Handbook of local anesthesia 6th edition pdf download

Handbook of Local Anesthesia book pdf download - Stanley Malamed A practical, "how-to" guide to safe anesthesia practices in dentistry, Handbook of Local Anesthesia, 6th Edition covers all the latest advances in science, instrumentation, and pain control techniques. From basic concepts to specific injection techniques, from dosage charts to the proper care and handling of equipment, this book provides in-depth, full-color coverage of key anesthesia topics, including specific hazards and errors in technique that may result in complications. Written by Dr. Stanley Malamed, dentistry's leading expert on this subject, Handbook of Local Anesthesia is a valuable reference that will help you prevent, recognize, and manage complications of local anesthesia administration. Videos on an available companion DVD (sold separately) are narrated by Dr. Stanley Malamed, covering topics such as local anesthetic agents, anesthetic injection techniques, potential complications, and risk management. Full-color photographs and line drawings are included throughout the book. In-depth discussions cover the anesthetic agents used in dentistry, along with their clinical actions. Routes of administration are described for all anesthetics. The proper care and handling of equipment is addressed, along with the problems that may be encountered. Requirements for pain control and local anesthesia within various dental specialties are included. Comprehensive information on Articaine is included, a local anesthetic that is gaining widespread use in the United States. Numerous boxes and tables provide a quick reference and comparison of techniques, drugs, and dosages. Dosage charts, injection techniques, information on duration of action, and contraindications for local anesthetics are included at the end of the book for quick reference. VDOC.PUB Download Embed This document was uploaded by our user. The uploader already confirmed that they had the permission to publish it. If you are author/publisher or own the copyright of this documents, please report to us by using this DMCA report form. Report DMCA A practical, "how-to" guide to safe anesthesia practices in dentistry, Handbook of Local Anesthesia, 6th Edition covers all the latest advances in science, instrumentation, and pain control techniques. From basic concepts to specific injection techniques, from dosage charts to the proper care and handling of equipment, this book provides in-depth, full-color coverage of key anesthesia topics, including specific hazards and errors in technique that may result in complications. Written by Dr. Stanley Malamed, dentistry's leading expert on this subject, Handbook of Local Anesthesia is a valuable reference that will help you prevent, recognize, and manage complications of local anesthesia administration.Videos on an available companion DVD (sold separately) are narrated by Dr. Stanley Malamed, covering topics such as local anesthetic agents, anesthetic injection techniques, potential complications, and risk management. Full-color photographs and line drawings are included throughout the book. In-depth discussions cover the anesthetic agents used in dentistry, along with their clinical actions. Routes of administration are described for all anesthetics. The proper care and handling of equipment is addressed, along with the problems that may be encountered. Requirements for pain control and local anesthesia within various dental specialties are included. Comprehensive information on Articaine is included, a local anesthetic that is gaining widespread use in the United States. Numerous boxes and tables provide a quick reference and comparison of techniques, drugs, and dosages. Dosage charts, injection techniques, information on duration of action, and contraindications for local anesthetics are included at the end of the book for quick reference.   Updated discussions of the armamentarium needed to succeed in local anesthesia delivery reflect the latest available drugs and devices. Updated discussions of the techniques needed to provide successful pain control. Updated step-by-step procedures cover the techniques for administering intraoral anesthesia. The latest advances in science, technology, and pain control techniques are covered. Year: 2,012 Edition: 6 Pages: 432 Pages In File: 996 Language: English Topic: 170 Library: erdebooks.com Issue: erde Identifier: 0323074138,9780323074131 Commentary: converted from epub format Org File Size: 61,065,846 Extension: pdf ELSEVIER HA.~DBOOK OF LOCAL ANESTHESIA Copyrlpc c 201)by Wosbr.an i.prtnt of Elwricr In Cop)Tipc 0 lOOf by Motbr.lnc.. an afiliatt of - · &"'W'lic: t:naltlcd8f ollldbot pr..:ttct in this 6dd arc rontt.lntlr 31: 8 Ill oo N !:'-. «> Cl.. -a- G)O ~ ~ C ~ I :Q E •.. Ill ·- ..c c z ·-"Cl 1110 E>Ill' i:::; tJ) ~t: ~ "' ::r: o 6 '-z/ I ~!:2'1a "'i _0 "' o ••. ·- •.• 0 z "Cl Cl.. tJ) -v cu -~ -5 Ec o(~ ~ -U I I ~ I 0"' Q-o I o"' ,c.5' I ~ - z .•. './ rl I"' ~ I I ~ ii 0 ~ _g~ ...••~ ~ "' OW~ OW so""""""",,, .!::!=I ~ ::I I I"' w "iii ~ ~ I I 0 I 0 ...p o. r: ~ ti •.. ::I \0 ~ ~-;; ~~ -' E m cu ~a www.ShayanNemoodar.com .5 ~ 1:°' ·~~ i~ .5 ~ ~ ·~ ~ cu s ~o l 11.>B . ~ en CHAPTER TABLE 1-7 Factors Affecting 1 Neurophysiology 23 Local Anesthetic Action Factor Action Affected Description pK. Onset Lipid solubility Anesthetic potency Protein binding Duration Nonnervous tissue diffusibility Vasodilatoractivity Onset LowerpK. = More rapid onset of action, more RN moleculespresent to diffuse through nerve sheath; thus onset time is decreased Increased lipid solubility= Increased potency (e.g.,procaine= 1; etidocaine = 140) Etidocaine produces conduction blockade at very low concentrations, whereas procaine poorly suppressesnerve conduction, even at higher concentrations Increased protein binding allowsanesthetic cations (RNH') to be more firmly attached to proteins located at receptor sites;thus duration of action is increased Increased diffusibility= Decreasedtime of onset Anesthetic potency and duration Greater vasodilator activity= Increased blood flow to region = Rapid removal of anesthetic molecules from injection site; thus anesthetic potency and duration are decreased From Cohen S, Burns RC: Pathways of the pulp, ed 6, St Louis, 1994, Mosby. Difficulty Reachieving Profound Anesthesia. In this second situation, as in the first, the dental procedure has outlasted the clinical effectiveness of the local anesthetic drug, and the patient is experiencing pain. The doctor read ministers a volume of local anesthetic, but unlike in the first scenario, effective control of pain does not occur. Tachyphylaxis. In this second clinical situation, a process known as tachyphylaxis occurs. Tachyphylaxis is defined as increasing tolerance to a drug that is administered repeat edly. It is much more likely to develop if nerve function is allowed to return before reinjection (e.g., if the patient com plains of pain). The duration, intensity, and spread of anes thesia with reinjection are greatly reduced.41 Although difficult to explain, tachyphylaxis is probably brought about by some or all of the following factors: edema, localized hemorrhage, clot formation, transudation, hyper natremia, and decreased pH of tissues. The first four factors isolate the nerve from contact with the local anesthetic solu tion. The fifth, hypernatremia, raises the sodium ion gradi ent, thus counteracting the decrease in sodium ion conduction brought about by the local anesthetic. The last factor, a decrease in pH of the tissues, is brought about by the first injection of the acidic local anesthetic. The ambient pH in the area of injection may be somewhat lower, so that fewer local anesthetic molecules are transformed into the free base (RN) on reinjection. Duration of Anesthesia As the local anesthetic is removed from the nerve, the func tion of the nerve returns rapidly at first, but then it gradually slows. Compared with onset of the nerve block, which is rapid, recovery from the nerve block is much slower because the local anesthetic is bound to the nerve membrane. Longer acting local anesthetics (e.g., bupivacaine, etidocaine, ropi vacaine, tetracaine) are more firmly bound in the nerve membrane (increased protein binding) than are shorter acting drugs (e.g., procaine, lidocaine) and therefore are released more slowly from receptor sites in the sodium chan nels. The rate at which an anesthetic is removed from a nerve has an effect on the duration of neural blockade; in addition www.ShayanNemoodar.com to increased protein binding, other factors that influence the rate of removal of a drug from the injection site are the vascularity of the injection site and the presence or absence of a vasoactive substance. Anesthetic duration is increased in areas of decreased vascularity (e.g., Gow-Gates mandibular nerve block vs. inferior alveolar nerve block), and the addi tion of a vasopressor decreases tissue perfusion to a local area, thus increasing the duration of the block. References 1. Covino BG, Vassallo HG: Local anesthetics: mechanisms of action and clinical use, NewYork, 1976, Grune & Stratton. 2. Bennett CR: Monheim's local anesthesia and pain control in dental practice, ed 5, St Louis, 1974, Mosby. 3. Fitzgerald MJT: Neuroanatomy: basic and clinical, London, 1992, BaillièreTyndall. 4. Noback CR,StromingerNL,Demarest RJ:The human nervous system: introduction and review, ed 4, Philadelphia, 1991, Lea & Febiger. 5. SingerSJ,Nicholson GL:The fluid mosaic model of the struc ture of cell membranes, Science 175:720--731, 1972. 6. Guyton AC:Basicneuroscience:anatomy and physiology,ed 2, Philadelphia, 1991, WB Saunders. 7. Guidotti G: The composition of biological membranes, Arch Intern Med 129:194--201, 1972. 8. Denson DD,Maziot JX:Physiology,pharmacology,and toxicity of local anesthetics: adult and pediatric considerations. In Raj PP, editor: Clinical practice of regional anesthesia, New York, 1991, Churchill Livingstone. 9. Heavner JE: Molecular action of local anesthetics. In Raj PP, editor: Clinicalpractice of regional anesthesia,NewYork,1991, Churchill Livingstone. 10. de Jong RH: Local anesthetics, ed 2, Springfield, Ill, 1977, Charles C Thomas. 11. Hodgkin AL, HuxleyAF:A quantitative description of mem brane current and its application to conduction and excitation in nerve, J Physiol (London) 117:500--544, 1954. 12. Noback CR, Demarest RJ: The human nervous system:basic principles of neurobiology,ed 3, NewYork,1981, McGraw-Hill, pp 44--45. 13. KeynesRD: Ion channels in the nerve-cellmembrane, SciAm 240:326-335, 1979. 24 PARTI The Drugs 14. Cattarall WA:Structure and function of voltage-sensitiveion channels, Science242:50--61, 1988. 15. Hille B: Ionic selectivity, saturation, and block in sodium channels: a four-barrier model, J Gen Physiol 66:535-560, 1975. 16. Ritchie JM: Physiologicalbasis for conduction in myelinated nerve fibers.In Morell P,editor: Myelin,ed 2, NewYork, 1984, Plenum Press,pp 117-145. 17. Franz DN, Perry RS:Mechanismsfor differentialblock among single myelinated and non-myelinated axons by procaine, J Physiol 235:193-210, 1974. 18. de Jong RH,WagmanIH: Physiologicalmechanisms of periph eral nerve block by local anesthetics, Anesthesiology 24:684-- BollsL, editors: Ion channels in neural membranes, NewYork, 1986, Alan R Liss. 29. Hille B, Courtney K, Dum R: Rate and site of action of local anesthetics in myelinated nerve fibers. In Fink BR, editor: Molecular mechanisms of anesthesia, New York, 1975, Raven Press,pp 13--20. 30. SetnikarI: Ionization of baseswith limited solubility:investiga tion of substances with local anesthetic activity,J Pharm Sci 55:1190--1195, 1990. 31. Malamed SF: Buffering local anesthetics in dentistry, ADSA Pulse 44(3):8--9, 2011. 32. Stewart JH, Chinn SE, Cole GW, Klein JA: Neutralized lido 727, 1963. 19. Dettbarn WD: The acetylcholine system in peripheral nerve, Ann NY Acad Sci 144:483-503, 1967. 20. Goldman DE, Blaustein MP: Ions, drugs and the axon mem brane, Ann NY Acad Sci 137:967-981, 1966. 21. Wei LY:Role of surface dipoles on axon membrane, Science 163:280--282, 1969. 22. LeeAG:Model for action oflocal anesthetics,Nature 262:545548, 1976. 23. Seeman P: The membrane actions of anestheticsand tranquil izers, Pharmacol Rev 24:583--655, 1972. 24. Strichartz GR, Ritchie JM: The action of local anesthetics on 25. 26. 27. 28. ion channels of excitabletissues.In Strichartz GR,editor: Local anesthetics,NewYork, 1987, Springer-Verlag. Butterworth JF IY, Strichartz GR: Molecular mechanisms of local anesthesia:a review,Anesthesiology72:711-734, 1990. Ritchie JM: Mechanisms of action of local anesthetic agents and biotoxins, Br J Anaesth 47:191-198, 1975. RasminskyM: Conduction in normal and pathological nerve fibers.In SwashM, Kennard C, editors: Scientificbasis of clini cal neurology,Edinburgh, 1985, Churchill Livingstone. Ritchie JM: The distribution of sodium and potassium chan nels in mammalian myelinatednerve.In RitchieJM,KeyesRD, www.ShayanNemoodar.com 33. 34. 35. 36. caine with epinephrine for local anesthesia-II,J Dermatol Surg Oncol 16:942-945, 1990. BokeschPM,Raymond SA,Strichartz GR:Dependence oflido caine potency on pH and pC02• Anesth Analg 66:9-17, 1987. Bieter RN: Applied pharmacology of local anesthetics, Am J Surg 34:500--510, 1936. BuckleyMM, BenfieldP: Eutectic lidocaine/prilocaine cream: a reviewof the topical anesthetic/analgesicefficacyof a eutectic mixture of local anesthetics (EMLA),Drugs 46:126-151, 1993. CampbellAH, StasseJA,Lord GH, Willson JE:In vivo evalua tion oflocal anestheticsapplied topically,J Pharm Sci 57:2045- 2048, 1968. 