CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/10778294

https://www.iajps.com/volumes/volume11-february-2024/25-issue-02-february-24/

Available online at: http://www.iajps.com Review Article

A REVIEW ARTICLE ON ARTICAINE -LOCAL ANESTHETIC DRUG

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Abstract:

Articaine is an amide-type LA that has an onset and duration of anaesthesia similar to those of other intermediate-acting amide LAs. The most significant benefit of articaine over lidocaine is that it may have somewhat faster onset and greater depth of action. Articaine is 1.5 times as potent and only 0.6 times as toxic as lidocaine and has been shown to be superior in achieving successful anaesthesia following infiltration. It is not for injection in children under 4 years of age. However, the use of inferior alveolar nerve blocks can be almost eliminated in children by using articaine due to its ability to anaesthetize teeth effectively by infiltration up to the first permanent molar region. In addition, diffusion of articaine on to the palatal surface may also eliminate the discomfort of palatal infiltration. It can also be used in patients taking beta-blockers.

Keywords*: articaine, regional anesthesia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, neurotoxicity*

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*Please cite this article in press R. Jona Methusala et al., **A Review Article On Articaine -Local Anesthetic Drug**, Indo Am. J. P. Sci, 2024; 11 (02).*

INTRODUCTION:

Articaine is an intermediate-potency, short-acting amide local anesthetic with a fast metabolism due to an ester group in its structure. It is effective with local infiltration or peripheral nerve block in dentistry, when administered as a spinal, epidural, ocular, or regional nerve block, or when injected intravenously for regional anesthesia. In comparative trials, its clinical effects were not generally significantly different from those of other short-acting local anesthetics like lidocaine, prilocaine, and chloroprocaine, and there is no conclusive evidence demonstrating above-average neurotoxicity. Articaine proved to be suitable and safe for procedures requiring a short duration of action in which a fast onset of anesthesia is desired,
eg, dental procedures and ambulatory spinal anesthesia, in normal and in special populations

Articaine is a dental amide-type local anesthetic. It is the most widely used local anesthetic in a number of European countries and is available in many countries. It is the only local anaesthetic to contain a thiophene ring, meaning it can be described as 'thiophenic'; this conveys lipid solubility.

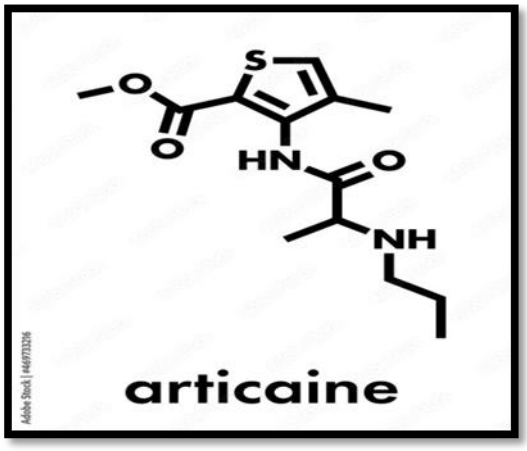
Brand Name: Septocaine

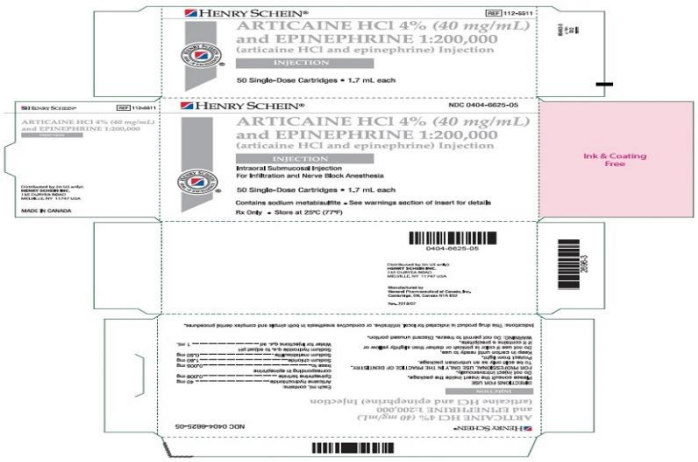
Geniric Name: Articaine

Dosage Form: Injection (Liq)

Treatment half-life:30 min

Metabolism: liver,plasma





Phases of Drug Development:

DRUG DISCOVERY:

Local anesthetics block peripheral nerves and are used to prevent pain, to provide motor blockade during surgical or dental procedures, for pain control during labor, or postoperatively and in the management of chronic pain.[1] Cocaine was the first reported ester-type local anesthetic for clinical use, in 1886, followed by procaine in 1904. In the search for less allergic compounds with a faster onset, the amide-type local anesthetic lignocaine was synthesized by Swedish chemist Nils Löfgren in 1943 and marketed as lidocaine in 1949. Since then, other amide local anesthetics have been introduced and used clinically for their favorable onset time and duration, eg, mepivacaine, prilocaine, bupivacaine, etidocaine, and ropivacaine. Among this group, articaine, originally synthesized as carticaine, entered dentistry practice in 1973. Epidural administration and comparison with lidocaine started in 1974. In 1984, it was released in Canada, followed by the UK in 1998, the rest of Europe and the US in 2000, and Australia in 2005. Currently, articaine 4% with adrenaline 5 µg/mL is widely used in dentistry.

CHARACTERIZATION OF DRUG:

Articaine 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride) differs from the other amide local anesthetics because it contains a thiophene ring and. The thiophene ring allows greater lipid solubility, which facilitates diffusion across the lipid-rich nerve membrane to access target receptors. In addition, articaine contains an ester group, so that hydrolyzation occurs in the plasma by nonspecific cholinesterases, further metabolism, and excretion, primarily in the kidneys.

