.11 in the plain and freshly added epinephrine solutions respectively. While neither solution precipitated at physiologic pH, the difference in manufacturer did affect precipitation at higher doses. Note that the addition of epinephrine to the Astra solution *decreased* the starting pH, while addition to the ESI solutions, *increased* mean starting pH. The Lidocaine (1%) solution also demonstrated the hypothesized inverse relationship between bicarbonate dose and precipitation time with a Pearson Correlation Coefficient of $r = -.905$ ($p < .05$). These data may differ from previously published results

reflecting a different precipitation formation definition. Because no precipitate formed with Lidocaine (2%) solutions, the second hypothesis was rejected.

Data were collected, but subsequently excluded, on Lidocaine (1%) multidose vials, manufactured by Abbott, that contained *methylparaben*. The presence of this preservative, known to be incompatible with alkaline solutions, facilitated rapid precipitation. For this reason, all local anesthetic solutions used for regional blockade are "methyl-paraben-free" or (MPF).

All Lidocaine solutions were able to be safely alkalinized to physiologic pH without concern regarding precipitate formation, if solutions were preservative free and appropriate sodium bicarbonate doses were used. Lidocaine has the fastest onset of the amide local anesthetics and the benefit of decreased latency, by the addition of sodium bicarbonate, may not be as profound as with longer acting agents. For this reason, many clinicians may elect not to alkalinize Lidocaine solutions for regional nerve blocks or epidurals. However, when used for *localization* and not regional blockade, alkalinization of Lidocaine may reduce initial patient discomfort experienced from infiltration of an acidic solution.

Mepivacaine (1%) with and without epinephrine required a higher dose of sodium bicarbonate to reach physiologic pH than Lidocaine, and the solutions precipitated more quickly as well. Freshly added epinephrine further reduced their precipitation time. The pK of Mepivacaine is almost one-half of a logarithm less than Lidocaine (7.6 and 7.9 respectively). Manufacturers also acidify Mepivacaine solutions more than Lidocaine solutions (4.5-6.8 and 5.0-7.0 respectively). Catecholamine addition further reduces the pH of Mepivacaine solutions by 0.1- 0.2 logarithms. Consequently, higher doses of sodium bicarbonate are required for the solutions to reach physiologic pH with resultant decreased time to precipitate formation. In fact, the Mepivacaine (1%) with epinephrine solution demonstrated the greatest negative degree of linear relationship

Table 17.

Adjusted Bicarbonate Dose for 20 ml vials of Local Anesthetic

Local Anesthetic Solution (20 milliliter vials)	**Dose of Sodium Bicarbonate (8.4%, 1 meq/ml) ****
Lidocaine 1%	**1.6 mls**
Lidocaine 1% with epinephrine	**1.6 mls**
Lidocaine 2%	**1.2 mls**
Lidocaine 2% with epinephrine	**1.2 mls**
Mepivacaine 1%	**2.0 mls**
Mepivacaine 1% with epinephrine	**2.0 mls**
Chloroprocaine-HCL 3%	**0.8 mls**
Chloroprocaine-HCL 3% with epinephrine	**0.8 mls**

** The bicarbonate dose listed will adjust solution to physiologic pH without precipitation formation.

Note: Local anesthetic solutions not listed can not be alkalinized to physiologic pH without formation of precipitate.

between bicarbonate dosage and precipitate formation, of all local anesthetic solutions studied, with a Pearson Correlation Coefficient of - .976 ($p \leq .05$). Mepivacaine can be safely alkalinized to physiologic pH as long as the sample is administered within 30 minutes of mixing, particularly if the solution contains freshly added epinephrine.

Mepivacaine (2%) solutions behaved similarly to Bupivacaine solutions by precipitating rapidly while never reaching physiologic pH. Solutions both with and without epinephrine demonstrated negative degrees of linear relationship between bicarbonate dosage and mean precipitation formation time with Pearson Correlation Coefficients of -.876 and -.971 ($p \leq .05$) respectively. The inconsistent elevation of pH with higher incremental doses of bicarbonate to the Mepivacaine (2%) with epinephrine solution demonstrates that rapid formation of precipitate not only decreases buffering capacity but produces unpredictable chemical reactions. Based upon these results, it may not be prudent to alkalinize Mepivacaine (2%) solutions prior to administration due to the high probability of precipitate formation. A more dilute concentration (i.e. 1%) can be alkalinized without compromising patient safety.