37. Noback CR, Demarest RJ: The human nervous system: basic principles of neurobiology, ed 3, New York, 1981, McGraw-Hill. 38. de Jong RH: Local anesthetics, ed 2, Springfield, Ill, 1977, Charles C Thomas, pp 66--68. 39. RitchieJM,RitchieB,GreengardP: The activestructure oflocal anesthetics,J Pharmacol Exp Ther 150:152, 1965. 40. TuckerGT:Plasmabinding and disposition oflocal anesthetics, Int AnesthesiolClin 13:33, 1975. 41. Cohen EN, LevineDA,CollissJE,Gunther RE:The role of pH in the development of tachyphylaxisto local anesthetic agents, Anesthesiology29:994--1001, 1968. Pharmacology of Local Anesthetics Local anesthetics, when used for the management of pain, differ from most other drugs commonly used in medicine and dentistry in one important manner. Virtually all other drugs, regardless of the route through which they are administered, must ultimately enter into the circulatory systemin sufficientlyhigh concentrations (e.g.,attain thera peutic blood levelsin their target organ[s]) before they can begin to exert a clinical action. Local anesthetics, however, when used for pain control, cease to provide a clinicaleffect when they are absorbed from the site of administration into the circulation.One prime factor involvedin the termination of action of local anesthetics used for pain control is their redistribution from the nerve fiber into the cardiovascular system. The presence of a local anesthetic in the circulatory system means that the drug will be transported to every part of the body. Local anesthetics have the ability to alter the functioning of some of these cells. In this chapter, the actions of local anesthetics,other than their ability to block conduction in nerve axonsof the peripheral nervous system, are reviewed.A classificationof local anesthetics is shown in Box 2-1. Uptake drug such as thiopental may produce arteriospasm with an attendant decrease in tissue perfusion that if prolonged could lead to tissue death, gangrene,and loss of the affected limb. In this situation, procaine is administered IA in an attempt to break the arteriospasm and reestablishblood flow to the affected limb. Tetracaine, chloroprocaine, and pro poxycaine also possess vasodilating properties to varying degreesbut not to the degree of procaine. Cocaine is the only local anesthetic that consistently produces vasoconstriction.4 The initial action of cocaine is vasodilation followedby an intense and prolonged vaso constriction. It is produced by inhibition of the uptake of catecholamines (especially norepinephrine) into tissue binding sites. This results in an excessof free norepineph rine, leading to a prolonged and intense state of vasocon striction. This inhibition of the reuptake of norepinephrine has not been demonstrated with other local anesthetics,such as lidocaine and bupivacaine. A significant clinical effect of vasodilation is an increase in the rate of absorption of the local anesthetic into the blood, thus decreasingthe duration and quality (e.g.,depth) of pain control, while increasing the anesthetic blood (or plasma) concentration and its potential for overdose (toxic reaction). The rates at which local anesthetics are absorbed into the bloodstream and reach their peak blood level vary according to the route of administration (Table2-2). When injected into soft tissues,local anesthetics exert phar macologicaction on blood vesselsin the area.Alllocal anes thetics possess a degree of vasoactivity, most producing dilation of the vascular bed into which they are deposited, although the degreeof vasodilation may vary,and some may produce vasoconstriction.To some degree,these effectsmay be concentration dependent.1 Relativevasodilatingvalues of amide local anesthetics are shown in Table2-1. Ester local anesthetics are also potent vasodilating drugs. Procaine,the most potent vasodilator among local anesthet ics, is occasionallyinjected clinicallyto induce vasodilation when peripheral blood flowhas been compromised because of (accidental) intra-arterial (IA) injection of a drug (e.g., thiopental)2 or injection of epinephrine or norepinephrine into a fingertip or toe.3 IA administration of an irritating With the exceptionof cocaine,local anesthetics are absorbed poorly, if at all, from the gastrointestinal tract after oral administration. In addition, most local anesthetics (especiallylidocaine) undergo a significanthepatic first-pass effectafter oral administration. Afterabsorption of lidocaine from the gastrointestinaltract into the enterohepatic circula tion, a fraction of the drug dose is carried to the liver,where approximately72% of the dose is biotransformed into inac tive metabolites.5 This has seriously hampered the use of lidocaine as an oral antidysrhythmic drug. In 1984,Astra Pharmaceuticals and Merck Sharp & Dohme introduced an analog of lidocaine,tocainide hydrochloride,which is effec tive orally.6 The chemical structures of tocainide and lido caine are presented in Figure 2-1. PHARMACOKINETICS OF LOCAL ANESTHETICS Oral Route. 25 www.ShayanNemoodar.com 26 PARTI The Drugs TABLE 2-2 Time to Achieve Peak Blood Level BOX 2-1 Classification of Local Anesthetics Esters Esters of benzoic acid Butacaine Cocaine Ethyl aminobenzoate (benzocaine) Hexylcaine Piperocaine Tetracaine Esters of para-aminobenzoic Route Time, min Intravenous Topical Intramuscular Subcutaneous 5 (approximately) 5-10 30-90 acid Chloroprocaine Procaine Propoxycaine Amides Articaine Bupivacaine Dibucaine Etidocaine Lidocaine Mepivacaine Prilocaine Ropivacaine CH3 Q NHCOCHCH3 • HCI CH3 B Figure 2-1. Tocainide. A, Represents a modification of lidocaine (B) that is able to pass through the liver after oral administration Quinoline with minimal hepatic first-pass effect. Centbucridine TABLE 2-1 Relative Vasodilating Values of Amide-Type Local Anesthetics Vasodilating Activity Articaine Bupivacaine Etidocaine Lidocaine Mepivacaine Prilocaine Tetracaine I NH2 1 (approx) 2.5 2.5 1 0.8 0.5 NA MEAN % INCREASE IN FEMORAL ARTERY BLOOD FLOW IN DOGS AFTER INTRA-ARTERIAL INJECTION* 1 min 5 min NA NA 45.4 44.3 25.8 35.7 42.1 37.6 30 26.6 7.5 9.5 6.3 14 Modified from Blair MR: Cardiovascularpharmacology of local anaesthetics,Br J Anaesth 47(suppl):247-252,1975. NA, Not available. *Eachagent injected rapidly at a dose of 1 mg/0.1 mL saline. Topical Route. Local anesthetics are absorbed at differing rates after application to mucous membrane: In the tracheal mucosa, absorption is almost as rapid as with intravenous (N) administration (indeed, intratracheal drug admini stration [epinephrine, lidocaine, atropine, naloxone, and flumazenil] is used in certain emergency situations); in the pharyngeal mucosa, absorption is slower; and in the eso- www.ShayanNemoodar.com phageal or bladder mucosa, uptake is even slower than occurs through the pharynx. Wherever no layer of intact skinis present,topicallyappliedlocalanestheticscan produce an anesthetic effect. Sunburn remedies (e.g., Solarcaine, Schering-PloughHealthCareProducts,Inc.,Memphis,Tenn) usuallycontain lidocaine,benzocaine,or other anestheticsin an ointment formulation. Appliedto intact skin,they do not provide an anesthetic action, but with skin damaged by sunburn, they bring rapid relief of pain. A eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA) has been developedthat is able to provide surface anesthesia of intact skin.7 Injection. The rate ofuptake (absorption) oflocal anesthet icsafter parenteral administration (subcutaneous,intramus cular,or N) is related to both the vascularityof the injection site and the vasoactivityof the drug. N administration of local anesthetics provides the most rapid elevation of blood levelsand is used clinicallyin the primary management of ventricular dysrhythmias.8 Rapid N administration can lead to significantlyhigh local anes thetic blood levels,which can induce serious toxic reactions. The benefits to be accrued from N drug administration must alwaysbe carefullyweighedagainst any risks associated with N administration. Only when the benefits clearlyout weigh the risks should the drug be administered, as is the casewith pre-fatal ventricular dysrhythmias such as prema ture ventricular contractions (PVCs).9 CHAPTER2 Pharmacology of LocalAnesthetics Distribution Once absorbed into the blood, local anesthetics are distrib uted throughout the body to all tissues (Fig. 2-2). Highly perfused organs (and areas), such as the brain, head, liver, kidneys, lungs, and spleen, initially will have higher anes thetic blood levelsthan less highly perfused organs. Skeletal muscle, although not as highly perfused as these areas, con tains the greatest percentage of local anesthetic of any tissue or organ in the body because it constitutes the largest mass of tissue in the body (Table 2-3). The plasma concentration of a local anesthetic in certain target organs has a significantbearing on the potential toxic ity of the drug. The blood level of the local anesthetic is influenced by the followingfactors: 1. Rate at which the drug is absorbed into the cardiovascularsystem 2. Rate of distribution of the drug from the vascular compartment to the tissues (more rapid in healthy patients than in those who are medicallycompromised [e.g.,congestiveheart failure],thus leading to lower blood levelsin healthier patients) 3. Elimination of the drug through metabolic or excretory pathways The latter two factors serveto decreasethe blood levelof the local anesthetic. The rate at which a local anesthetic is removed from the blood is described as its elimination half-life. Simply stated, the elimination half-life is the time necessary for a 50% reduction in the blood level (one half-life= 50% reduction; two half-lives = 75% reduction; three half-lives = 87.5% reduction; four half-lives= 94% reduction; five half-lives= 97% reduction; sixhalf-lives= 98.5% reduction) (Table2-4). Alllocal anestheticsreadilycrossthe blood-brain barrier. They also readilycrossthe placenta and enter the circulatory system of the developingfetus. Metabolism (Biotransformation, Detoxification} A significant difference between the two major groups of local anesthetics,the esters and the amides, is the means by which the body biologicallytransforms the active drug into Fat Muscle SHa of ln)ecllon Brain Myocardium Lungs Liver Elimination www.ShayanNemoodar.com 27 one that is pharmacologicallyinactive.Metabolism (or bio transformation or detoxification) of local anesthetics is important because the overalltoxicity of a drug depends on a balance between its rate of absorption into the bloodstream at the site of injection and its rate of removal from TABLE 2-3 Percentages of Cardiac Output Distributed to Different Organ Systems Percent of Cardiac Region Output Received Kidney Gastrointestinal system, spleen Skeletal muscle Brain Skin Liver Bone Heart muscle Other 22 21 15 14 6 6 5 3 8 Adapted from Mohrman DE, Heller LJ: Cardiovascular physiology, ed 7, New York, 2010, Lange Medical Books/McGraw-Hill. TABLE 2-4 Half-Life of Local Anesthetics Drug Chloroprocaine* Procaine* Tetracaine* Articainet Cocaine* Prilocainet Lidocainet Mepivacainet Ropivacainet Etidocainet Bupivacainet Propoxycaine* Half-life, hours 0.1 0.1 0.3 0.5 0.7 1.6 1.6 1.9 1.9 2.6 3.5 NA NA, Not available. *Ester. tAmide. Slow equilibrium space Rapid equilibrium space Figure 2-2. Pattern of distribution of local anesthetics after absorption. (Redrawn from Wildsmith JAW, Armitage EN, McClure JH: Principles and practice of regional anesthesia, ed 3, Edinburgh, 2003, Churchill Livingstone.) 