Articaine blocks nerve conduction by reversibly binding to the α-subunit of the voltage-gated sodium channels within the inner cavity of the nerve, similar to other local anesthetics. Binding of articaine to the sodium channel reduces sodium influx so that the threshold potential will not be reached and impulse conduction stops. The blocking action of articaine on the sodium channel is state dependent: it has the highest affinity for the open state, an intermediate affinity for the inactivated state, and the lowest affinity for the resting state

The degree of neuronal block is affected by the diameter of the nerve. Larger-diameter fibers (touch/pressure/ motor) require higher concentrations of local anesthetic compared with small myelinated fibers (pain afferents). Articaine is lipid soluble, highly protein-bound (94%), and has a dissociation constant (pKa) of 7.8. Articaine is an intermediate-potency, short-acting local anesthetic with a fast onset of action

FORMULATIONS OF ARTICAINE DRUG:

Articaine has been commonly compared with its predecessor, lidocaine hydrochloride .since its introduction in 1948 lidocaine has maintained status as the mostly widely used local dental anesthesia in most countries proven efficacy with low allergenicity and toxicity over long term clinical use and research have confirmed the value and safety of this drug .Thus it become the gold standard to which all new local anesthetics are compared .several injectable lidocaine formulations have been approved by the FDA for dental application :2%without vasoconstrictor 2%with epinephrine 1:50,000 and 2 with epinephrine 1:100,000 .The 2% lidocaine with 1:100000 epinephrine formulations continues to be the most commonly used local anesthetic agent for routine dental procedure in united states .

Deposite the gold standard status of lidocaine numerous reports and editorial have supported and recognized the use of articaine .An editorial in the journel of the American Dental Associate acknowledge that articaine has garnered a majority of the dental market in many of the countries in which it is available .Another editorial quoted a drug companys marketing approach .Articaine has become the most popular local anesthetic for dentists wherever it has been introduced.

PHARMACOKINETICS ASPECTS AND ARICAINE DRUG DEPOSITION:

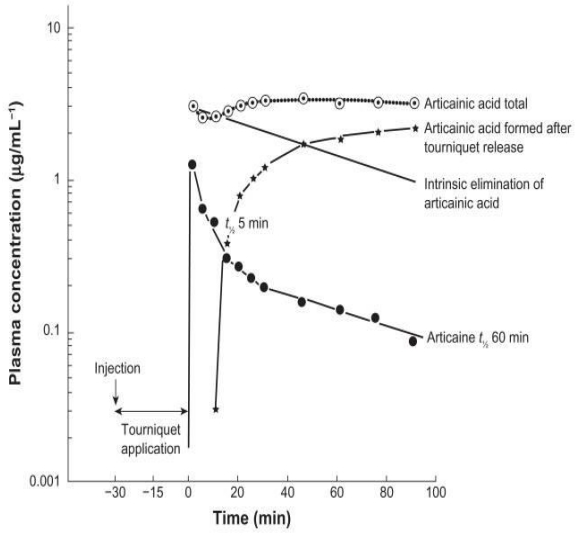
Articaine is 4-methyl-3(2-[propylamino]propionamido)-2-thiophenecarboxylic acid, methyl ester hydrochloride with a molecular weight of 320.84. It is the only amide local anesthetic that contains a thiophene ring. In addition, articaine is the only widely used amide local anesthetic that also contains an ester linkage . Ester LAs undergo metabolism (biotransformation, detoxification) as soon as the drug diffuses into capillaries and veins (hydrolysis by plasma esterase). Amide LAs enter the blood as still active drugs, circulating throughout the body until they enter the liver where they undergo metabolism by hepatic microsomal enzymes. Unlike the other amide local anesthetics that undergo metabolism in the liver, the biotransformation of articaine occurs in both the liver and in plasma.

ABSORPTION AND DISTRIBUTION

Local anesthetic drugs are administered to the areas around the nerves to be blocked, eg, the skin,

subcutaneous tissues, retrobulbar, intrathecal, and epidural spaces. Some of the drug will be absorbed into the systemic circulation; how much will depend on the vascularity of the area to which the drug has been applied and intrinsic effects of the drug or its additives on vessel diameter. Articaine, like most local anesthetics at concentrations that are used clinically, has a vasodilatory effect, increasing its systemic absorption. This is countered in preparations with epinephrine 1:60,000, 1:100,000, and 1:200,000 (5 µg/mL).[10]

The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. The more protein-bound the agent, the longer the duration of action, as free drug is more slowly made available for metabolism. Based on its physiochemical and stereochemical properties, protein binding of articaine is 94%.



METABOLISM AND ELIMINATION

The molecular structure of articaine is characterized by having both lipophilic and hydrophilic ends connected by a hydrocarbon chain. The "CO linkage" between the hydrocarbon chain and the lipophilic aromatic ring classifies articaine as being an ester local anesthetic, in which the link is metabolized in the serum by plasma cholinesterase. Articaine is quickly metabolized via hydrolysis into its inactive metabolite articainic acid, which is partly metabolized in the kidney into articainic acid glucuronide.