Chloroprocaine-HCL (3%) was alkalinized to physiologic pH without the formation of precipitate within a three hour time period. However, when pH exceeded 7.5 precipitation occurred in 35 minutes or less. Freshly added epinephrine further reduced the mean time to precipitate formation. While this research was only conducted on a 3% concentration, it is likely that a lower dose of bicarbonate would be required and mean precipitation time would be prolonged in lower concentrations of Chloroprocaine-HCL (i.e. 1%, 2%). All preparations of Chloroprocaine-HCL, manufactured by Astra, contain 0.111 mg/ml of disodium EDTA dihydrate. This may contribute to precipitation when higher pH's are reached. Chloroprocaine-HCL was the only ester local anesthetic included in this research. Its pK, at 8.7, is approximately one logarithm higher than all of the amide local anesthetics. Chloroprocaine-HCL is also

acidified the most by manufacturers (initial pH range of 2.7-4.0). Once neutral pH was exceeded, a crystalline precipitate promptly appeared. While it is possible to safely alkalinize Chloroprocaine-HCL, like Lidocaine, it naturally has a rapid onset and the benefits of alkalinization may not be clinically apparent.

Bupivacaine in all concentrations studied, both with and without epinephrine, could not be alkalinized to physiologic pH because all reactions were limited by the rapid formation of precipitate. While all solutions demonstrated a negative degree of linear relation between bicarbonate dose and mean time to precipitate formation, only the Bupivacaine (0.25%) solution was statistically significant with a Pearson Correlation Coefficient - .875 ($p \leq .05$). Precipitation was so rapid in all other Bupivacaine solutions, despite minute bicarbonate dosing intervals, that resultant mean precipitation intervals were too similar for the relationship to be statistically significant. The Bupivacaine (0.25%) solutions were manufactured by Sanofi-Winthrop. The mean starting pH of Bupivacaine (0.25%) was 5.89; freshly added epinephrine subsequently *raised* the pH to a mean of 5.91. It appears that the addition of freshly added epinephrine to Bupivacaine (0.25%) may lend stability to the alkalinization reaction. At equipotent bicarbonate dose addition, the solution with epinephrine took up to four times longer to precipitate than the plain solution. For example, .007 milliliters of sodium bicarbonate added to plain Bupivacaine (0.25%) alkalinized the solution to a mean pH of 7.07 forming precipitate at a mean time of 16 minutes, while Bupivacaine (0.25%) with epinephrine reached a mean pH of 6.94 yet did not precipitate until a mean time of 71 minutes.

Bupivacaine (0.5%) presented considerable challenges in this alkalinization study due to the solutions propensity to precipitate at even minute doses of bicarbonate addition. The solutions studied were manufactured by Astra and had mean starting pH's of 5.47 and 5.32 in the plain and freshly added epinephrine solutions

respectively. Sample amount was increased to 10 milliliters in an attempt to facilitate accurate addition of bicarbonate dosages before precipitate formation occurred. Even at very small doses of bicarbonate addition, the maximum pH achieved in the plain solution was 7.16 with immediate precipitation. The lowest dose added reached a final mean pH of 5.6 while precipitating in 16 minutes. The epinephrine solution measurements were inconsistent with what would be expected with incremental bicarbonate dose addition. A mechanical pipette calibrated to deliver 5 - 50 angstroms was used but accuracy of the instrument at such low doses was questionable. Rapid precipitation of Bupivacaine (0.5%) precludes the ability to safely alkalinize the solution prior to patient administration. As Bupivacaine (0.25%) with epinephrine demonstrated, the addition of freshly added epinephrine may in fact prolong the mean time to initial formation of precipitate. However, this provides no guarantee that precipitation will not occur prior to administration. Bupivacaine has the highest pK (8.1) of the amide local anesthetics and manufacturers also acidify it the most (starting pH 4.0-6.5). For these reasons, attempts to alkalinize Bupivacaine solutions, especially those with higher concentrations, to physiologic pH were unsuccessful and not recommended for clinical practice.

Study Limitations

Various limitations of this in vitro alkalinization study impacted the results obtained. The applied definition of precipitation, equipment calibration and accuracy, use of local anesthetic solutions by different manufacturers and limited availability of certain solutions, and varying degrees of room temperature affected the data obtained and are discussed individually.

Mean time to precipitation, for the purpose of this study, was documented as the *first* observation of any type of precipitate. An oily film or a single crystalline haze were considered positive precipitates, regardless of their tendency to dissipate with agitation. Solutions that initially exhibited only an oily precipitate, proceeded to a crystalline formation over time. Types of precipitate varied initially with type of solution but final crystalline formations were similar. Examples of precipitate are presented in Figure 6. Previously published research may conflict with these results due to a different application concerning the dissipation of precipitation with agitation of the solution.