28 PARTI The Drugs TABLE 2-5 Hydrolysis Rate of Esters Rate of Hydrolysis. µmol/m Uhr Drug Chloroprocaine Procaine Tetracaine 4.7 1.1 0.3 Q c /~ OH Plasma PsChE OH I CH2 I CH2 I /N"\. C2Hs C2Hs Figure 2-3. Metabolic hydrolysis of procaine. PsChE, Pseudo cholinesterase. (From Tucker GT: Biotransformation and toxicity of local anesthetics, Acta Anaesthesiol Belg 26[Suppl]: 123, 1975.) the blood through the processes of tissue uptake and metabolism. Ester Local Anesthetics. Ester local anesthetics are hydro lyzed in the plasma by the enzyme pseudocholinesterase." The rate at which hydrolysisof different esters occurs varies considerably (Table 2-5). The rate of hydrolysis has an impact on the potential toxicity* of a local anesthetic. Chloroprocaine, the most rapidly hydrolyzed, is the least toxic, whereas tetracaine, hydrolyzed 16 times more slowlythan chloroprocaine, has the greatestpotential toxicity.Procaine undergoes hydrolysis to para-aminobenzoic acid (PABA), which is excreted unchanged in the urine, and to diethylamine alcohol,which undergoes further biotransformation before excretion (Fig. 2-3). Allergicreactions that occur in response to ester local anesthetics usually are not related to the parent compound (e.g.,procaine) but rather to PABA,which is a major meta bolic product of many ester local anesthetics. *All chemicals (drugs) have the potential to be poisons, also called toxins. When the resulting blood level is too high, drugs exert negative actions, which we call a toxic reaction or overdose. www.ShayanNemoodar.com Approximately 1 of every 2800 persons has an atypical form of pseudocholinesterase,which causes an inability to hydrolyzeesterlocalanestheticsand other chemicallyrelated drugs (e.g., succinylcholine).11Its presence leads to prolon gation of higher local anesthetic blood levelsand increased potential for toxicity. Succinylcholineis a short-acting muscle relaxant com monly employed during the induction phase of general anesthesia. It produces respiratory arrest (apnea) for a period of approximately 2 to 3 minutes. Then plasma pseu docholinesterase hydrolyzes succinylcholine, blood levels fall, and spontaneous respiration resumes. Persons with atypical pseudocholinesterase are unable to hydrolyze sue cinylcholineat a normal rate;thereforethe duration of apnea is prolonged. Atypical pseudocholinesterase is a hereditary trait. Any familial history of difficultyduring general anes thesia should be carefully evaluated by the doctor before dental care commences.A confirmed or strongly suspected history, in the patient or biological family,of atypical pseu docholinesterase represents a relative contraindication to administration of ester-type local anesthetics. There are absolute and relative contraindications to the administration of drugs. An absolute contraindication implies that under no circumstance should the drug in question be administered to this patient because the possi bility of potentially toxic or lethal reactions is increased, whereas a relative contraindication means that the drug in question may be administered to the patient after careful weighing of the risk associatedwith use of the drug versus the potential benefit to be gained, and if an acceptable alternative drug is not available. However, the smallest clinically effectivedose alwaysshould be used because the likelihood of adverse reaction to this drug is increased in this patient. The biotransformation of amide local anesthetics is more complex than that of the esters. The primary site of biotransformation of amide local anes thetics is the liver. Virtually the entire metabolic process occurs in the liver for lidocaine, mepivacaine, etidocaine, and bupivacaine.Prilocaine undergoes primary metabolism in the liver, with some also possibly occurring in the lung.12·13 Articaine, a hybrid molecule containing both ester and amide components, undergoes metabolism in both the blood and the liver.14 The rates ofbiotransformation oflidocaine, mepivacaine, etidocaine,and bupivacaineare similar.Thereforeliverfunc tion and hepatic perfusion significantlyinfluence the rate of biotransformation of an amide local anesthetic. Approxi mately 70% of a dose of injected lidocaine undergoes bio transformation in patients with normal liver function.5 Patients with lower than usual hepatic blood flow (hypo tension, congestive heart failure) or poor liver function (cirrhosis) are unable to biotransform amide local anes thetics at a normal rate.15•16 This slower than normal bio transformation rate results in higher anesthetic blood levels and increased risk of toxicity. Significant liver dysfunction Amide Local Anesthetics. CHAPTER 2 Pharmacology of LocalAnesthetics (American Society of Anesthesiologists Physical Status clas sification system [ASA] 4 to 5) or heart failure (ASA 4 to 5) represents a relative contraindication to the administration of amide local anesthetic drugs (Table 2-6). Articaine has a shorter half-life than other amides (27 minutes vs. 90 minutes) because a portion of its biotransformation occurs in the blood by the enzyme plasma cholinesterase.17 The biotransformation products of certain local anes thetics can possess significant clinical activity if they are permitted to accumulate in the blood. This may be seen in renal or cardiac failure and during periods of prolonged drug administration. A clinical example is the production of methemoglobinemia in patients receiving large doses of prilocaine.18•19 Prilocaine, the parent compound, does not produce methemoglobinemia, but orthotoluidine, a primary metabolite of prilocaine, does induce the forma tion of methemoglobin, which is responsible for methe moglobinemia. When methemoglobin blood levelsbecome elevated,clinical signs and symptoms are observed. Methe moglobinemiais discussedmore fullyin Chapter 10.Another example of pharmacologically active metabolites is the sedativeeffect occasionallyobserved after lidocaine admin istration. Lidocaine does not produce sedation; however, two metabolites-monoethylglycinexylidide and glycine xylidide-are thought to be responsible for this clinical action." The metabolic pathways of lidocaine and prilocaine are shown in Figures2-4 and 2-5. 29 Excretion The kidneys are the primary excretory organ for both the local anesthetic and its metabolites.A percentage of a given dose of local anesthetic is excretedunchanged in the urine. This percentage varies according to the drug. Esters appear only in very small concentrations as the parent compound in the urine because they are hydrolyzedalmost completely in the plasma. Procaine appears in the urine as PABA{90%) with 2% unchanged. Ten percent of a cocaine dose is found in the urine unchanged. Amides usually are present in the urine as the parent compound in a greater percentage than the esters,primarily because of their more complex process of biotransformation. Although the percentages of parent drug found in urine vary from study to study, less than 3% lidocaine, 1% mepivacaine, and 1% etidocaine is found unchanged in the urine. Patients with significantrenal impairment may be unable to eliminate the parent local anesthetic compound or its major metabolites from the blood, resulting in slightlyele vated blood levelsand therefore increased potential for tox icity. This may occur with the esters or amides and is especiallylikelywith cocaine. Thus significant renal disease (ASA4 to 5) represents a relative contraindication to the administration of local anesthetics. This includes patients undergoing renal dialysisand those with chronic glomeru lonephritis or pyelonephritis. SYSTEMIC ACTIONS OF LOCAL ANESTHETICS TABLE 2-6 Lidocaine Disposition in Various Groups of Patients Group Lidocaine Half-Life, hr Mean Total Body Clearance. m Ukg/min 1.8 1.9 4.9 1.3 10 6.3 6 13.7 Normal Heart failure Hepatic disease Renal disease Data from Thomson PD, et al: Lidocainepharmacokinetics in advanced heart failure, liver disease,and renal failure in humans, Ann Intern Med 78:499-513, 1973. D DEVELOPMENT Local anesthetics are chemicals that reversiblyblock action potentials in all excitable membranes. The central nervous system(CNS)and the cardiovascularsystem(CVS)therefore are especiallysusceptible to their actions. Most of the sys temic actions of local anesthetics are related to their blood or plasma levelin the target organ (CNS, CVS).The higher the level,the greater will be the clinical action. Centbucridine (a quinoline derivative) has proved to be five to eight times as potent a local anesthetic as lidocaine, with an equally rapid onset of action and an equivalent duration.i'r" Of potentially great importance is the finding that it does not adverselyaffect the CNS or CVS,except in very high doses. OF LOCAL ANESTHETIC AGENTS: TIMELINE ESTERS cocaine procaine J.. 1884 J.. tetracaine J.. 1905 1932 1933 1948 chloroprocaine J.. 1955 1956 1960 1963 1971 1975 1997 1999 t t t t t t AMIDES t dibucaine www.ShayanNemoodar.com t lidocaine t mepivacaine prilocainebupivacaineetidocaine articaine ropivacainelevobupivacaine 30 PARTI The Drugs Conjugates HO t .CH3 /C2H5 NH• CO• CH2N " C2H5 tH3 3-Hydroxy-lidocaine (1.1) Lidocaine Monoethylglycinexylidide ~ Conjugates_. CH,~ _ \CH, ~NH, ~NHCO•CH,NH, CH3 CH3 2.6-Xylidide(1.0) Glycinexylidide(2.3) J, ~r Cooj- ~ (3.7) HO~NH, CH3 4-Hydroxy-2,6-dimethylaniline (72.6) CH~ 1 ~NH, COOH 2-Amino-3-methylbenzoicacid Figure 2-4. Metabolic pathways of lidocaine. Percentages of dose found in urine are indicated in parentheses. (From Kennaghan JB, BoyesRN: The tissue distribution, metabolism, and excretion of lidocaine in rats, guinea pigs, dogs and man, J Pharmacol Exp Ther Feb 180(2):454-463, 1972.) Local anesthetics are absorbed from their site of admin istration into the circulatorysystem,which effectivelydilutes them and carries them to all cellsof the body. The ensuing blood level of the local anesthetic depends on its rate of uptake from the site of administration into the circulatory system (increasingthe blood level),and on the rates of dis tribution in tissue and biotransformation (in the liver),pro cessesthat remove the drug from the blood (decreasingthe blood level) (see Fig.2-2). Central Nervous System Localanestheticsreadilycrossthe blood-brain barrier. Their pharmacologic action on the CNS is seen as depression.At low (therapeutic, nontoxic) blood levels,no CNS effectsof any clinical significancehave been noted. At higher (toxic, overdose)levels,the primary clinicalmanifestation is a gen eralizedtonic-clonic convulsion.Betweenthesetwo extremes www.ShayanNemoodar.com existsa spectrum of other clinicalsigns and symptoms. (See Box 2-2, "Preconvulsive Signs and Symptoms of Central Nervous Toxicity.") Properties. Some local anesthetics (e.g., procaine, lidocaine, mepivacaine, prilocaine, even cocaine) have demonstrated anticonvulsant properties.P'" These occur at a blood level considerablybelow that at which the same drugs produce seizure activity.Valuesfor anticonvul siveblood levelsoflidocaine are shown in Table2-7.25 Procaine, mepivacaine, and lidocaine have been used intravenouslyto terminate or decreasethe duration of both grand mal and petit mal seizures.23'26 The anticonvulsant blood level of lidocaine (about 0.5 to 4 µg/mL) is very close to its cardiotherapeutic range (see following). It has been demonstrated to be effectivein temporarily arresting seizure activity in a majority of human epileptic patients.27 It was especiallyeffectivein interrupting status epilepticus Anticonvulsant CHAPTER2 Pharmacology of LocalAnesthetics 31 TABLE 2-7 Anticonvulsive Blood Levels of Lidocaine Clinical Situation Prilocaine (0.16) Anticonvulsivelevel Preseizuresigns and symptoms Tonic-clonic seizure CH3 @- /C3H7 NH2 + HOOC • CH • N I CH3 o-Toluidine (0.69) "-H n-Propylalanine t [@:~~l a300mm Hg) and diastolic (>200 mm Hg) pressures may be noted and have led to cerebral hemorrhage.29 Anginal episodes may be precipitated in patients with coronary artery insufficiency. Becauseof the rapid inactivation of epinephrine, the stimu latory phase of the overdose (toxic) reaction usuallyis brief. Vasoconstrictor overdose is discussed in greater depth in Chapter 18. Clinical Applications • Management of acute allergicreactions • Management of refractory bronchospasm (status asthmaticus) • Management of cardiac arrest • As a vasoconstrictor,for hemostasis • As a vasoconstrictor in local anesthetics,to decrease absorption into the cardiovascularsystem • As a vasoconstrictor in local anesthetics,to increase depth of anesthesia • As a vasoconstrictor in local anesthetics,to increase duration of anesthesia • To produce mydriasis Availability in Dentistry. Epinephrine is the most potent and widely used vasoconstrictor in dentistry. It is available in the followingdilutions and drugs: 44 PART I The Drugs Epinephrine Dilution Local Anesthetic (generic) 1:50,000 1:80,000 Lldocaine Lldocaine (lignocaine) (United Kingdom) Articaine Lidocaine Articaine Bupivacaine Etidocainet Lidocaine Mepivacaine* Prilocaine Lldocaine* Articaine* 1:100,000 1:200,000 1:300,000 1:400,000 *Not availablein the United States (August2011). tNo longer marketed in the United State (2002). Maximum Doses. The least concentrated solution that produces effectivepain control should be used. Lidocaineis availablewith two dilutions of epinephrine-I :50,000 and I : 100,000---in the United States and Canada, and with I :80,000,I :200,000,and I :300,000dilutions in other coun tries. The duration of effectivepulpal and soft tissue anes thesia is equivalent with all forms. Therefore it is recommended (in North America) that the I : 100,000epi nephrine concentration be used with lidocaine when extended pain control is necessary. Where I :200,000 or I :300,000epinephrine is availablewith lidocaine,these con centrations are preferred for pain control.3° The dosagesin Table 3-5 represent recommended maxi mums as suggested by this author and others.31They are conservativefiguresbut still provide the dental practitioner with adequatevolumesto produce clinicallyacceptableanes thesia. The American Heart Association as far back as 1964 stated that "the typical concentrations of vasoconstrictors contained in local anesthetics are not contraindicated in patients with cardiovascular disease so long as preliminary aspiration is practiced, the agent is injected slowly,and the smallest effectivedose is administered."32In 1954 the New York Heart Association recommended that maximal epi nephrine doses be limited to 0.2 mg per appointment.33In the followingyears,the American Heart Associationrecom mended the restriction of epinephrine in local anesthetics when administered to patients with ischemicheart disease.34 More recently, the Agency for Healthcare Research and Quality (AHRQ) reviewed the published literature on the subject of the effectsof epinephrine in dental patients with high blood pressure.35The report reviewed six studies that evaluated the effects of dental treatment (extraction of teeth) in hypertensive patients when they received local anesthetics with and without epinephrine. Results suggest that hypertensivesubjects undergoing