The pharmacokinetics and metabolism of articaine have been studied in ten patients undergoing intravenous regional anesthesia using 40 mL articaine 0.5% (200 mg).During tourniquet application and regional analgesia, 55% of the administered dose was already hydrolyzed by plasma (20%) and tissue (35%) esterase activity. After releasing the tourniquet, articaine and its metabolite articainic acid appeared in the blood; articaine was rapidly eliminated with a half-life of approximately 60 minutes . Low systemic concentrations and rapid metabolism of articaine also have been observed in a study during and after tumescent local anesthesia (infusion) for liposuction using dosages up to 38.2 mg/kg body weight.[14] Average maximum plasma concentrations (C_{max}) for articaine ranged from 136 (hips) to 264 ng/mL (abdomen); the average extent of absorption (AUC) ranged from 827 to 2203 ng · h/mL. The corresponding C_{max} and AUC values for articainic acid were substantially higher, ranging from 1719 to 7292 ng/mL and from 13,464 ng · h/mL (chin) to 74,962 ng · h/mL (abdomen), respectively. In liposuction, part of the applied drug is removed in the aspirate, and around 30% of the infused dose was recovered in the plasma.

Metabolism and elimination of exogenous substances in general depend significantly on normal function of the liver and kidney(s). Metabolism of local anesthetics produces metabolites that are more water soluble and ready to excrete than the parent compounds. Articaine is metabolized in the serum by plasma cholinesterase; although synthesis of cholinesterase is decreased in patients with liver diseases, fast hydrolysis is presumably preserved in their erythrocytes.[15] Seventy-five percent of articainic acid is excreted unchanged; the rest is glucuronidated by the kidneys before excretion. In patients with severe renal failure, both metabolites can accumulate, which in theory can cause local anesthetic systemic toxicity (LAST). The pharmacokinetics of lidocaine have been studied in renal-failure patients receiving hemodialysis.[16] Case reports describing other local anesthetics associate LAST with underlying cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. The American Society of Regional Anesthesia and Pain Medicine advises that heightened vigilance may be warranted in these patients, particularly if they are at the extremes of age .(Pharmacodynamics of local anesthetics in children are comparable to those in adults; pharmacokinetics, on the other hand, differ significantly. Special caution should be observed when using the amide local anesthetics because a lower intrinsic clearance or a decreased serum protein binding can easily lead to an increased risk of toxic reactions in younger patients.[17] The route of administration is one of the main determinants of safety in the use of local anesthetics in neonates and children; the application of articaine in children is mainly for those

undergoing dental procedures for which local anesthesia is required or as an addition to general anesthesia. The absorption of local anesthetics from mucous membrane after topical anesthesia is increased in children due to a greater local blood flow and cardiac output than in adults. In a study investigating 27 children 3–12 years of age, the authors advised the use of 2% articaine in pediatric dentistry because of the lower C_{max} and the shorter half-life.[18] They showed a shorter time to maximum concentration and increased clearance compared to investigations in adults. Based on their findings, they concluded there is no need to lower the articaine dose administered to adults in mg/kg for children. Vasoactive agents like epinephrine are very effective in reducing systemic uptake of local anesthetics, resulting in a longer duration and a lower C_{max}.[19] Articaine 4% with epinephrine 1:100,000 was also shown to be effective and safe for use in pediatric dentistry. Among patients 4–13 years of age, the only adverse event directly related to articaine was accidental lip injury; no pharmacokinetic investigation was performed.

PRECLINICAL TOXICITY STUDIES:

Leuschner and LeBlanc[40] examined the toxicity of articaine (CAS 23964-58-1) and of a respective preparation (Septanest SP; 4% articaine HCl and adrenaline 10 µg/ml in in vitro and in vivo experiments. Repeated subcutaneous (s.c.) administration of articaine HCl in rats and dogs demonstrated no pathomorphological systemic changes even at systemically toxic doses. The no-effect level (NOEL) was 25 mg/kg/day articaine HCl s.c. for the rat and 40 mg/kg/day articaine HCl s.c. for the dog Reproduction.

The toxicity of articaine (CAS 23964-58-1) and of a respective preparation (Septanest SP; 4% articaine HCl and epinephrine 1: 100,000) was examined in in vitro and in vivo experiments. The following endpoints were examined: repeated dose toxicity, reproduction toxicity, mutagenic potential and local tolerance. Repeated s.c. administration of articaine HCl in rats and dogs demonstrated no pathomorphological systemic changes even at systemically toxic doses. The no-effect level (NOEL) was 25 mg articaine HCl/kg b.w./day s.c. for the rat and 40 mg articaine HCl/kg b.w./day s.c. for the dog. Reproduction studies were performed in rats and rabbits at doses up to more than 10 times the maximum recommended human dose of 7 mg articaine HCl/kg b.w. and revealed no evidence of harm to the foetus or to other aspects of reproduction, even at doses toxic to the parental animals. Four standard in vitro and in vivo mutagenicity studies have shown no mutagenic potential up to cytotoxic concentrations or up to the maximum tolerated dose level. The local tolerance of articaine HCl was good to very good. The preclinical data indicate that articaine HCl does not possess any relevant side-effects or gross toxicity and can be considered a safe local anaesthetic.

INVESTIGATIONAL ARTICAINE APPLICATION:

Articaine is used for pain control. Like other local anesthetic drugs, articaine causes a transient and completely reversible state of anesthesia (loss of sensation) during (dental) procedures.

In dentistry articaine is used mainly for infiltration injections. Articaine, while not proven, has been associated with higher risk of nerve damage when used as a block technique. However, articaine is able to penetrate dense cortical bone — as found in the lower jaw (mandible) — more than most other local anaesthetic.

In people with hypokalmic sensory overstimulation, lidocaine is not very effective but articaine works well

Studies comparing lidocaine and articaine found that articaine is more effective than lidocaine in anaesthetizing the posterior first molar region. Articaine has been found to be 3.81 times more likely than lidocaine to produce successful anaesthesia when used for infiltration injections. However, there is no evidence to support the use of articaine over lidocaine for inferior alveolar nerve blocks.[] Furthermore, articaine has been demonstrated to be superior to lidocaine for use of supplementary infiltration following persistent pain despite a successful inferior dental nerve block with lidocaine.

