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Vasoconstrictors in Local Anesthesia for Dentistry

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Addition of a vasoconstrictor to a local anesthetic may have several beneficial effects: a decrease in the peak plasma concentration of the local anesthetic agent, increase in the duration and the quality of anesthesia, reduction of the minimum concentration of anesthetic needed for nerve block, and decrease of blood loss during surgical procedures. The addition of a vasoconstrictor to a local anesthetic may also have detrimental effects. A review of the literature indicates that vasoconstrictor concentrations in local anesthetics marketed for dental use in the United States are not always optimal to achieve the purposes for which they are added. In most cases, a reduced concentration of vasoconstrictor could achieve the same goal as the marketed higher concentration, with less side-effect liability.

All local anesthetics currently available for dental use in the United States (US) have vasodilating activity and increase blood flow in the tissues into which they are injected. Increased blood flow at the site of injection may promote increased blood concentrations of the anesthetic agent, with greater likelihood of overdose reactions. Increased blood flow may also result in a shorter duration of anesthetic action; the degree to which the anesthetic action is shortened clinically also depends upon other specific factors, such as tissue binding of the drug. If the purpose of the local anesthetic injection is to allow a soft tissue or osseous surgical procedure to be performed, increased local blood flow may result in increased intraoperative bleeding and complicate the performance of the surgical procedure.

Addition of a vasoconstrictor to a local anesthetic solution has several potentially beneficial effects. It may decrease the peak plasma concentration of the local anesthetic agent,[1,2] increase the duration of anesthesia and improve its quality,[3,4] decrease the minimum concentration of local anesthetic agent needed for nerve block,[5–7] and reduce blood loss during surgical procedures.[8,9] The only vasoconstrictors marketed in the US in combination with local anesthetics are epinephrine, levonordefrin, and norepinephrine; all are sympathomimetic amines. The following discussion will primarily concern epinephrine, the best studied and most widely used vasoconstrictor. The other vasoconstrictors used in local anesthetics in the US, namely levonordefrin and norepinephrine, have not been examined extensively and will be only briefly mentioned.

Epinephrine produces its vasoconstrictor effects by binding to and stimulating both α_1-, and α_2-adrenergic receptors located in walls of arterioles. Epinephrine also has β_2-adrenergic activity and may cause vasodilation in tissues, such as skeletal muscle, which have a predominance of β_2-adrenergic receptors. In tissues that have approximately equal numbers of α and β receptors, the β effects of epinephrine will normally predominate due to greater sensitivity of the β receptors to epinephrine. At the low systemic concentrations normally associated with dental anesthesia, epinephrine can increase heart rate (a β_1-adrenergic effect), cardiac output, and peripheral vasodilation. Local anesthetics with epinephrine marketed for dental use in the US contain either 1 : 50,000 (0.02 mg/mL), 1 : 100,000 (0.01 mg/mL), or 1 : 200,000 (0.005 mg/mL) concentrations of the vasoconstrictor. When epinephrine is administered intravenously, it has a half-life of 1 to 3 min.

Levonordefrin and norepinephrine, like epinephrine, are direct-acting sympathomimetic amines; their actions are directly exerted on adrenergic receptors. Levonordefrin and especially norepinephrine have qualitatively less β_2 activity than epinephrine. Levonordefrin is supplied for dental use in the US only in a 1 : 20,000 (0.05 mg/mL) concentration. The 1 : 20,000 solution of levonordefrin is believed to have about the same clinical activity and cardiovascular side-effect liability as an equal volume of 1 : 100,000 epinephrine[10]; however, data from one animal study suggest that inadvertent intravas-

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cular injection of 1:20,000 levonordefrin might cause greater stress on the cardiovascular system than the standard concentration of epinephrine.[11] Norepinephrine is supplied for dental use in a 1:30,000 (0.033 mg/mL) strength.

POTENTIAL BENEFITS

While it is generally accepted that addition of a vasoconstrictor will retard local anesthetic absorption into the systemic circulation,[12] not all studies have demonstrated delayed local anesthetic absorption. Goebel et al[13] studied peak plasma concentrations of local anesthetics after maxillary supraperiosteal infiltration of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine or the same volume of 2% lidocaine without vasoconstrictor. These investigators found that addition of 1:100,000 epinephrine did not significantly alter the peak plasma concentration of lidocaine. Even if local anesthetic absorption is retarded, it is not absolutely certain that this will provide an additional margin of safety. The vasoconstrictor is also absorbed into the systemic circulation, and its presence could conceivably lower the threshold of the central nervous system or cardiovascular system to the local anesthetic agent.

Although adding epinephrine or other vasoconstricting agents to local anesthetics usually will increase the duration of anesthetic action, this is not true for all local anesthetic drugs in all concentrations. Keesling and Hinds[14] studied the depth and duration of local anesthesia with lidocaine combined with various strengths of epinephrine. Epinephrine concentrations of 1:250,000 to 1:300,000 were as effective in prolonging the duration of lidocaine as was 1:50,000 epinephrine. Gangarosa and Halik[3] also studied the effects of epinephrine concentration on lidocaine local anesthesia, and found 1:300,000 epinephrine to be as effective on depth and duration of anesthesia and degree of hemostasis as 1:100,000 epinephrine. Kennedy et al,[15] in a report of the cardiorespiratory effects of epinephrine in local anesthesia, stated that increasing the concentration of epinephrine above 1:200,000 does not increase the duration of a local anesthetic block. However, Cowan,[16] using a minimum dosage technique, reported that the duration of anesthesia increased as epinephrine concentration was raised to 1:100,000 from 1:200,000.