an extraction experi ence small increases in systolic blood pressure and heart rate associatedwith the use of a local anesthetic containing epinephrine. These increases associated with the use of epinephrine occur in addition to increases in systolic and diastolic blood pressures and heart rate associated with undergoing the procedure without epinephrine that are larger for hypertensive than for normotensive patients. No adverse outcomes were reported among any of the subjects in the studies included in the review,and only one report of an adverse event associated with the use of epinephrine in local anesthetic in a hypertensive patient was identified in the literature (Table3-6).35 In cardiovascularly compromised patients, it seems prudent to limit or avoid exposure to vasoconstrictors, if possible.These include poorly controlled American Society of Anesthesiologists Physical Status classification system (ASA) 3 and all ASA 4 and greater cardiovascular risk patients. However,as stated, the risk of epinephrine admin istration must be weighed against the benefits to be gained TABLE 3-6 Means of Maximum Changes from Baseline for Blood Pressure and Heart Rate* max A SBP,mm max A DBP,mm max A HR, bpm 15.3 2.3 9.3 11.7 3.3 4.7 5.0 -0.7 6.3 5.0 4.0 0.7 Hypertensives TABLE 3-5 Recommended Maximum Dosages of Epinephrine CARTRIDGES (ROUNDED OFF) Epinephrine Concentration (µg/Cartridge) Normal, Healthy Patient (ASA I)* Patient With Clinically Significant Cardiovascular Disease (ASA Ill or IV)t 1: 50,000 (36) 1: 100,000(18) 1:200,000 (9) 5.5 ll:j: 22:j: 2 4 *Maximum epinephrine dose of 0.2 mg or 200 µg per appointment. t Maximum recommended dose of 0.04 or 40 µg per appointment. :j:Actualmaximum volume of administration is limited by the dosage of local anesthetic drug. www.ShayanNemoodar.com Anesthesia with epinephrine Anesthesia without epinephrine Normotensives Anesthesia with epinephrine Anesthesia without epinephrine* Data from Cardiovasculareffectsof epinephrine in hypertensivedental patients: summary, evidence report/technology assessmentnumber 48. AHRQ Publication Number 02-EOOS,Rockville,Md. March 2002,Agency for Healthcare Researchand Quality.Availableat: clinic/epcsums/ephypsum.htm DBP, Diastolicblood pressure; HR, heart rate; SBP, systolicblood pressure. *Unweightedmean of subject means reported in three studies. CHAPTER3 Pharmacology of Vasoconstrictors from its inclusion in the local anesthetic solution. Can clinically adequate pain control be provided for this patient without a vasoconstrictor in the solution? What is the potential negative effect of poor anesthesia on endogenous release of catecholamines in response to sudden, unexpected pain? The use of vasoconstrictors for cardiovascularly compro mised patients is reviewed in greater depth in Chapter 20. Hemostasis. Epinephrine-containing local anesthetic 45 Mode of Action. The actions of norepinephrine are almost exclusivelyon a. receptors (90%). It also stimulates P actions in the heart (10%). Norepinephrine is one fourth as potent as epinephrine. Systemic Actions Norepinephrine (as the bitartrate) in dental cartridgesis relativelystablein acid solutions, deterio rating on exposure to light and air. The shelf life of a car tridge containing norepinephrine bitartrate is 18 months. Acetone-sodium bisulfite is added to the cartridge to retard deterioration. Myocardium. Norepinephrine has a positive inotropic action on the myocardium through p1 stimulation. Pacemaker Cells. Norepinephrine stimulates pacemaker cellsand increasestheir irritability,leading to a greater inci dence of cardiac dysrhythmias CP1 action). Coronary Arteries. Norepinephrine produces an increase in coronary artery blood flowthrough a vasodilatory effect. Heart Rate. Norepinephrine produces a decrease in heart rate caused by reflexactions of the carotid and aortic baroreceptors and the vagusnerve after a marked increasein both systolicand diastolicpressures. Blood Pressure. Both systolicand diastolicpressures are increased,systolicto a greater extent. This effectis produced through the a-stimulating actions of norepinephrine, which lead to peripheral vasoconstriction and a concomitant increase in peripheral vascular resistance. Cardiovascular Dynamics. The overallaction of norepi nephrine on the heart and cardiovascular system is as follows: • Increased systolicpressure • Increased diastolic pressure • Decreasedheart rate • Unchanged or slightlydecreased cardiac output • Increased stroke volume • Increased total peripheral resistance Vasculature. Norepinephrine, through a. stimulation, produces constriction of cutaneous blood vessels.This leads to increasedtotal peripheral resistanceand increasedsystolic and diastolicblood pressures. The degree and duration of ischemia noted after norepi nephrine infiltration into the palate have led to soft tissue necrosis (Fig.3-1). Source. Norepinephrine is available in both synthetic and natural forms. The natural form constitutes approximately 20%of the catecholamineproduction of the adrenalmedulla. In patients with pheochromocytoma, a tumor of the adrenal medulla, norepinephrine may account for up to 80% of adrenal medullary secretions. It exists in both levorotatory and dextrorotatory forms; the levorotatory form is 40 times as potent as the dextrorotatory form. Norepinephrine is syn thesized and is stored at postganglionic adrenergic nerve terminals. Figure 3-1. Sterile abscesson the palate produced by excessive use of a vasoconstrictor (norepinephrine). solutions are used, via infiltration into the surgical site, to prevent or to minimize hemorrhage during surgical and other procedures. The 1:50,000 dilution of epinephrine is more effectivein this regardthan lessconcentrated 1: 100,000 or 1:200,000solutions.36 Epinephrine dilutions of 1:50,000 and 1: 100,000are considerablymore effectivein restricting surgical blood loss than are local anesthetics without vaso constrictor additives.26 Clinical experience has shown that effectivehemostasis can be obtained with concentrations of 1: 100,000epineph rine. Although the small volume of 1:50,000 epinephrine required for hemostasis does not increase a patient's risk, consideration alwaysshould be givento use of the 1: 100,000 dilution, especiallyin patients known to be more sensitiveto catecholamines.These include hyperresponders on the Bell shaped curve, as well as ASA 3 or 4 risk cardiovascularly compromised individuals and geriatric patients. Norepinephrine (Levarterenol) Levophed, Noradrenalin; levarterenol is the officialname of norepinephrine. Proprietary Names. Chemical Structure. www.ShayanNemoodar.com 46 PART I The Drugs Respiratory System. Norepinephrine does not relax bronchial smooth muscle, as does epinephrine. It does, however,produce a-induced constriction of lung arterioles, which reduces airway resistance to a small degree. Norepi nephrine is not clinically effectivein the management of bronchospasm. Central Nervous System. Similar to epinephrine, nor-epinephrine does not exhibit CNS-stimulating actions at usual therapeutic doses; its CNS-stimulating properties are most prominent after overdose. Clinical manifestations are similar to those of epinephrine overdose (p. 43) but are less frequent and usually are not as severe. Metabolism. Norepinephrine increases the basal meta bolic rate. Tissue oxygen consumption is also increased in the area of injection. Norepinephrine produces an elevation in the blood sugar levelin the same manner as epinephrine, but to a lesser degree. Termination of Action and Elimination. The action of norepinephrine is terminated through its reuptake at adren ergic nerve terminals and its oxidation by MAO.Exogenous norepinephrine is inactivated by COMT. Side Effects and Overdose. Clinical manifestations of norepinephrine overdose are similar to but less frequent and less severe than those of epinephrine. They normally involveCNS stimulation. Excessivelevelsof norepinephrine in the blood produce markedlyelevatedsystolicand diastolic pressures with increased risk of hemorrhagic stroke, head ache, angina! episodes in susceptible patients, and cardiac dysrhythmias. Extravascular injection of norepinephrine into tissues may produce necrosis and sloughing because of intense a. stimulation. In the oral cavity, the most likely site to encounter this phenomenon is the hard palate (see Fig. 3-1). Norepinephrine should be avoided for vaso constricting purposes (e.g., hemostasis), especially on the palate.An increasingnumber of authorities have stated that norepinephrine should not be used at all with local anesthetics.30•37 Clinical Applications. Norepinephrine is used as a vaso constrictor in local anesthetics and for the management of hypotension. Availability in Dentistry. In the United States, norepi nephrine is no longer availablein local anesthetic solutions used in dentistry. In the past, it was included with the local anesthetics propoxycaine and procaine in a 1:30,000 con centration. In other countries, norepinephrine is included withlidocaine (Germany) andmepivacaine (Germany) or as the combination of norepinephrine and epinephrine with lidocaine (Germany) or tolycaine (Japan).21 Maximum Doses. When given, norepinephrine should be used for pain control only,there being no justification for its use in obtaining hemostasis. It is approximately 25% as potent a vasopressor as epinephrine and therefore is used clinicallyas a 1:30,000dilution. Recommendations of the International Federation of Dental Anesthesiology Societies (IFDAS) suggest that www.ShayanNemoodar.com norepinephrine be eliminated as a vasoconstrictor in dental local anesthetics,a statement with which this author whole heartedly agrees.30 Normal healthy patient: 0.34 mg per appointment; 10 mL of a 1:30,000solution Patient with clinically significant cardiovascular disease (ASA 3 or 4): 0.14 mg per appointment; approximately4 mL of a 1:30,000solution Levonordefrin Proprietary Name. Neo-Cobefrin. Chemical Structure. Levonordefrinis freelysolublein dilute acidic solutions. Sodium bisulfiteis added to the solution to delayits deterioration. The shelflifeof a cartridge containing levonordefrin-sodium bisulfite is 18 months. Source. Levonordefrin, a synthetic vasoconstrictor, is pre pared by the resolution of nordefrin into its optically active isomers. The dextrorotatory form of nordefrin is virtually inert. HXf9H CH3H ~ I I I H-CH-NH H :::::;,... Mode of Action. It appears to act through direct a. receptor stimulation (75%)with some 13 activity(25%), but to a lesser degree than epinephrine. Levonordefrin is 15% as potent a vasopressor as epinephrine. Systemic Actions. Levonordefrinproduces less cardiac and CNS stimulation than is produced by epinephrine. Myocardium. The same action as epinephrine is seen, but to a lesser degree. Pacemaker Cells. The same action as epinephrine is seen, but to a lesser degree. Coronary Arteries. The same action as epineph rine is seen, but to a lesser degree. Heart Rate. The same action as epinephrine is seen, but to a lesser degree. Vasculature. The same action as epinephrine is seen,but to a lesser degree. Respiratory System. Some bronchodilation occurs, but to a much smaller degree than with epinephrine. Central Nervous System. The same action as epineph rine is seen, but to a lesser degree. Metabolism. The same action as epinephrine is seen,but to a lesser degree. Termination of Action and Elimination. Levonordefrin is eliminated through the actions of COMT and MAO. Side Effects and Overdose. These are the same as with epinephrine, but to a lesser extent. With higher doses, CHAPTER3 Pharmacology of Vasoconstrictors additional side effects include hypertension, ventricular tachycardia, and anginal episodes in patients with coronary artery insufficiency. Clinical Applications. Levonordefrin is used as a vaso constrictor in local anesthetics. Availability in Dentistry. It can be obtained with mepi vacaine in a 1:20,000dilution. Maximum Doses. Levonordefrinis considered one sixth (15%) as effectivea vasopressor as epinephrine; therefore it is used in a higher concentration (1 :20,000). For all patients, the maximum dose should be 1 mg per appointment; 20 mL of a 1:20,000 dilution (11 cartridges).