BIOANALYTICAL TESTING AND CLINICAL TRIALS:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may notreflect the rate observed in practice

The reported adverse reaction are derived from clinical trials in united states and the united kingdom .Table 1 display the adverse reaction reported in clinical trials where 882 individuals were exposed to articaine hcl and epinephrine containing epinephrine 1:100,000 Table 2 display the adverse reaction reported in clinical trials where 182 individuals were exposed to articaine HCL and Epinephrine containing

epinephrine 1:100,000 and 179 individuals were exposed to articaine HCL and Epinephrine containing epinephrine 1:200,000

Adverse reaction observed in at least 1% of patients

TABLE 1:Adverse Reaction in controlled Trials with an Incident of 1%or Greater in Patients Administered Articaine HCL and Epinephrine Containing Epinephrine Articaine HCL and Epinephrine 1:100,000

Body system/Reaction	**Articaine HCL and Epinephrine containing epinephrine 1:100,000(N=882)INCIDENCE**
Body as a whole	13(1%)
Face edema	13(1%)
Head ache	31(4%)
Infection	10(1%)
Pain	114(13%)
Digestive system	114(13%)
Gingivitis	13(1%)
Nervous system	11(1%)
Paresthesia	11(1%)

TABLE 2 :Adverse Reaction in controlled trials with an Incidence of 1%or Greater in patients Administered Articaine HCL and Epinephrine containing Epinephrine 1:200,000 and Articaine HCL and epinephrine containg epinephrine 1:100,000

Reaction	**Articaine HCL and epinephrine 1:200,000(N=179)** **Incidence**	**Articaine HCL and epinephrine 1:100,000(N=182)** **Incidence**
Pain	11(6.1%)	14(7.6%)
ADR'S	33(18%)	35(19%)
Headache	9(5%)	6(3.2%)
Positive blood aspiration into syrige	3(1.6%)	6(3.2%)
Trisumus	1(0.5%)	3(1.6%)
Nausea and emesis	3(1.6%)	0(0%)
Sleepiness	2(1.1%)	1(0.5%)
Numbeness and tingling	1(0.5%)	2(1%)
Palpitation	0(0%)	2(1%)
Ear symptoms (earache,otitismedia)	1(0.5%)	2(1%)
Cough,persistent cough	0(0%)	2(1%)

TABLE 3: Adverse reaction in controlled Trials with an incidence of less than 1%but considered clinically

Relevant in patients Administered Articaine HCL and Epinephrine

Body system	**Reactions**
Body as a whole	Asthenia;back pain;injection site pain;burning sensation above injection site;malaise;neck pain
Cardivascular system	Hemorrhage;migraine;syncope;tachycardia;elevated blood pressure
Hemic and Lymphatic system	Ecchymosis;lymphadenopathy
Metabolic and Nutritional system	Edema;thirst
Skin and Appendages	Pruritus;skin disorder

HISTORICAL APPROACHES IN DRUG DISCOVERY:

Ayurveda:

In the United States, Ayurveda is considered complementary and alternative medicine (CAM). Because herbs are considered as dietary supplements, they do not meet the same standards and regulations as that of the pharmaceutical industry. The July 2001 issue of JAMA discusses extensively the use of herbal medicines in the perioperative settings.[The American Society of Anaesthesiologist (ASA) has acknowledged the adverse reaction potential of herbal medicines and recommended patients to "stop taking all herbal medications two weeks before surgery". The ASA has also published a bulletin, "What you should know about herbal and dietary supplement use and anaesthesia" for patient awareness. However, these recommendations are difficult to implement as most preoperative checks are carried out only a few days prior to the surgery.

In a first of its kind study, Anna Lee and coworkers allowed patients to take herbal products in the perioperative period, and the complications arising from this were studied. The researchers concluded that the common practice of taking over-the-counter herbal tea or soups is not detrimental; however, taking traditional Chinese herbal medicines (TCHM) by prescription before surgery is likely to cause problems as they contain potent herbs at higher doses.

NEW APPROACHES IN DRUG DISCOVERY:

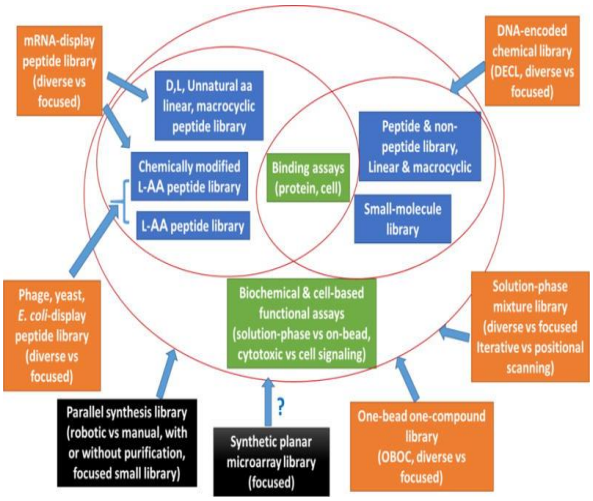
As a new drug for local dental anesthesia, articaine has become popular in the clinic in recent years. In this review, we describe the development of articaine, explain its mechanism of action, compare its efficacy with that of other commonly used local anesthetics in dental treatment, and summarize the application of articaine in special populations. In conclusion, the anesthetic efficacy of articaine in clinical dental treatment is better than that of lidocaine, and its safety is not statistically different from that of lidocaine. In particular, articaine has several advantages and can be selected flexibly for clinical use. Atecaine has great potential for wide application in dental clinics in the near future.