Calibration and accuracy of instrumentation may have influenced results of the study. A calibrated pipette with a range of 5 - 50 angstroms was used for addition of sodium bicarbonate to the Bupivacaine solutions. In such minute doses, it was impossible to discern dosage differences with the naked eye; thus accuracy of administration could not be verified. This, coupled with the propensity of Bupivacaine to rapidly precipitate, made the data obtained inconclusive. The pH meter used was calibrated with certified buffer solutions before each set of data was collected. Accuracy of the pH meter is described in chapter three.

The use of local anesthetic solutions produced by different manufacturers likewise impacted results obtained. While mean starting pH's fell within manufacturer guidelines, this range often differed by up to 2 logarithms. The addition of epinephrine to solutions manufactured by Astra lowered initial mean pH; whereas, the addition of epinephrine to ESI and Sanofi-Winthrop solutions *raised* initial mean pH. Manufacturers acidify local anesthetic solutions by the addition of either sodium hydroxide or hydrochloric acid, but they do not specify the amount that is used in their package inserts. It is possible that the acidifying agent, in various doses, reacts

differently with catecholamines and sodium bicarbonate, and therefore impacts pH and subsequent formation of precipitate.

Funding limitations and time constraints prevented this study from being comprehensive. Under optimum conditions, measurements would have been obtained on *all* available concentrations and brands of local anesthetics currently being manufactured. Furthermore, one concentration of bicarbonate was used in this study (8.4%, 1 meq/ml). Replication with various available concentrations may produce different results and further dilution of local anesthetic solutions in lesser concentrations.

Finally, measurements were taken at room temperature to simulate clinical practice. Temperature of the laboratory varied between 65 and 73 degrees Fahrenheit which may have influenced the rate of reaction of the solutions.

Implications for Research and Practice

Results of this study provide several useful recommendations for clinical application of alkalinization of local anesthetics with sodium bicarbonate. Alkalinization to physiologic pH can be safely accomplished in the following solutions regardless of the presence of freshly added epinephrine: Lidocaine (1%, 2%), Mepivacaine (1%), Chloroprocaine-HCL (3%). Mepivacaine (1%) should be administered within thirty minutes of the addition of bicarbonate. Mean time to precipitate formation varies with local anesthetic solution, concentration, presence of epinephrine, and amount of sodium bicarbonate added. It is safest to alkalinize immediately prior to administration to avoid the possibility of precipitation formation. Appropriate sodium bicarbonate doses for addition to 20 milliliter vials of solution are listed in Table 17. Alkalinization of multi-dose vials of local anesthetic solutions containing methylparaben is not recommended. Precipitation formed by the addition of sodium bicarbonate to local

anesthetic solutions is white and may be concealed by the clinical use of opaque and semiopaque syringes. While addition of freshly added epinephrine to Bupivacaine solutions may prolong mean time to initial formation of precipitate, results are inconclusive and clinical application of alkalinization remains questionable.

Potential areas for further research in the area of alkalinization of local anesthetic solutions were identified by the limitations and results of this study. A comprehensive study that includes various local anesthetic solutions, concentrations, and pharmaceutical company brand names would address the variability of precipitation and pH. As new local anesthetics become available, for example Ropivacaine, in vitro study of their alkalinization characteristics is warranted before application in clinical practice. In future studies of the alkalinization of Bupivacaine solutions, technical errors can be minimized by the use of a larger sample size (i.e., 20-30 milliliters). The potential for greater solution stability regarding pH and precipitation by the fresh addition of epinephrine to Bupivacaine may be clinically beneficial if results could be reproduced. Finally, clinical investigations that compare the practitioner's time spent alkalinizing local anesthetic solutions and the resultant decreased latency intervals would identify the real-time benefit of local anesthetic solution alkalinization.

Summary

Many anesthesia providers alkalinize local anesthetic solutions to reduce latency of regional blockade. The purpose of this study was to determine the dose of sodium bicarbonate necessary to elevate solutions to physiologic pH while maximizing time to precipitation formation. Most local anesthetics, regardless of the addition of epinephrine, can be safely alkalinized to physiologic pH without precipitate formation. Appropriate bicarbonate doses for addition to each local anesthetic studied, final pH,

and mean precipitation times can be utilized by anesthesia providers who chose to alkalinize anesthetic solutions. Proper alkalinization will decrease both the chance of precipitation formation and latency to anesthesia. Future studies are necessary to investigate the variability between pharmaceutical brand names and alkalinization characteristics of new anesthetic agents. The time required to alkalinize local anesthetic solutions may nullify the advantage of such practice in the clinical setting for many providers.

APPENDIX A

LIDOCAINE

Table 2.

Lidocaine 1%: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.26	.04	None	00
0.40 mls	7.43	.03	None	00
0.50 mls	7.54	.04	82 minutes	2 minutes
0.60 mls	7.59	.06	69 minutes	3 minutes
0.70 mls	7.68	.03	66 minutes	1 minute

Table 3.