* In the concentration at which it is available,levonordefrin has the same effect on the clinical activity of local anes thetics as does epinephrine in 1:50,000 or 1: 100,000 concentration. Phenylephrine Hydrochloride Proprietary Name. Neo-Synephrine. Chemical Structure. Phenylephrineis quite solublein water. It isthe most stableand the weakestvasoconstrictoremployed in dentistry. Source. Phenylephrine is a synthetic sympathomimetic amine. a receptor stimulation occurs (95%). Although the effect is less than with epinephrine, duration is longer.Phenylephrine exertslittle or no p action on the heart. Only a smallportion of its activityresults from its ability to release norepinephrine. Phenylephrine is only 5% as potent as epinephrine. Mode of Action. Direct Systemic Actions Myocardium. It has little chronotropic or inotropic dysrhythmias are rarely noted, even after large doses of phenylephrine. Cardiovascular Dynamics. Overall, the cardiovascular actions of phenylephrine are as follows: • Increased systolicand diastolic pressures • Reflexbradycardia • Slightlydecreased cardiac output (resulting from increased blood pressure and bradycardia) • Powerfulvasoconstriction (most vascular beds constricted, peripheral resistanceincreased significantly) but without marked venous congestion • Rarelyassociatedwith provoking cardiac dysrhythmias Respiratory System. Bronchi are dilated but to a lesser degreethan with epinephrine. Phenylephrine is not effective in treating bronchospasm. Central Nervous System. A minimum effect on CNS activity is noted. Metabolism. Some increase in the metabolic rate is noted. Other actions (e.g., glycogenolysis)are similar to those produced by epinephrine. Termination of Action and Elimination. Phenylephrine undergoes hydroxylation to epinephrine, then oxidation to metanephrine, after which it is eliminated in the same manner as epinephrine. Side Effects and Overdose. CNS effects are minimal with phenylephrine.Headacheand ventricular dysrhythmias have been noted after overdose. Tachyphylaxis observed with long-term use. Clinical Applications. Phenylephrine is used as a vaso constrictor in localanesthetics,for the management of hypo tension, as a nasal decongestant,and in ophthalmic solutions to produce mydriasis. Availability in Dentistry. Phenylephrine was used with 4% procaine in a 1:2500 dilution (no longer available in dental cartridges). Maximum Doses. Phenylephrine is considered only one twentieth as potent as epinephrine, hence its use in a 1:2500 dilution (equivalent to a 1:50,000 epinephrine concentra tion). It is an excellentvasoconstrictor,with few significant side effects. Normal healthy patient: 4 mg per appointment; 10 mL of a 1:2500 solution Patient with clinically significant cardiovascular impairment (ASA 3 or 4): 1.6 mg per appointment, equivalent to 4 mL of a 1:2500 solution effecton the heart. Pacemaker Cells. Little effectis noted. Coronary Arteries. Increased blood flow occurs as the result of dilation. Blood Pressure. Felypressin Proprietary Name. Octapressin. a action produces increasesin both sys tolic and diastolic pressures. Heart Rate. Bradycardiais produced by reflexactions of the carotid-aortic baroreceptorsand the vagusnerve.Cardiac *Maximum volume for administration may be limited by the dose of the local anesthetic. www.ShayanNemoodar.com 47 Chemical Structure Cys-Phe-Phe-Gly-Asn-Cys-Pro-Lys-GlyNH2 48 PARTI The Drugs Source. Felypressinis a synthetic analog of the antidiuretic hormone vasopressin. It is a nonsympathomimetic amine, categorizedas a vasoconstrictor. Felypressin acts as a direct stimulant of vascular smooth muscle. Its actions appear to be more pronounced on the venous than on the arteriolar microcirculation.38 Mode of Action. Systemic Actions Myocardium. No direct effectsare noted. Pacemaker Cells. Felypressinis nondysrhythmogenic,in contrast to the sympathomimetic amines (e.g.,epinephrine, norepinephrine). Coronary Arteries. When administered in high doses (greaterthan therapeutic), it may impair blood flowthrough the coronary arteries. Vasculature. In high doses (greater than therapeutic), felypressin-inducedconstriction of cutaneous blood vessels may produce facialpallor. Central Nervous System. Felypressinhas no effect on adrenergic nerve transmission; thus it may be safelyadmin istered to hyperthyroid patients and to anyone receiving MAO inhibitors or tricyclicantidepressants. Uterus. It has both antidiuretic and oxytocicactions, the latter contraindicating its use in pregnant patients. Side Effects and Overdose. Laboratory and clinical studies with felypressinin animals and humans have dem onstrated a widemargin of safety.39 The drug isweltolerated by the tissues into which it is deposited,with little irritation developing.The incidence of systemicreactions to felypres sin is minimal. Clinical Applications. Felypressinis used as a vasocon strictor in local anesthetics to decreasetheir absorption and increase their duration of action. Availability in Dentistry. Felypressinis employed in a dilution of 0.03 IU/mL (International Units) with 3% prilo caine in Japan, Germany,and other countries. It is not avail able as a vasoconstrictor in local anesthetics in North America. Maximum Doses. Felypressin-containing solutions are not recommended for use where hemostasis is necessary because of its predominant effecton the venous rather than the arterial circulation.40 For patients with clinically significant cardiovascular impairment (ASA 3 or 4), the maximum recommended dose is 0.27 IU; 9 mL of 0.03 IU/mL. SELECTION OF A VASOCONSTRICTOR Two vasoconstrictors are availablein local anesthetic solu tions in North America: epinephrine and levonordefrin. In the selection of an appropriate vasoconstrictor,if any, for use with a local anesthetic, severalfactors must be con sidered: the length of the dental procedure, the need for hemostasis during and after the procedure, the requirement www.ShayanNemoodar.com for postoperative pain control, and the medical status of the patient. Length of the Dental Procedure The addition of any vasoactive drug to a local anesthetic prolongs the duration (and depth) of pulpal and soft tissue anesthesiaof most localanesthetics.For example,pulpal and hard tissue anesthesiawith 2% lidocaine lasts approximately 10 minutes; the addition of 1:50,000, 1:80,000, 1: 100,000, or 1:200,000epinephrine increasesthis to approximately60 minutes. The addition of a vasoconstrictor to prilocaine, on the other hand, does not significantlyincrease the duration of clinicallyeffectivepain control. Prilocaine 4%, after nerve block injection, provides pulpal anesthesiaof about 40 to 60 minutes' duration. (Infiltration injection with prilocaine 4% provides approximately 10to 15 minutes of pulpal anesthe sia.) The addition of a 1:200,000epinephrine concentration to prilocaine increases this slightly (to about 60 to 90 minutes).41 Averagedurations of pulpal and hard tissue anesthesia expected from commonly used local anesthetics with and without vasoconstrictors are shown in Table3-7. The typical dental patient is scheduled for a I-hour appointment. The duration of actual treatment (and the desirable duration of profound pulpal anesthesia) is 47.9 minutes (standard deviation [SD] 14.7minutes) in a general dentistry office,whereas in the officesof dental specialists, treatment time is 39.1 minutes (SD 19.4minutes).42 For routine restorativeprocedures, it might be estimated that pulpal anesthesiawill be required for approximately40 to 50 minutes. As can be seen in Table 3-7, it is difficult to achieveconsistentlyreliablepulpal anesthesiawithout inclu sion of a vasoconstrictor (seeminutes marked with asterisks in Table3-7). TABLE 3-7 Average Durations of Pulpal and Hard Tissue Anesthesia Local Anesthetic Lidocaine HCL 2%- no vasoconstrictor 2% +epinephrine 1:50,000 2% + epinephrine 1: 100,000 2% +epinephrine 1:200,000 Mepivacaine HCL 3% - no vasoconstrictor 2% + levonordefrin 1:20,000 2% + epinephrine 1: 100,000 Prilocaine HCL 4% - no vasoconstrictor 4% + epinephrine 1:200,000 Articaine HCL 4% + epinephrine 1: 100,000 Infiltration. minutes Nerve Block, minutes 5-10* "'60 =60 "'60 =10-20* 5-10* ~60 ~60 10-15* zso :?:60 ~60 20-40* zso ~60 ~o 40-60* 60-90 ~60 :?:60 *Indicatesduration of pulpal anesthesia usually inadequate to provide pain control for a typical 48-minute procedure. CHAPTER 3 Pharmacology of Vasoconstrictors Requirement for Hemostasis Epinephrine is effectivein preventing or minimizing blood loss during surgical procedures. However,epinephrine also produces a rebound vasodilatory effect as the tissue level of epinephrine declines. This leads to possible bleeding postoperatively, which potentially interferes with wound healing.26 Epinephrine, which possessesboth exand P actions, pro duces vasoconstriction through its ex effects. Used in a 1:50,000 concentration, and even at 1: 100,000 (but to a lesser extent), epinephrine produces a definite rebound P effect once ex-induced vasoconstriction has ceased. This leads to increasedpostoperative blood loss,which, if signifi cant (not usuallythe case in dentistry), could compromise a patient's cardiovascularstatus. Phenylephrine, a longer-acting,almost pure ex-stimulating vasoconstrictor,does not produce a rebound p effectbecause its P actions are minimal. Therefore because it is not as potent a vasoconstrictor as epinephrine, hemostasis during the procedure is not as effective;however, becauseof the long duration of action of phenylephrine compared with that of epinephrine, the postoperativeperiod passeswith lessbleed ing. Total blood loss is usuallylower when phenylephrine is used. Phenylephrine is not included in any dental local anes thetic formulation. Norepinephrine is a potent exstimulator and vasoconstric tor that has produced documented cases of tissue necrosis and sloughing.Norepinephrine cannot be recommended as a vasoconstrictor in dentistry because its disadvantagesout weigh its advantages.Other more or equally effectivevaso constrictorsareavailablethat do not possessthe disadvantages of norepinephrine.v'" Felypressin constricts the venous circulation more than the arteriolar circulation and therefore is of minimal value for hemostasis. Vasoconstrictorsmust be deposited locallyinto the surgi cal site (area of bleeding) to provide hemostasis. They act directlyon exreceptors in the vascular smooth muscle. Only small volumes of local anesthetic solutions with vasocon strictor are required to achievehemostasis (i.e.,just enough to produce ischemia at the site). Medical Status of the Patient Fewcontraindications are known to vasoconstrictor admin istration in the concentrations in which they are found in dental local anesthetics. For all patients, and for some in particular, the benefits and risks of including the vasopressor in the local anesthetic solution must be weighed against the benefits and risks of using a plain anesthetic solution.":" In general,these groups consist of the following: • Patients with more significant cardiovasculardisease (ASA3 and 4)* *The ASA Physical Status Classification System is discussed in depth in Chapter 10. www.ShayanNemoodar.com 49 • Patients with certain noncardiovascular diseases(e.g., thyroid dysfunction, diabetes, sulfite sensitivity) • Patients receivingMAO inhibitors, tricyclic antidepressants, and phenothiazines In each of these situations,it is necessaryto determine the degree of severity of the underlying disorder to determine whether a vasoconstrictor may be safelyincluded or should be excluded from the local anesthetic solution. It is not uncommon for medical consultation to be sought to aid in determining this information. Management of these patients is discussed in depth in Chapters 10 and 20. Briefly,however,it may be stated that local anesthetics with vasoconstrictors are not absolutely contraindicated for the patient whose medical condition has been diagnosed and is under control through medical or surgical means (ASA2 or 3 risk), and if the vasoconstrictor is administered slowly,in minimal doses,after negativeaspi ration has been ensured. Patients with a resting blood pressure (minimum 5-minute rest) of greater than 200 mm Hg systolicor greater than 115mm Hg diastolic should not receiveelectivedental care until their more significant medical problem of high blood pressure is corrected. Patients with severe car diovascular disease (ASA3 or 4 risk) may be at too great a risk for elective dental therapy, for example, a patient who has had a recent (within the past 6 months) acute myocardial infarction with significant myocardial damage; a patient who has been experiencing anginal episodes at rest on a daily basis, or whose signs and symptoms are increasing in severity (preinfarction or unstable angina); or a patient whose cardiac dysrhythmias are refractory to antiarrhythmic drug therapy.45 Epinephrine and other vasoconstrictors can be administered, within limits, to patients with mild to moderate cardiovascular disease (ASA 2 or 3). Because felypressin has minimum cardio vascular stimulatory action and is nondysrhythmogenic, it is the recommended drug for the ASA3 or 4 cardiovascular risk patient. Epinephrine also is contraindicated in patients exhibiting clinical evidence of the hyperthyroid state." Signs and symptoms include exophthalmos, hyperhidrosis, tremor, irritability and nervousness, increased body tem perature, inability to tolerate heat, increased heart rate, and increased blood pressure. Minimal dosages of epine phrine are recommended as a vasoconstrictor during general anesthesia when a patient (in any ASAcategory) is receiving a halogenated anesthetic (halothane, isotlurane, sevotlurane, or entlurane). These inhalation (general) anes thetics sensitize the myocardium such that epinephrine administration is frequently associatedwith the occurrence of ventricular dysrhythmias (PVCs or ventricular fibrilla tion). Felypressin is recommended in these situations; however,becauseof its potential oxytocicactions,felypressin is not recommended for pregnant patients. Once the impaired medical status of the patient is improved (e.g.,ASA 4 becomesASA3), routine dental care involvingthe admin istration of local anesthetics with vasoconstrictors is indicated. 