COMBINATORIAL CHEMISTRY:

Several combinatorial methods have been developed to create focused or diverse chemical libraries with a wide range of linear or macrocyclic chemical molecules: peptides, non-peptide oligomers, peptidomimetics, small-molecules, and natural product-like organic molecules.Each combinatorial approach has its own unique high-throughput screening and encoding strategy. In this article, we provide a brief overview of combinatorial chemistry in drug discovery with emphasis on recently developed new technologies for design, synthesis, screening and decoding of combinatorial library. Examples of successful application of combinatorial chemistry in hit discovery and lead optimization are given. The limitations and strengths of combinatorial chemistry are also briefly discussed. We are now in a better position to truly leverage the power of combinatorial technologies for the discovery and development of next-generation drugs. Overview of combinatorial technologies. The various combinatorial technologies are shown in orange (diverse and focused libraries) and black (focused small library), the nature of chemical compounds is shown in blue, and the two broad groups of screening assays are shown in green. Depicted within the red ovals are the screening assays and nature of library compounds pertaining to each technology. The question mark indicated that, in practice, synthetic planar microarray is limited to peptides and simple oligomers.

Ultra- High – Throughput Screening:

The trend towards assay miniaturization for high-throughput and ultra-high-throughput screening continues to spur development of homogeneous, fluorescence-based assays in higher density, smaller volume microplate formats. Recently, first-generation microfluidic devices have been designed for performing continuous-flow biochemical and cell-based assays. These devices provide orders-of-magnitude reduction in reagent consumption, and offer the potential for implementing high-throughput screening in formats that integrate up-front compound handling with unique assay functionality.



Over the past decade, a variety of scientific advances and economic pressures have driven the need for improved drug discovery screening technology 1, 2. These include the growing number of potential therapeutic targets emerging from the field of functional genomics, the rapid development of large compound libraries derived from parallel and combinatorial chemical synthesis techniques, and the ever increasing pressure to reduce development costs while enhancing commercial competitiveness in the pharmaceutical industry. Recent estimates of the number of individual genes in the human genome (~10,000) and the number of unique chemical structures theoretically attainable using existing chemistries (~100 million) suggest that up to 10^{12} assays would be required to completely map the structure-activity space for all potential therapeutic targets .

The demand for screening large compound collections against an increasing number of therapeutic targets has stimulated technology development in the areas of assay automation, miniaturization, and detection methodologies. Assay throughput was initially addressed by adoption of the 96-well microplate format and the use of liquid-dispensing and plate-handling robotics for automation [2]. Although this assay format is still widely used, many screening groups are presently moving towards 384-well and higher density, smaller volume plate formats 3, 4. Typical 'high-throughput' screening (HTS) programs in the pharmaceutical industry now operate at throughput rates on the order of 10,000 compounds per assay per day [2], with some laboratories working at 'ultra-high throughput' rates in excess of 100,000 assays per day.

CPCSEA Guidelines for the Care and Use of Laboratory Animals:

GOAL:

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioral research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals.

VETERNARY CARE :

Adequate veterinary care must be provided and is the responsibility of a veterinarian or a person who has training or experience in laboratory animal sciences and medicine.Daily observation of animals can be accomplished by someone other than a veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behavior,and well-being is conveyed to the attending veterinarian.The veterinarian can also contribute to the establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation.Institutional requirements will determine the need for full-time or part-time or consultative veterinary services.

QUARANTINE, STABILIZATION and SEPARATION:

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey) Effective quarantine procedures should be used for non-human primates to help limit exposure

of human's zoonotic infections. Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological, and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals. Physical separation of animals by species is recommended to prevent interspecies disease physiological and behavioral changes due to interspecies conflict. Such separation is usually accomplished by housing different species in separate rooms; however, cubicles, laminar-flow units, cages that have filtered air or separate ventilation, and isolators shall be suitable alternatives. In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviorally compatible.

SUREILLANCE, DIAGNOSIS, TREATMENT, and CONTROL OF DISEASE:

All animals should be observed for signs of illness,injury, or abnormal behavior by animal house staff. Asa rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2).Unexpected deaths and signs of illness, distress, o rother deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony.If an entire room of animals is known or believed to be exposed to an infectious agent (e.g. Mycobacterium Tuberculosis in non-human primates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be made available.

ANIMAL EXPERIMENT INVOLVING HAZARDOUS AGENT:

Institutions should have policies governing experimentation with hazardous agents. Institutional Biosafety Committee whose members are knowledgeable about hazardous agents are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues. This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions (Annexure– 8).Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Biosafety Committee and Institutional Animal Ethics Committee (IAEC).

DURATION OF EXPERIMENT:

No animal should be used for experimentation for more than 3 years unless adequate justification is provided.

PHYSICAL RESTRAINT OF ANIMAL FOR EXAMINATION:

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal.Prolonged restraint of any animal, including thechairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives.The following are important guidelines for the use of restraint equipments: Restraint devices cannot be used simply as a convenience in handling or managing animals.The period of restraint should be the minimum required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to adapt to the equipment.Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions or illness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporary or permanent removal of the animal from restraint.

(a) Building materials :should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces including vermin and pest resistance.

(b) Corridor(s): should be wide enough to facilitate the movement of personnel as well as equipments and should be kept clean.

(c) Utilities :such as water lines, drain pipes and electrical connections should preferably be accessible through service panels or shafts in corridors outside the animal rooms. (d) Animal room: doors should be rust, vermin and dust proof. They Should fit properly within their

frames and provided with an observation window. Door closures may also

(e) Exterior windows :Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary to provide alternate sources of light and ventilation. In primate rooms, windows can be provided.