Lidocaine 1% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.05	.11	None	00
0.40 mls	7.41	.03	80 minutes	00
0.50 mls	7.57	.04	78 minutes	00
0.60 mls	7.77	.03	70 minutes	3 minutes
0.70 mls	7.91	.04	51 minutes	7 minutes

LIDOCAINE

Table 4.

Lidocaine 2%: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.40	.03	None	00
0.40 mls	7.59	.06	None	00
0.50 mls	7.69	.05	None	00
0.60 mls	7.75	.05	None	00
0.70 mls	7.77	.02	None	00

Table 5.

Lidocaine 2% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.35	.03	None	00
0.40 mls	7.46	.10	None	00
0.50 mls	7.64	.05	None	00
0.60 mls	7.73	.04	None	00
0.70 mls	7.88	.06	None	00

MEPIVACAINE

Table 6.

Mepivacaine 1%: Mean final pH and mean precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.20 mls	6.78	.10	44 minutes	00
0.30 mls	7.14	.14	44 minutes	1 minute
0.40 mls	7.32	.01	42 minutes	4 minutes
0.50 mls	7.42	.07	37 minutes	8 minutes
0.60 mls	7.51	.05	26 minutes	1 minute
0.70 mls	7.67	.03	24 minutes	1 minute

Table 7.

Mepivacaine 1% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.19	.06	36 minutes	10 minutes
0.40 mls	7.37	.04	27 minutes	3 minutes
0.50 mls	7.43	.04	23 minutes	2 minutes
0.60 mls	7.49	.08	17 minutes	3 minutes
0.70 mls	7.57	.02	15 minutes	2 minutes

MEPIVACAINE

Table 8.

Mepivacaine 2%: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.10	.06	19 minutes	00
0.40 mls	7.17	.02	11 minutes	2 minutes
0.50 mls	7.17	.01	9 minutes	00
0.60 mls	7.23	.07	8 minutes	00
0.70 mls	7.35	.02	7 minutes	00

Table 9.

Mepivacaine 2% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.30 mls	7.11	.15	6 minutes	2 minutes
0.40 mls	6.87	.04	5 minutes	1 minute
0.50 mls	6.85	.13	4 minutes	00
0.60 mls	6.87	.13	4 minutes	1 minute
0.70 mls	7.17	.03	3 minutes	00

CHLOROPROCAINE-HCL

Table 10.

Chloroprocaine 3%: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.10 mls	6.95	.15	None	00
0.20 mls	7.35	.03	None	00
0.30 mls	7.57	.04	35 minutes	1 minute
0.40 mls	7.71	.07	17 minutes	2 minutes
0.50 mls	7.85	.02	12 minutes	00

Table 11.

Chloroprocaine 3% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.10 mls	6.92	.12	None	00
0.20 mls	7.32	.06	None	00
0.30 mls	7.51	.10	26 minutes	1 minute
0.40 mls	7.74	.12	21 minutes	1 minute
0.50 mls	7.84	.02	16 minutes	1 minute

BUPIVACAINE

Table 12.

Bupivacaine 0.25%: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.005 mls	6.72	.02	None	00
0.006 mls	6.73	.01	None	00
0.007 mls	7.07	.08	16 minutes	00
0.008 mls	7.02	.12	12 minutes	4 minutes
0.009 mls	7.09	.04	11 minutes	1 minute

Table 13.

Bupivacaine 0.25% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose.

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.007 mls	6.94	.06	71 minutes	11 minutes
0.008 mls	6.97	.09	76 minutes	1 minute
0.009 mls	7.16	.07	54 minutes	9 minutes
0.010 mls	7.16	.10	19 minutes	00

BUPIVACAINE

Table 14.

Bupivacaine 0.5 %: Mean final pH and precipitation time at bicarbonate dose. **

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.010 mls	5.60	.04	16 minutes	5 minutes
0.030 mls	6.53	.44	2 minutes	1 minute
0.050 mls	7.00	.04	< 1 minute	00
0.070 mls	7.05	.18	Immediate	00
0.100 mls	7.16	.05	Immediate	00

Table 15.

Bupivacaine 0.5% with Epinephrine: Mean final pH and precipitation time at bicarbonate dose. **

Bicarbonate Dosage (mls)	Mean Final pH	Standard Deviation	Mean Precipitate Time (minutes)	Standard Deviation
0.005 mls	6.61	.02	None	00
0.007 mls	6.65	.03	None	00
0.009 mls	6.72	.03	None	00
0.010 mls	6.61	.14	63 minutes	00
0.020 mls	6.82	.05	33 minutes	12 minutes

** *10 milliliter solution samples*

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