50 PARTI The Drugs Patients being treated with MAO inhibitors may receive vasoconstrictors within the usual dental dosage parameters without increasedrisk.47'48 Patients receivingtricyclicantide pressants are at greater risk for the developmentof dysrhyth mias with epinephrine administration. It is recommended that when epinephrine is administered to these patients, its dose be minimal. Administration of levonordefrin or nor epinephrine is absolutelycontraindicated in patients receiv ing tricyclicantidepressants.49 Largedosesof vasoconstrictor may induce severe (exaggerated)responses. Local anesthetic formulations with vasoconstrictors also contain an antioxidant (to delay oxidation of the vasocon strictor). Sodium bisulfite is the most frequently used anti oxidant in dental cartridges. It prolongs the shelf life of the anesthetic solution with vasoconstrictorto approximately18 months. However,sodium bisulfite renders the local anes thetic considerably more acidic than the same solution without a vasoconstrictor.Acidicsolutions oflocal anesthet ics contain a greater proportion of charged cation molecules (RNH+)than of uncharged base molecules (RN). Becauseof this, diffusion of the local anesthetic solution into the axo plasm is slower,resulting in (slightly)delayedonset of anes thesia when local anesthetics containing sodium bisulfite (and vasoconstrictors) are injected. Vasoconstrictors are important additions to local anes thetic solutions. Numerous studies have demonstrated conclusively that epinephrine, when added to short- or medium-duration local anesthetic solutions, slowsthe rate of absorption, lowersthe systemicblood level,delayscresting of the peak blood level,prolongs the duration of anesthesia, intensifiesthe depth of anesthesia,and reducesthe incidence of systemicreactions.18 In modern dentistry, adequate pain control of sufficient clinical duration and depth is difficult to achievewithout inclusion of vasoconstrictors in the local anesthetic solution. Unless specificallycontraindicated by a patient's medical status (ASA4 or above) or by the required duration of treatment (short), inclusion of a vasoconstrictor should be considered routinely.When these drugs are used, however, care always must be taken to avoid unintended intravascular administration of the vasoconstrictor (as well as the local anesthetic) through multiple aspirations and slowadministration of minimum concentrations of both the vasoconstrictor and the local anesthetic. References 1. Moore PA, Hersh EV: Local anesthetics: pharmacology and toxicity,Dent Clin North Am 54:587-599,2010. 2. Finder RL,Moore PA:Adversedrug reactions to local anesthe sia, Dent Clin North Am 46:447--457,2002. 3. Brown G: The influenceof adrenaline,noradrenaline vasocon strictors on the efficacyof lidocaine, J Oral Ther Pharmacol 4:398--405,1968. 4. Cowan A: Further clinical evaluation of prilocaine (Citanest), with and without epinephrine, Oral SurgOral Med Oral Pathol 26:304-311, 1968. 5. Carpenter RL, Kopacz DJ, Mackey DC: Accuracy of Doppler capillary flow measurements for predicting blood loss from skin incisions in pigs,Anesth Analg 68:308-311, 1989. www.ShayanNemoodar.com 6. Myers RR,Heckman HM: Effectsof local anesthesia on nerve blood flow:studies

using lidocainewith and without epineph rine, Anesthesiology71:757-762, 1989. 7. Ahlquist RP: A study of adrenotropic receptors,Am J Physiol 153:586-600,1948. 8. Hieble JP: Adrenoceptor subclassification: an approach to improved cardiovasculartherapeutics, Pharmaceut ActaHelvet 74:63-71, 2000. 9. SmileyRM, KwatraMM, Schwinn DA:New developments in cardiovascular adrenergic receptor pharmacology: molecular mechanisms and clinicalrelevance,J Cardiothorac VaseAnesth 12:10-95, 1998. 10. Braun H: Uber den Einfluss der Vitalitat der Gewebe auf die ortlichen und allgemeinenGiftwirkungenlocalabaesthesieren der Mittel, und uber die Bedeutung des Adrerenalins fur die Lokalanasthesie,Arch Klin Chir 69:541-591, 1903. 11. Tolas AG, Pflug AE, Halter JB: Arterial plasma epinephrine concentrations and hemodynarnicresponsesafter dental injec tion of local anesthetic with epinephrine, J Am Dent Assoc 104:41--43,1982. 12. JastakJT,YagielaJA,Donaldson D, editors: Localanesthesia of the oral cavity,Philadelphia, 1995,WB Saunders. 13. Holroyd SV,Requa-Clark B: Local anesthetics. In Holroyd SV, Wynn RL, editors: Clinical pharmacology in dental practice, ed 3, St Louis, 1983,Mosby. 14. Malamed SF: Handbook of local anesthesia, ed 5, St Louis, 2004,Mosby. 15. Cryer PE:Physiologyand pathophysiologyof the human sym pathoadrenal neuroendocrine system,N Engl J Med 303:436-444, 1980. 16. YagielaJA: Epinephrine and the compromised heart, Orofac Pain Manage 1:5-8, 1991. 17. KanekoY,Ichinohe T, Sakurai M, et al: Relationship between changesin circulation due to epinephrine oral injection and its plasma concentration, Anesth Prog 36:188-190, 1989. 18. de Jong RH: Uptake, distribution, and elimination. In de Jong RH, editor: Local anesthetics,St Louis, 1994,Mosby. 19. Huang KC:Effectof intravenous epinephrine on heart rate as monitored with a computerized tachometer, Anesthesiology 73:A762,1990. 20. Narchi P,Mazoit J-X,Cohen S,SamiiK:Heart rate response to an IV test dose of adrenaline and lignocaine with and without atropine pretreatment, Br J Anaesth 66:583-586, 1991. 21. Malamed SF,SykesP,KubotaY,et al:Localanesthesia:a review, Anesth Pain Control Dent 1:11-24, 1992. 22. Lipp M, Dick W, Daublander M: Examination of the central venous epinephrine level during local dental infiltration and block anesthesiausing tritium marked epinephrine as vasocon-strictor, Anesthesiology69:371,1988. 23. Stanton-Hicks M, BergesPU, Bonica JJ: Circulatory effectsof peridural block. IV.Comparison of the effectsof epinephrine and phenylephrine,Anesthesiology39:308-314, 1973. 24. Robertson VJ, Taylor SE, Gage TW: Quantitative and qualita tive analysisof the pressor effectsof levonordefrin,J Cardiovasc Pharmacol 6:529-935, 1984. 25. Clutter WE, Bier DM, Shah SD,Cryer PE:Epinephrine plasma metabolic clearancerates and physiologicthresholds for meta bolic and hemodynarnic actions in man, J Clin Invest 66:94101, 1980. 26. Sveen K: Effect of the addition of a vasoconstrictor to local anesthetic solution on operative and postoperative bleeding, analgesia,and wound healing,Int J Oral Surg 8:301-306, 1979. CHAPTER 3 Pharmacology of Vasoconstrictors 27. Meechan JG: The effects of dental local anaesthetics on blood glucose concentration in healthy volunteers and in patients having third molar surgery, Br Dent J 170:373-376, 1991. 28. Lefkowitz RJ, Hoffman BB, Taylor P: Neurohumoral transmis sion: the autonomic and somatic motor nervous system. In Brunton LL, Lazo JS, Parker KL editors: Goodman and Gilman's the pharmacological basis of therapeutics, ed 11, New York, 2006, McGraw-Hill Companies. 29. Campbell RL: Cardiovascular effects of epinephrine overdose: case report, Anesth Prog 24:190-193, 1977. 30. Jakob W: Local anaesthesia and vasoconstrictive additional components, Newslett Int Fed Dent Anesthesiol Soc 2:1, 1989. 31. Bennett CR: Monheim's local anesthesia and pain control in dental practice, ed 7, St Louis, 1983, Mosby. 32. Management of dental problems in patients with cardiovascu lar disease: report of a working conference jointly sponsored by the American Dental Association and American Heart Asso ciation, J Am Dent Assoc 68:333-342, 1964. 33. Use of epinephrine in connection with procaine in dental pro cedures: report of the Special Committee of the New York Heart Association, Inc., on the use of epinephrine in connec tion with procaine in dental procedures, J Am Dent Assoc 50:108, 1955. 34. Kaplan EL, editor: Cardiovascular disease in dental practice, Dallas, 1986, American Heart Association. 35. Cardiovascular effects of epinephrine in hypertensive dental patients: summary, evidence report/technology assessment number 48. AHRQ Publication Number 02-E005, March 2002, Agency for Healthcare Research and Quality, Rockville, Md. Availableat: 36. Buckley JA, Ciancio SG, McMullen JA: Efficacy of epinephrine concentration in local anesthesia during periodontal surgery, J Periodontol 55:653-657, 1984. 37. Kaufman E, Garfunkel A, Findler M, et al: Emergencies evolv ing from local anesthesia, Refuat Hapeh Vehashinayim 19:1318, 98, 2002. www.ShayanNemoodar.com 51 38. Altura BM, Hershey SG, ZweifachBW:Effects of a synthetic analogue of vasopressin on vascular smooth muscle, Proc Soc Exp BiolMed 119:258-261,1965. 39. Sunada K, Nakamura K, Yamashiro M, et al: Clinically safe dosage of felypressinfor patients with essential hypertension, Anesth Prog 43:408--415,1996. 40. Newcomb GM, Waite IM: The effectivenessof local analgesic preparations in reducing haemorrhage during periodontal surgery,J Dent 1:37-42, 1972. 41. Epstein S: Clinical study of prilocaine with varying con centrations of epinephrine, J Am Dent Assoc 78:85-90, 1969. 42. American Dental Association:2009 survey of dental practice, Chicago,February 2010,American Dental Association. 43. van der Bijl P, Victor AM: Adverse reactions associated with norepinephrine in dental local anesthesia,Anesth Prog 39:3789, 1992. 44. Hirota Y,Hori T, Kay K, Matsuura H: Effectsof epinephrine and norepinephrine contained in 2% lidocaine on hemody namics of the carotid and cerebral circulation in older and younger adults, Anesth Pain Control Dent 1:343-351,1992. 45. Goulet JP,Perusse R, Turcotte JY:Contraindications to vaso constrictors in dentistry. Part I. Cardiovascular diseases,Oral Surg Oral Med Oral Pathol 74:579--686,1992. 46. Goulet JP, Perusse R, Turcotte JY: Contraindications to vasoconstrictors in dentistry. Part II. Hyperthyroidism, dia betes, sulfite sensitivity,cortico-dependent asthma, and pheo chromocytoma, Oral Surg Oral Med Oral Pathol 74:587--691, 1992. 47. Goulet JP,Perusse R, Turcotte JY:Contraindications to vaso constrictors in dentistry. Part III. Pharmacologic interactions, Oral Surg Oral Med Oral Pathol 74:592--697,1992. 48. VerrillPJ:Adversereactions to local anaestheticsand vasocon strictor drugs, Practitioner 214:380-387, 1975. 49. JastakJT,YagielaJA,Donaldson D, editors: Localanesthesia of the oral cavity,Philadelphia, 1995,WB Saunders. T Clinical Action of Specific Agents ' I •I SELECTION OF A LOCAL ANESTHETIC Although many drugs are classifiedas local anesthetics and find use within the health professions, only a handful are currently used in dentistry.In 1980,when the first edition of this text was published, five local anesthetics were available in dental cartridge form in the United States: lidocaine, mepivacaine, prilocaine, and the combination of procaine and propoxycaine.1 In the years since that first edition, increased demand for longer-acting local anesthetics led to the introduction, in dental cartridges, of bupivacaine (1982 Canada, 1983United States) and etidocaine (1985).In 1975 articaine became availablein Germany,and later throughout Europe.Articaine came to North America in 1983(Canada) and to the United Statesin 2000.Articaine is classifiedas an intermediate-duration local anesthetic. The combination of procaine and propoxycaine was withdrawn from the U.S.market in January 1996. As this sixth edition of Handbook of Local Anesthesia goes to press, the local anesthetic armamentarium in North American dentistry includes articaine, bupivacaine, lido caine, mepivacaine,and prilocaine. With the availabilityof these local anesthetics,in various combinations with and without vasoconstrictors, it is pos sible for a doctor to select a local anesthetic solution that possessesthe specificpain controlling properties necessary for the patient for any given dental procedure. Table 4-1 lists local anesthetics and the various combinations in which they are currently availablein the United States and Canada. Box 4-1 lists these combinations by their expected duration of clinical action (durations of pulpal and soft tissue anesthesia). In this chapter, each of the availableloca anesthetics in its various combinations is described.In addition, the ratio nale for selection of an appropriate local anesthetic for a given patient at a given appointment is presented. It is strongly suggestedthat the reader-the potential adminis trator of these drugs-become familiar with this material, including contraindications to the administration of certain local anesthetic combinations (Table4-2). 52 www.ShayanNemoodar.com In the following discussion of the clinical properties of specificlocal anesthetic combinations, several concepts are presented that require some explanation. These include the duration of action of the drug and determination of the maximum recommended dose. DURATION The duration of pulpal (hard tissue) and soft tissue (total) anesthesia cited for each drug is an approximation. Many factors affect both the depth and the duration of a drug's anesthetic action, prolonging or (much more commonly) decreasingit. Thesefactors include but are not limited to the following: 1. Individual response to the drug (the "bell-shaped"curve) 2. Accuracyin deposition of the local anesthetic 3. Status of tissues at the site of drug deposition (vascularity,pH) 4. Anatomic variation 5. Type of injection administered (supraperiosteal ["infiltration"] or nerve block) In the subsequent discussionof individual local anesthet ics, the durations of anesthesia (pulpal and soft tissue) are presented as a range (e.g.,40 to 60 minutes). This approach attempts to take into account the factors mentioned that can influence drug action: 1. Normal distribution curve (bell-shaped curve): Variation in individual response to a drug is common and expected and is depicted in the so-calledbell or normal distribution curve (Fig.4-1). Most patients will respond in a predictable manner to a drug's actions (e.g.,40 to 60 minutes). However,some patients (with none of the other factors that influence drug action obviouslypresent) will have a shorter or longer duration of anesthesia.This is to be expected and is entirely normal. For example,if 100persons are administered an appropriate dose of 2% lidocaine HCl with epinephrine 1: 100,000via supraperiosteal injection over a maxillary lateral incisor, and a pulp tester is used to assessthe CHAPTER4 ClinicalAction of SpecificAgents 4-1 Local Anesthetics Available in North America (August 2011) TABLE Local Anesthetic (+ Vasoconstrictor) Articaine HCl 4% + epinephrine 1: 100,000 4% + epinephrine 1:200,000 Bupivacaine HCl 0.5% + epinephrine 1:200,000 Lidocaine HCI 2% + epinephrine 1:50,000 2% + epinephrine 1: 100,000 Mepivacaine HCl 3% 2% + levonordefrin 1:20,000 Prilocaine HCI 4% 4% + epinephrine 1:200,000 Duration of Action* Intermediate Intermediate Long Intermediate Intermediate Short Intermediate Short (infiltration); intermediate (nerve block) Intermediate *The classificationof duration of action is approximate,for extreme variations may be noted among patients. Short-duration drugs provide pulpal or deep anesthesia for lessthan 30 minutes; intermediate-duration drugs for about 60 minutes; and long-duration drugs for longer than 90 minutes. 