(f) Floors :Floors should be smooth, moisture proof, nonabsorbent, skid-proof, resistant to wear, acid, solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

(g) Drains :Floor drains are not essential in all rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. Where floor drains are used, the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity, drainage must be adequate to allow rapid removal of water and drying surface

(h) Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors and corners. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure

Preclinical study :

The study was carried out on 50 patients at outpatient Department of oral and maxillofacial surgery who needed bilateral maxillary premolar extractions for orthodontic purpose. Patients included in this study (Table 4).

were in the age group of 15-25 years, both genders and systemically healthy. Bleeding disorders, hypertensive, diabetic, pregnant, allergic to local anesthetics, reluctant and medically compromised patients were excluded from the study.

All the patients were checked for normal vital signs. Detailed medical history was taken along with clinical examination. All the patients were explained about visual analog scale (VAS) before injecting local anesthesia. Single practitioner injected anesthesia to all patients with slow injection patients. Pain experience was analyzed on VAS. All the data were statistically analyzed.

Experimental sites (Group 1) were injected with 0.5-1 ml of 4% articaine HCL containing 1:100000 adrenaline, incrementally in the buccal vestibule. No palatal anesthesia was injected, but the desired anesthetic effect was achieved with the above.

On the other hand, control sites (Group 2) were injected with 0.8-1 ml of 2% lignocaine HCL containing 1:100000 adrenaline, incrementally in the buccal vestibule. When the objective symptoms were checked, it was found that palatal anesthesia was absent hence additional 0.5 ml was injected to obtain a desired result.

After assessing the signs and symptoms of obtaining complete anesthesia, maxillary first premolar were extracted using forceps techniques. In the process of extraction, patients were periodically questioned about the pain. They evaluated pain using 100 mm VAS during and after the extraction.
This study was conducted with 50 patients aged between 15 and 25 years. All the parameters, i.e., drug volume, time of onset, duration of anesthesia and pain rating were recorded for entire pThe mean administered volume of articaine and lignocaine were 0.779 ± 0.1305 and 1.337 ± 0.2369 respectively. It should be noted that the articaine volume administered was almost half of the lignocaine.

	N	Mean	Standard deviation	T	*P* value
Pair 1					
Group 1 (articaine)	50	0.779	0.1305	22.251	<0.0005
Group 2 (lignocaine)	50	1.337	0.2369		

The mean onset time of lignocaine anesthesia was 1.337 ± 0.2369, whereas in articaine group the mean time was 1.012 ± 0.2058 min. This indicates that onset time of articaine was significantly less than lidocaine ($P < 0.0005$) (Table 5).

Buccal		Palatal	
Articaine	Lignacaine	Articaine	Lignacaine
1.3	0.7	1.8	99.1
VAS: Visual analogue scale			

Pain rating showed that there was no significant difference in pain score in articaine palatal and buccal group ($P > 0.8892$), whereas a significant difference was noted in lignocaine palatal and buccal group (Tables 4). Duration of pain in Group 1 was 69.08 ± 18.247 and 55.66 ± 6.414 in Group 2 patients. Duration of anesthesia is articaine group is more than the lignocaine group. In the entire study, there was no injection complication (Table6)

	N	Mean	Standard deviation	T	*P* value
Pair 1					
Group 1 (articaine)	50	1.012	0.2058	22.396	<0.0005
Group 2 (lignocaine)	50	3.432	0.7323		

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	N	Mean	Standard deviation	*P* value
Pair 1				
Group 1 (articaine buccal)	50	1.3	3.648	0.8892
Group 2 (lignocaine palatal)	50	1.8	4.115	
Pair 2				
Group 1 (lignocaine buccal)	50	0.7	1.824	<0.0005
Group 1 (lignocaine palatal)	50	98.68	0.6209	

	N	Mean	Standard deviation	T	*P* value
Pair 1					
Group 1 (articaine)	50	69.08	18.247	5.948	<0.0005
Group 2 (lignocaine)	50	55.66	6.414		

In this study, we observed that the palatal infiltration was required in approximately 98% of cases when lignocaine was used, whereas in articaine group palatal anesthesia was never required. This gives immense comfort to patients as he is not exposed to second prick. This property can be attributed to a "thiophene ring" in its molecular structure, which makes it more lipophilic and this accounts for its diffusion properties across all the tissues.5 Articaine is metabolized in the liver, tissues and blood and

hence it is cleared out very fast from the body. This is the only anesthetic agent, which is inactivated from our body in two ways.

Articaine is one of the less used anesthetic agents in dentistry. Literatures have proved its usefulness about its efficacy and safety. It also relieves the patients from an additional injection. Reports of reactions are very rare and can happen in other agents too. Rapid inactivation in liver and plasma reduces the risk of the drug overdose. Certain added advantages like shorter time of onset, longer duration of action and greater diffusion property makes it an ideal anesthetic agent to be used in dentistry.