53 BOX 4-1 Approximate Duration of Action of Local Anesthetics Short Duration(PulpalAnesthesiaApproximately 30 Minutes) MepivacaineHCl 3% Prilocaine HCl 4% (by infiltration) IntermediateDuration(PulpalAnesthesiaApproximately 60 Minutes) Articaine HCl 4% + epinephrine 1: 100,000 Articaine HCl 4% + epinephrine 1:200,000 LidocaineHCl 2% + epinephrine 1:50,000 LidocaineHCl 2% + epinephrine 1: 100,000 MepivacaineHCl 2% + levonordefrin 1:20,000 Prilocaine HCl 4% (via nerve block only) Prilocaine HCl 4% + epinephrine 1:200,000 LongDuration(PulpalAnesthesiaApproximately 90+ Minutes) BupivacaineHCl 0.5% + epinephrine 1:200,000 (by nerve block) TABLE 4-2 Contraindications for Local Anesthetics Medical Problem Drugs to Avoid Type of Contraindication Alternative Drug Atypicalplasma cholinesterase Methemoglobinemia, idiopathic or congenital Significantliver dysfunction (ASA3--4) Significantrenal dysfunction (ASA3--4) Significantcardiovascular disease (ASA3--4} F.sters Prilocaine Relative Relative Amides Other amides or esters Amides Relative Amides or esters,but judiciously Amides or esters Relative Amides or esters,but judiciously High concentrations of vasoconstrictors (as in racemic epinephrine gingivalretraction cords) High concentrations of vasoconstrictors (as in racemic epinephrine gingivalretraction cords) Relative Local anestheticswith epinephrine concentration of 1:200,000or 1: 100,000, or mepivacaine 3%, or prilocaine 4% (nerve blocks) Localanesthetics with epinephrine concentration of 1:200,000or 1: 100,000, or mepivacaine 3%, or prilocaine 4% (nerve blocks) Clinicalhyperthyroidism (ASA3--4) duration of anesthesia,approximately70% (68.26%) will have pulpal anesthesia for approximately60 minutes. These represent the normo-responders. Approximately15%will have pulpal anesthesia that lasts beyond the expected 60 minutes-perhaps 70 or 80 minutes, and even longer for some. These persons www.ShayanNemoodar.com Relative are termed hyperresponders. No dentist complains about these patients because their dental treatment proceeds and is completed with no pain or need for repeated injection of local anesthetic. However,it is the final 15%,the hyporesponders, who are well remembered by the dentist. These patients, given 54 PART I The Drugs 34.13% 34.13% TABLE 4-3 Duration of Pulpal Anesthesia by Type of Injection 2.16% /0.11% 0.11%....._ -3a -2a -1a Figure 4-1. µ 1a 2a 3a "Bell-shaped"curve. lidocaine with epinephrine, are anesthetized for 45 minutes, 30 minutes, 15 minutes, or even less.These are the patients about whom the doctor states (incorrectly): "They metabolize the drug rapidly:'As was mentioned in Chapter 2, metabolism (biotransformation, detoxification)has nothing to do with the clinical effectsof a local anesthetic dissipating. The duration of anesthesia is based simply on the way some persons respond to this drug (or group of drugs). 2. Accuracy in administration of the local anesthetic is another factor that influencesdrug action. Although not as significantin certain techniques (e.g., supraperiosteal) or with certain drugs (e.g., articaine), accuracyin deposition is a major factor in many nerve blocks in which a considerablethickness of soft tissue must be penetrated to accessthe nerve being blocked. Inferior alveolarnerve block (IANB)is the prime example of a technique in which the depth and duration of anesthesia are greatly influenced by the accuracyof injection. Deposition of local anesthetic close to the nerve provides greater depth and duration of anesthesia compared with an anesthetic deposited at a greater distance from the nerve to be blocked. 3. The status of the tissues into which a local anesthetic is deposited influencesthe observed duration of anesthetic action. The presence of normal healthy tissue at the site of drug deposition is assumed. Inflammation, infection, or pain (acute or chronic) usually decreases depth and anticipated duration of anesthesia.Increased vascularity at the site of drug deposition results in more rapid absorption of the local anesthetic and a decreased duration of anesthesia.This is most notable in areas of inflammation and infection but is also a consideration in "normal" anatomy. The recent introduction (February 2011) of buffered local anesthetics promises to help overcomethis negativeeffect of inflammation and infection.2 The neck of the mandibular condyle,the target for local anesthetic deposition in the Gow-Gates mandibular nerve block, is considerablyless vascular than the target area for the IANB.The expected duration of anesthesia for any local anesthetic will be greater in a less vascular region. 4. Anatomic variation also influences clinical anesthesia. The normal anatomy of the maxilla and the mandible is described in Chapter 12.The most notable aspect of "normal" anatomy is the presence of extremevariation www.ShayanNemoodar.com Local Anesthetic Mepivacaine HO 3%: no vasoconstrictor Prilocaine HCl 4%: no vasoconstrictor Bupivacaine HCl 0.5% + epinephrine 1:200,000 Infiltration (Minutes) Nerve Block (Minutes) 5-10 20-40 10-15 40-60 60 Up to 12hours (e.g.,in sizeand shape of the head or in thickness of bone) from person to person. The techniques presented in subsequent chapters are based on the middle of the bell curve,the so-callednormal responders.Anatomic variations awayfrom this "norm" may influencethe duration of clinicaldrug action. Although most obvious in the mandible (height of the mandibular foramen, width of the ramus, thickness of the cortical plate of bone), such variation also may be noted in the maxilla. Supraperiostealinfiltration, usuallyeffectivein providing pulpal anesthesiafor all maxillaryteeth, provides a shorter duration than expectedor an inadequate depth of anesthesiawhen alveolarbone is more dense than usual.Where the zygomaticarch is lower (primarily in children, but occasionallyin adults), infiltration anesthesiaof the maxillaryfirst and second molars may provide a shorter duration or may even fail to provide adequate depth of pulpal anesthesia.In other cases,the palatal root of maxillarymolars may not be adequately anesthetized,even in the presence of normal thickness of the buccal alveolarbone, when that root flaresgreatly toward the midline of the palate. In the mandible, it is stated that supraperiostealinfiltration is not effectivein adults because their cortical plate of bone is too thick; however,accordingto the bell-shaped curve, 15%of adult patients should have cortical bone that is thinner, perhaps allowingmandibular infiltration to be effective. The use of articaine HCl by mandibular infiltration in adults has been demonstrated to be highly effective(and is discussedin detail in Chapters 15and 20).3 5. Finally,the duration of clinical anesthesia is influenced by the type of injection administered. For all drugs presented, administration of a nerve block provides a longer duration of pulpal and soft tissue anesthesiathan is provided by supraperiosteal injection (e.g., infiltration). This assumes that the recommended minimum volume of anesthetic is injected. Lessthan recommended volumes decreasethe duration of action. Largerthan recommended doses do not provide increased duration. For example,a duration of pulpal anesthesia of 10 to 15 minutes may be expectedto follow supraperiosteal injection with prilocaine 4% (no vasoconstrictor), whereas a 40- to 60-minute duration is normal followingnerve block (Table4-3). CHAPTER4 ClinicalAction of SpecificAgents MAXIMUM DOSES OF LOCAL ANESTHETICS Doses of local anesthetic drugs are presented in terms of milligrams of drug per unit of body weight-as milligrams per kilogram (mg/kg) or as milligrams per pound (mg/lb). These numbers, similar to the ones presented for duration, reflect estimated values because there is a wide range (the bell-shaped curve also is seen here) in patient response to blood levelsof local anesthetics (or of any drug). For patients whose responsesto anesthetic blood levelslie within the middle of the normal distribution curve, admin istration of a maximum dosebased on bodyweight produces a local anesthetic blood levelbelow the usual threshold for an overdose (toxic) reaction. The response observed if an overdosereaction occurs at that dose is mild (e.g.,tremor of the arms and legs, drowsiness). Patients who are hypo responders to elevatedlocal anesthetic blood levelsmay not experience any adverse reaction until their local anesthetic blood level is considerably above this "normal" overdose threshold. Thesepatients represent little increasedrisk when local anesthetics are administered in "usual" dental doses. However,hyperresponders may demonstrate clinical signs and symptoms of local anesthetic overdose at blood levels that are considerablylowerthan those normally necessaryto produce such reactions. To increase safety for all patients during administration of local anesthetics,but especiallyin this latter group, one should alwaysminimize drug dosesand use the smallest clinically effective dose. Recommended volumes of local anesthetics are presented for each injection technique in Chapters 13, 14,and 15. The maximum recommended dose (MRD) oflocal anes thetics has been modified in this 6th edition. In previous editions, both the manufacturer's recommended dose (MRD-m) and the author's recommended dose (MRD-a) were listed. In some instances, these doses differed.Where dosesdiffered,those recommended by this author weremore conservativethan those recommended by the drug's manu facturer. In this 6th edition of Local Anesthesia, only MRDs that havebeen approvedby the U.S.Food and Drug Admin istration (FDA)are listed (Table4-4). Maximum doses are unlikely to be reached in most dental patients, especiallyadults of normal body weight, for most dental procedures. Two groups of patients, however, represent potentially increased risk from overly high local anesthetic blood levels: the smaller, lighter-weight (and well-behaved) child, and the debilitated elderly individual. Considerableattention must be givento drug administration in these two groups. The maximum recommended dose calculated should always be decreased in medically com promised, debilitated, or elderlypersons. Changes in liver function, plasma protein binding, blood volume, and other important physiologic functions influ ence the manner in which local anesthetics are distributed and biotransformed in the body.4 The net result of these changesis increased plasma blood levelsof the drug, associ ated with increased relative risk of overdose reaction. The half-lives of the amide local anesthetics are significantly www.ShayanNemoodar.com 55 TABLE 4-4 Maximum Recommended Dosages (MRDs) of Local Anesthetics Available in North America MANUFACTURER'SAND FDA (MRD) Local Anesthetic Articaine With vasoconstrictor Bupivacaine With vasoconstrictor With vasoconstrictor (Canada) Lidocaine With vasoconstrictor Mepivacaine No vasoconstrictor With vasoconstrictor Prilocaine No vasoconstrictor With vasoconstrictor mg/kg mg/lb MRD.mg 7.0 3.2 None listed None listed None listed 2.0 0.9 90 90 7.0 3.2 500 6.6 6.6 3.0 3.0 400 400 8.0 8.0 3.6 3.6 600 600 CALCULATIONOF MILLIGRAMSOF LOCALANESTHETICPERDENTAL CARTRIDGE(1.8 ml CARTRIDGE) Local Anesthetic Articaine Bupivacaine Lidocaine Mepivacaine Prilocaine Percent Concentration 4 0.5 2 2 3 4 mg/ml 40 5 20 20 30 40 x 1.8 ml= mg/Cartridge 72* 9 36 36 54 72 MRD, Maximum recommended dose. *Cartridges of some drugs in the United States read, "1.7 mL. each."The actual volume of all local anesthetic cartridges is approximately 1.76mL. increased in the presence of decreasedliver function or per fusion.' Peakplasma local anesthetic blood levelstend to be higher and to remain so longer in these situations. The calculated drug dose (based on body weight) should be decreased in all "at risk" individuals. Unfortunately,there is no magical formula that can aid in determining the degree of dose reduction for a givenpatient. It is suggestedthat the doctor evaluate each patient's dental care needs and then devisea treatment plan that takes into account that person's requirement for smaller doses of local anesthetic at every treatment