ANIMAL MODELS IN PRECLINICAL RESEARCH:

Hyperalgesia appeared in carrageenan-inflamed paws (Table 1). The mean reaction time was 5.04 ± 0.2 s and 15.85 ± 0.3 s for inflamed ipsilateral versus contralateral healthy paw, respectively. The microemulsion applied to ipsilateral paw increased reaction time to heat. The AUC of paw withdrawal time versus time and the Emax increased by 89% ($P < 0.0130$) and 97% ($P < 0.0004$), respectively, with respect to inflamed untreated paws (control untreated). After application of Ametop® gel, AUC increased by 73% ($P = 0.0099$) and Emax by 58% (nonsignificant) compared with inflamed, untreated paws. In rats treated with EMLA cream, AUC increased by 58% and Emax by 43%, both increases being nonsignificant. The greatest analgesic effect was obtained after infiltration of amethocaine, with an increase in AUC and Emax of 239% ($P < 0.00001$)

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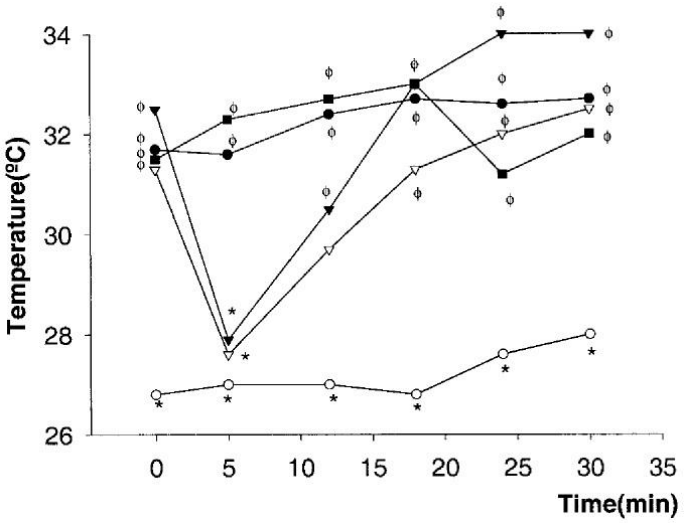
Treatment	Heat			Touch		
	AUC (s²)	Emax(s)	Tmax(min)	AUC(s²)	Emax(s)	Tmax(min)
Control untreated	122.2 ± 26.1	6.9 ± 1.4	-	124.4 ± 11.9	6.3 ± 0.9	-
Amethocaine 1% infiltration	413.8 ± 86.7*‡	18.2 ± 4.1*‡	11.8 ± 4.6‡	530.0 ± 127.6*	25.0 ± 5.3*	5 ± 0.0
Amethocaine 4% microemulsion	230.9 ± 29.8*†	13.6 ± 2.00*†	4.2 ± 1.3	221.4 ± 18.5*†	17.1 ± 3.2*†	5 ± 0.0
Amethocaine 4% gel	211.6 ± 62.5*†	10.9 ± 2.9†	13.8 ± 6.5‡	115.0 ± 14.0†‡	5.1 ± 1.1†‡	18.0 ± 6.4†‡
EMLA cream	193.0 ± 70.8†‡	9.9 ± 4.4†‡	14.2 ± 5.8‡	124.4 ± 11†‡	6.3 ± 0.9†‡	18.8 ± 5.9†‡

AUC = area under curve of paw withdrawal time versus time (1 to 30 min); Emax = maximum anesthetic effect; tmax = time of maximum effect after anesthetic application; EMLA = eutectic mixture of 2.5% lidocaine and 2.5% prilocaine
Results are mean ± SD of 5–9 rats. Amethocaine 1% was administered s.c. in the sole of the paw (0.1 mL).
The AUC of contralateral paw for heat (432.5 ± 18.5) or touch (569.9 ± 62.0) response did not change with any treatment.
*†‡ $P < 0.05$ versus control untreated, amethocaine infiltration, and amethocaine microemulsion, respectively.

d 163% ($P < 0.00001$), respectively.

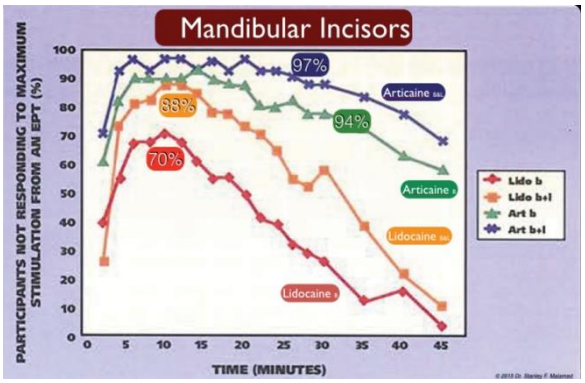
The peak effect (Tmax) occurred significantly faster after application of the amethocaine microemulsion than after amethocaine gel, EMLA cream, or amethocaine infiltration. In none of the rats tested was there an increased pain tolerance to heat in the contralateral healthy paws.(fig no 5)



Allodynia was clearly seen in carrageenan-treated edematous paws. The mean reaction time was 3.98 ± 0.3 s and 22.8 ± 0.3 s for ipsilateral inflamed and contralateral-healthy paws, respectively. Only topical microemulsion and amethocaine infiltration increased the paw withdrawal time after a light touch stimulus. Contralateral paws of inflamed rats were not affected by any, from 3 h to 3.5 h after carrageenan injection (0 to 30 min of treatment), the skin temperature of the ipsilateral paw was higher than that of the contralateral healthy paw ($P < 0.001$). After ipsilateral topical treatment with amethocaine microemulsion or vehicle, paw skin temperature decreased to a mean value that did not differ from that of contralateral healthy paws. Vehicle infiltration in the inflamed paw did not change its temperature. None of the amethocaine gel, EMLA cream, or the vehicle alone affected the temperature of the inflamed paw (data not shown) treatment.

Healthy rats selected for high sensitivity to heat-induced pain had paw withdrawal latency of 12.2 ± 0.5 s and 11.6 ± 0.4 s in the right and left paw, respectively (Tables 2 and 3). As seen in Table 2, all formulations tested produced analgesia in both ipsilateral and contralateral paws. All formulations showed activity in the ipsilateral paw, as evidenced by similar and significant increases in AUC and Emax as compared with healthy untreated paws. However, the effect of the microemulsion and amethocaine infiltration appeared before that of the gel. In the contralateral paw, all topical formulations produced similar increases in the AUC and Emax; however, the microemulsion acted faster than the gel or EMLA. A greater effect was seen with

amethocaine infilteration which always peakes at 5min



Treatment	Ipsilateral paw			Contralateral paw		
	AUC (s^2)	Emax(s)	Tmax(min)	AUC(s^2)	Emax(s)	Tmax(min)
Control untreated	269.7 ± 27.6	12.3 ± 1.3	-	268.3 ± 26.3	11.8 ± 1.3	-
Amethocaine 1% infiltration	561.8 ± 39.1‡	20 ± 0.0*	5 ± 0.0	431.2 ± 38.15*	18.0 ± 1,65*	14.0 ± 4.9‡
Amethocaine 4% microemulsion	445.0 ± 75.2†	19.1 ± 1.7*†	6.9 ± 1.7	394.7 ± 6.47*	17.8 ± 1.6*	6.0 ± 2.6†
Amethocaine 4% gel	419.6 ± 42.8*†	18.7 ± 1.6*†	14.5 ± 10.4†‡	417.7 ± 36.9*	18.3 ± 2.6*	10.8 ± 2.9‡
EMLA cream	404.5 ± 114.3*†	17.0 ± 3.1†	8.3 ± 5.5†‡	391.1 ± 60.8*	16.7 ± 2.2*	19.3 ± 9.5‡

AUC = area under curve of paw withdrawal time versus time (1 to 30 min); Emax = maximum anesthetic effect; tmax = time of maximum effect after anesthetic application; EMLA = eutectic mixture of 2.5% lidocaine and 2.5 % prilocaine

Results are mean ± SD of 5-9 rats. Amethocaine 1% was administered s.c. in the sole of the paw (0.1 mL).

Amethocaine 1% was administered s.c. in the sole of the paw (0.1 mL), whereas the microemulsion, gel, and cream were applied topically in the sole and palm of the paw (200 µL).

†‡ $P < 0.05$ versus control untreated, amethocaine infiltration, and amethocaine microemulsion, respectively.

TABLE NO 8

Healthy rats selected for high sensitivity to light touch-induced paw withdrawal had a reaction time of 5.8 ± 0.3 s and 6.7 ± 0.6 s for the right and left paw, respectively. In the ipsilateral paw, the amethocaine microemulsion increased the time of paw flick withdrawal after a light-touch

stimulus. After amethocaine gel and EMLA cream, a nonsignificant increase in both AUC and Emax was seen. Tmax was similar for all topical formulations. Amethocaine infiltration produced greater effects and peaked before that of topical formulations. In the contralateral paw, only the microemulsion and amethocaine infiltration produced significant increases in the touch-paw flick. In both cases, the effect appeared early at 6.8 ± 3.2 min and 7.0 ± 3.4 min, respectively.

BIOSTATISTICS IN PRECLINICAL STUDIES :

Introduction:

In this chapter, we discuss the basics of what you need to know about biostatistics in order to statistically analyze and interpret the data from your *in vitro* and preclinical *in vivo* experiments. Experiments are conducted to answer one or more specific scientific questions, and they must be designed so that they are likely to provide answers with minimal bias and appropriate measures of variability and significance. Here, we discuss different methods of analysis and their accompanying assumptions. In addition, we cover several different experimental design considerations as well as the subsequent interpretation and graphical presentation of data and statistical findings. Furthermore, we provide insight on both sides of the debates surrounding controversial issues such as testing multiple hypotheses in a single study and addressing outliers in the data. We conclude with a discussion of the future of biostatistics for *in vitro* and preclinical experiments, highlighting the importance of learning biostatistical software in your training. We suggest you read this chapter before you begin performing experiments and collecting data.

Summamarizing The Data:

As a new drug for local dental anesthesia, articaine has become popular in the clinic in recent years. In this review, we describe the development of articaine, explain its mechanism of action, compare its efficacy with that of other commonly used local anesthetics in dental treatment, and summarize the application of articaine in special populations. In conclusion, the anesthetic efficacy of articaine in clinical dental treatment is better than that of lidocaine, and its safety is not statistically different from that of lidocaine. In particular, articaine has several advantages and can be selected flexibly for clinical use. Atecaine has great potential for wide application in dental clinics in the near future.

Data Presentation:

Given articaine's ability to diffuse through the thick cortical plate of bone following infiltration in the adult mandible, Kanaa et al looked at the ability of articaine infiltration to increase the success rate of pulpal anesthesia following an inferior alveolar nerve block (IANB) with 2% lidocaine with epinephrine 1:80,000.19 Patients received IANBs at each of two occasions (2.0 mL) lidocaine with epinephrine). Then they received either a buccal infiltration of 4% articaine with epinephrine 1:100,000 or a 'dummy' injection in the buccal fold by the mandibular 1st molar. The 1st molar and 1st premolar were pulp tested every three minutes for 45 minutes.

Results are shown in Figures 2 and 3. In both teeth the additional articaine infiltration significantly increased the success rate of pulpal anesthesia (55.6% to 91.7% for 1st molar; 66.7% to 88.9% for 1st premolar). Though the study concluded at 45 minutes there was no indication that pulpal anesthesia was waning at that time.

CONCLUSION:

Pain management plays a crucial role in the success of any dental treatment in a pediatric patient. Minimising the fear and anxiety, a proper

management protocol can help develop a positive attitude. Evidence of superiority over other LA drugs, use of articaine - the choice will be based on the personal preference and experiences of individual clinicians.

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