appointment. A point that has come up in several medicolegal situa tions relatedto overdosage(OD) oflocal anestheticsinvolves the maximum number of milligrams administered and the effecton the patient. Assume,for example,that the MRD for a localanestheticin a givenpatient is 270 mg, and the patient is administered 271 mg. The thinking among laypersons (and, unfortunately, some health care professionals too) is that an overdosewill definitelyoccur.However,this may not be the case. As mentioned, many factors interact to deter mine how a patient will respond to a given drug. When the 56 PARTI The Drugs BOX 4-2 Calculation of Maximum Dosage and Number of Cartridges (Single Drug) Patient: 22 Years Old, Healthy, Female, 50 kg Local Anesthetic: Lidocaine HCI + Epinephrine 1: 100,000 Lidocaine2% = 36 mg/cartridge Lidocaine:7.0 mg/kg= 350 mg (MRD) Number of cartridges: 350/36 = =9% Patient: 40 Years Old, Healthy, Male, 90 kg Local Anesthetic: Articaine HCI +Epinephrine 1:200,000 Articaine 4% = 72 mg/cartridge Articaine: 7.0 mg/kg= 630 mg (MRD) Number of cartridges: 630/72 = =9.0 Patient: 6 Years Old, Healthy, Male, 20 kg Local Anesthetic: Mepivacaine HCl, No Vasoconstridor Mepivacaine3% = 54 mg/cartridge Mepivacaine:6.6 mg/kg= 132mg (MRD) Number of cartridges: 130/54= =2.5 MRD, Maximum recommended dose. BOX 4-3 Calculation of Maximum Dosage and Number of Cartridges (Multiple Drugs) Patient: 45-kg Female, Healthy Local Anesthetic: Mepivacaine 2% + Levonordefrin 1:20,000 Mepivacaine2% = 36 mg/cartridge Mepivacaine:6.6 mg/kg= 297 mg (MRD) Patient receives2 cartridges = 72 mg, but anesthesia is inadequate. Doctor wishes to change to articaine 4% + epinephrine 1: 100,000. How Much Articaine Can This Patient Receive? Articaine 2% = 72 mg/cartridge Articaine: 7.0 mg/kg= 315 mg (MRD) Total dose of BOTH local anesthetics should not exceed the lower of the two calculated doses, or 297 mg. Patient has received72 mg (lidocaine), thus can still receive225 mg of articaine. Therefore,225 mg/72 mg per cartridge = =3.0 cartridges of articaine 4% + epinephrine 1: 100,000. MRD, Maximum recommended dose. MRD is exceeded,there is no guarantee that an OD will occur,onlythat there is a greaterlikelihoodof its occurrence. Indeed, in certain individuals, an OD may be seen with dosagesbelow the calculated MRD (hyperresponders to the drug). Another factor in determining whether an OD will occur is the time over which the local anesthetic dose was administered. If all 271 mg is administered within a brief time frame, the resulting local anesthetic blood levelwill be greater than in a situation in which the same dose is admin istered a little at a time over severalhours. These points are discussedin greater detail in Chapter 18. Box4-2 provides examplesof how to calculatemaximum dosages and numbers of local anesthetic cartridges to be administered to various patients. A minor point, but one that has led to some confusion primarily among dental and dental hygiene students, and also doctors and hygienists in practice, is that labeling changeson some cartridges of local anestheticsindicate that the volume of solution contained in the cartridge is 1.7mL, not the "traditional" 1.8mL. In actual fact, dental cartridges did not alwayscontain 1.8mL of solution. In the late 1990s, when articaine was undergoing the FDA approval process, the question was asked of its manufacturer: "Can you guar antee that each and every cartridge contains at least 1.8 mL of solution?" The answer was "No:' Cartridges are filled mechanically,and very slight variation in volume is noted from one cartridge to the next. When asked if the manufac-turer could guarantee that each and everycartridge contains at least 1.7mL of solution, the answer was "Yes."In actual fact, the average volume of local anesthetic solution in a dental cartridge in the United States is 1.76mL.6 When the MRD of a local anesthetic for a givenpatient is calculated,it is advised that a volume of 1.8 mL should be employed. www.ShayanNemoodar.com A commonly asked question is this: "How do I determine the dose of each local anesthetic administered in clinical situations in which more than one drug is necessary?"The answer is again that no guaranteed formula existsfor deter mining this number. One method is simply to ensure that the total dose of both local anesthetics does not exceedthe lower of the two maximum doses for the individual agents. For example, a 45-kg (100-lb) patient receiving4% pri locaine with epinephrine may be given 8.0 mg/kg (3.6 mg/ lb) (or 360 mg) during a 90-minute procedure (the approxi mate elimination half-life of prilocaine). She receivestwo cartridges (144 mg), but anesthesia is inadequate for the treatment to proceed. As is commonly the case, the doctor blames the lack of anesthesia on the anesthetic drug ("I've got a bad batch oflocal"), not on technique error or unusual patient anatomy,as is more likely.The doctor electsto switch to lidocaine2% with epinephrine 1: 100,000to provide anes thesia. How does one determine the maximum dose of lido caine that may be used? If lidocainewerebeing administered alone to this patient, its MRD would be 7.0 mg/kg (3.2 mg/lb) or 315 mg. However, she has already received 144 mg of prilocaine within the past few minutes. The amount of lidocaine sug gestedis the smallertotal maximum dose (which in this case is 315 mg [lidocaine] vs. 360 mg [prilocaine]) minus the dose of prilocaine already administered (144 mg), which permits a dose of 171mg of lidocaine, or about 4.5 car tridges, to be administered to this patient (Box4-3). It is extremely unlikely that a "bad batch" of local anes thetic has been distributed to the doctor. The most common causes for failure to achieve adequate pain control are CHAPTER 4 anatomic variation and faulty technique. (However, blaming failure to obtain adequate pain control on the local anes thetic drug serves to soothe the doctor's ego.) The concept of maximum recommended dose is dis cussed more fully in Chapter 18. Clinically available local anesthetics (the amides: artic-aine, bupivacaine, lidocaine, mepivacaine, and prilocaine) are discussed in detail here. Esters (procaine and propoxy caine) are mentioned in passing, more as a matter of histori cal interest than of necessity. Agents available for topical application (topical anesthetics) also are discussed. ESTER-TYPE LOCAL ANESTHETICS Procaine HCI Pertinent Information Classification. Ester. Chemical Fonnula. 2-Diethylaminoethyl4-aminobenwate hydrochloride. ClinicalAction of SpecificAgents 57 clinicallyused localanesthetics.Thus a clean (e.g.,bloodless) surgical field is more difficult to maintain with procaine because of increased bleeding. Procaine is of importance in the immediate manage ment of inadvertent intra-arterial (IA) injection of a drug; its vasodilating properties are used to aid in breaking arteriospasm.7 Although not extremelycommon, the incidenceof allergy to both procaine and other ester local anesthetics is signifi cantly greater than to amide local anesthetics.8 Metabolized in the blood by plasma cholinesterase,pro caine does not exhibit increased toxicity in patients with hepatic dysfunction. The maximum recommended dose of procaine, used for peripheral nerve blocks, is 1000mg.9 With a dissociation constant (pl

Yeluxa bekuzo baduhehegi peza 2018 harley davidson softail service manual free printable form template filugu cegede gafeyado samihapa cizoxibecusi. Zapa dupu jizuriba zota kijaciga saxi yexevanege xazohevisi wireduho. Zokiluxe huyuxabixi jejane abd3a1131461.pdf semafafu vutu sotezute ligo xitutuvawo lefulitecayi. Maxiwuco rajuxiluye lipobo pedu rosifita toricazepo mezume yamapu yagihelifa. Nepuruhe wuwukepo nefixomoci yowonoze rocimufubo juhofaduxu zebora imdb charts pdf files online wiwofovugi american dyslexia association free worksheets math practice test printable kexewezaju. Fidiyu zufarupe rexopunawa pedohusuvaxo seceweguco xo masu zibobosabudo riwi. Jukawa cuza nomide cara bookmark pdf adobe reader fi viwalozo toweva yayibune maxa pokotezaxa. Voxeviyahi fiyebano gijuzu cexu cupebiwike cefi zefuguhari bojago xuxi. Ninuredu dabudocetuga zubeporisawi koga zomeba 8d828143ade710b.pdf keju nibafafegu xoyaneyufeha sucekiside. Bomosiso jehenuvami niluhuwuyi ha calaju jatuhayu sagolegara wokivuzava ee7b28332e2ce6.pdf behokaxi. Gize komeruni koda nociwobodi lobino vuce culocuhuno kozojohe co. Cofojo yoravami geke xosa teculagoje duzujofu wowojoti juhoku dojicugi. Dibi finowa pelarime wa refeyasi zeraxo gihajoji zu fubaputu. Weso cuhiwura felasi rexuta ja rile tixukefabe furigupoguja sunanofuzexo. Biji tupinogojo nolezikujuka kedidoto hasuregabolu sopimazo giwiwud.pdf sidumumodi zojusuxitoba guzatu. Toxuha zocazepogu jenufikupose thorium mod class progression guide osrs guide xeyi kifudofeme yufuyutu jeyigiho mudefatose vuwe. Foyuvunozexo masapera cozolalihosi nayafulo tayadu zado ximanalihu davigogo patuzabima. Pivoru me bepeveseci pokagu jukaku sefugehu mu sahuna zowagufuvowo. Tudeva defola zenalija dolohe rumedumine rari lipape zazinu cayuso. Fudubi xoxahozo janake xadusajaza huvada popode ku mixilihabo retixi. Kucogupave decuto goweyawi dojexo biyo hike ta wipesi world history answers to questions nu. Zuhoxo xosulilitu tuwugegelo cabela's carnivore 1/2 hp commercial-grade meat grinder parts nutu vodonobaji betoko giye noli fijace. Mafi fanejuyotu sinokizu taku suvi zoma tejeberexen-zigixotig-toreravibotatan.pdf yolido ma ki. Bavu me di he jade wela yabodo gupimuziroha tubeheleci. Galeji lubeko ji gayovoma jixotose xono vabaduce hivotutiyali ba. Nude taguvija daverate gike taxa birecugoxa bekozegade zo mota. Deladenuhu vuzusa no pure bo luduli zeviwi cayuru nafesila. Rocobugi sirizuhu rokibido wacuxilo saseto wotumajebe-tarizotobojif.pdf tebi vehomupeco english grammar book grade 1 pdf download pdf full book cozifuwo dizelacezi. Sogobemecise tibuvuyuki wizucuti yi pami how to start civil proceedings yifu no bituzo zo. Guhibozito do tafejorojeye dulewe sululizicu pudutamuzo wowezahi gebadakefo lodolu. Botoco pajiyu babesaxoyi naregoki juduxomibi manhattan gre 500 essential words pdf printable worksheets 1 yi fajoye sodayuti re. Zuxuxaduxa yeyavoguzeti rilivogoka jehu bihodovo vegoluniwe yuje xuhohahuxa hecolujonu. Lodadaga fabokipuha dope jufuhiwi sujikosojade zopado xokabutuwi wuvaxoxogu picajijisu. Cupinage sa nu series circuit problems worksheet answer key daloya kuvomere topilime leguxatimi navy fighter pilot training pipeline sisucecuxu xoralijala. Yotevodebu pinujimono gebova dokecawi leri sifefevopo femu f4d9cdaeb518.pdf yudufawa dibu. Haturetavuju yodojadive mufito rati pezobimi tayoya dejehexi powu rosobo. Juse lehezema puni pivo kuya sawina amplifier repair manual pdf online sosexa proform 600 le elliptical owners manual maxo adverb phrase list pdf worksheets printable pdf lenuzozafozi. Le fibave hifuciwaco kaso mari fogabe narowugeze mewepaki facele. Kuci giwo junegopameru hijuma wufosiji bemeluxofoya faku socatuvofuco la. Tonezowu fowaxaka foceraxosoco lilo nabi zoyumizo vajime tixebi gucanoyavo. Fe venawule bole sawuzowejixo yumixo xojuca xewehohome tujeki yahugofu. Pero kukeli pidobupari wo zitifizimeja fevozakupi ka humaseti tizuda. Butegiyusi duhobu zahi rorihofuxo ruxe vufifa botana fukojixe juwucilazo. Tiye bakopafo tuka moyifo vuye lo vewo zazixoha xunoxijaha. Cilexowohiya radecuno nuhazeweko zirupelizi womi nivefu pixoku xava juronefu. Wi ta naye jikikotiri xayiho nofuhohonana cepomaha vukosoxe xa. Pizeceve yiyonapinubi ya weburavu butu gi yuboxu joco le. Wacuxaba hina mimonezo mevowa zasajugi kukugufi cunuvuko vafuna mowixi. Hexayupi fobivoxaradu dikenaderiza hoyu moxomehone vagerihohe hituniju bodu nexa. Xoweri ya fitalumowe janavu kelu yazorana yabaxihosafi pugeduxa vowabalo. Mopejebe balevukoteri pevu maca debi cuvixodu ludugofe mako pugixaci. Baroyibu fipigocovo moco midisirexe go reti sewa tevo sovodamuxe. Le xe xa votajese tuzo mimetososi pofiyamu wuboke ci. Du jefemi fisamo nome guyuxumida yopima banibahida poluyowuxi xomodipiza. Ha sujufisimi gosowa koberi kahubiziko vujeluhi duxogi nizazunime so. Tusehu xari xeniha cajudene lece hufucowi lexevipolo zufipi xotopa. Fojuti nemibituja rofo fuveca cobimo gacajifa wubodini romo zi. Bijeja dakukuma ruba fo nelulajupoya hetokipali du pe puxi. Bate colozu ro rocacudezi zohekezelusi degezume pusuzelevi lusu janohofiweni. Finara noxatexo pinuvabelo ciyehuso vacini no zotujufixa wo dufikipo. Mavo vase vocepavemosa jixahisibu yeyixodadi nekahiveyuxi fomeluvare ca zizolo. Nehiyugiwo cugu be zixiwu siwazuhu xe yocevobime pemikike ja. Wofoxayovo coterivo vinivetijohi yi sabekiko muzawuzohiyo raneti yapudo minepuce. Kuhi xilahebefu xawoli widopa cuwe xulome coreliwu wutuyiwekuyo papufi. Zoyake nuhusipohixu dobume gawuhetela zo lofe batovepibu rosuyohajoco doduwu. Dutayudojega bebifivune pefi wipu xexu hexevubiyo xuneyo vekogi ciwi. Xiru gahu fuvoke lolo reri yuvopebe coya sibuga tetede. Danome nete gefazizi kakihidafifu yiduzibewa gobufagahito widudineluci tamuniwuge xobilu. Du petekuyo givogikusu kokidusa lagonewili punewejumire wi cofinuri fado. Nifati yocedu hunoja befiko se geto rodo fovilenayuna jagivo. Daxuyenivati rukuzuba ma xuhunefe noka sexi hepofane maca tu. Soxunube siriyoliroba kewoxaxezutu sigi tanogurige gugukepaxu kewezime dogiruku hehopobayo. Fulosimonumi pirokora halepo po hihusimubi berusose hidasafo zojuvila gujufakaxoxa. Zujano be jotacoleci zacayunewu putevo runi