SYSTEMIC UPTAKE AND CARDIOVASCULAR EFFECTS

Several studies have looked at the systemic responses to administration of catecholamines in doses associated with local anesthetic injections for dentistry. Five min after intraoral injection of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine (18 μg of epinephrine), Tolas and coworkers[17] found plasma epinephrine concentrations to be 240 ± 69 pg/mL (mean ± SD) compared to a baseline level of 98 ± 38 pg/mL. When lidocaine without vasoconstrictor was injected, plasma epinephrine did not differ significantly from baseline. In the healthy subjects in this study, heart rate, mean arterial pressure, and rate-pressure product were not significantly different from baseline after epinephrine injection. Cioffi et al,[18] in a study of hemodynamic and plasma catecholamine responses to amalgam restoration of a single tooth with local anesthesia (also 1.8 mL of 2% lidocaine with 1:100,000 epinephrine), found plasma epinephrine to increase from a baseline of 28 ± 8 pg/mL to 105 ± 28 pg/mL 5 (mean ± SE) min after injection. Heart rate increased in parallel with the plasma epinephrine concentration, but mean arterial pressure was unaltered. Chernow et al[19] found a transient increase in heart rate for 2 min after inferior alveolar nerve block with epinephrine-containing local anesthetic. Eight min after injection, plasma epinephrine levels were 3.5 times greater than preinjection control without significant hemodynamic response.

Two studies in which 54 μg of epinephrine was administered demonstrated significant cardiovascular system changes.[20,21] In these studies, the use of 5.4 mL of 2% lidocaine with 1:100,000 epinephrine for unilateral maxillary and mandibular third molar extractions resulted in plasma epinephrine titers 5 min after injection that were approximately five times greater than baseline. Both heart rate and systolic blood pressure were significantly increased. Plasma epinephrine, blood pressure, and heart rate were not significantly increased when 2% lidocaine without vasoconstrictor was used for third molar extractions on the opposite sides. Knoll-Köhler et al,[22] in a study of cardiovascular and serum catecholamine responses to third molar removal with local anesthesia, found that an increase in circulating epinephrine concentrations to more than six times the previously reported threshold for blood pressure increase[23] did not cause significant hemodynamic changes. A tentative conclusion that may be reached from these studies is that, in healthy patients, administration of the dose of epinephrine found in one standard cartridge of 2% lidocaine with 1:100,000 epinephrine results very quickly in plasma epinephrine two times greater than baseline. This increase is not associated with any biologically significant cardiovascular change. Administration of three standard cartridges of the same local anesthetic/vasoconstrictor combination is associated with a fivefold increase in plasma epinephrine; significant cardiovascular system changes may occur, but are not consistently associated with this dose.

It is reported that the threshold plasma epinephrine level for an increase in blood pressure is 50 to 100 pg/

mL, the threshold for an increase in systolic blood pressure is 75 to 125 pg/mL, and the threshold for a decreased diastolic blood pressure is 150 to 200 pg/mL.[23] However, the study from which these threshold values were determined used only six healthy subjects. As mentioned previously, the mean maximum circulating epinephrine concentrations after administration of 18 μg of epinephrine were from 105 to 240 pg/mL, and the maximum plasma epinephrine reported after 54 μg of epinephrine was 302 ± 142 pg/mL (mean ± SD).[21] The cardiovascular changes that should have occurred based upon threshold values did not occur with 18 μg of epinephrine, but were seen when 54 μg was administered.

ADVERSE EFFECTS

Unfortunately, the effects of vasoconstrictors are not always beneficial. The cardiac excitatory action of epinephrine, which is desired in the management of medical emergencies such as anaphylaxis, may be detrimental to a patient with reduced cardiovascular system reserve. Angina or myocardial infarction could conceivably result if the patient's cardiovascular system is unable to respond to the demands caused by actions of the vasoconstrictor. Epinephrine may indirectly cause central nervous system excitation, as well have effects on metabolism and bronchial and gastrointestinal smooth muscle. Signs and symptoms of vasoconstrictor toxicity include hypertension, tachycardia, tremors, headache, palpitations, and cardiac dysrhythmias.

While vasoconstrictors administered with local anesthetics may have minimal effects on healthy patients, they may cause significant changes in patients with hypertension, heart disease, hypokalemia, and other medical conditions, and may interact with other drugs that a patient may be taking or receiving as part of the anesthetic management. Most studies of the systemic effects of vasoconstrictors in local anesthetic solutions are carried out in healthy patient populations. Abraham-Inpijn and others[24] recorded changes in blood pressure, heart rate, and the electrocardiogram during and after tooth extraction under local anesthesia for both normotensive and hypertensive (preoperative systolic blood pressure ≥ 160 mm Hg, or diastolic blood pressure ≥ 95 mm Hg) patients. Thirty-eight of 40 patients received 2% lidocaine with 1 : 80,000 epinephrine. Both groups showed a statistically significant increase in blood pressure, but the hypertensive patients experienced greater increases. Also noted was a 7.5% incidence of potentially dangerous cardiac dysrhythmias in the hypertensive group. In a study of catecholamine effects on cardiovascular function Kiyomitsu et al[25] found that the addition of 1 : 80,000 epinephrine to 2% lidocaine resulted in increased cardiac output, heart rate, and stroke volume and decreased afterload and mean arterial pressure. These hemodynamic changes were more severe in older patients.

Barkin and Middleton[26] used electrocardiogram (ECG) monitoring in 225 patients undergoing oral surgical procedures with local anesthetic only (2% lidocaine with 1 : 100,000 epinephrine). Thirty-six patients (16%) were noted to have either preoperative or intraoperative dysrhythmias. No distinction was made between a dysrhythmia detected before local anesthetic/vasoconstrictor injection, and those occurring after injection, but the overall incidence of dysrhythmia was sufficient that the authors recommended routine precordial stethoscope or ECG monitoring of all patients receiving local anesthetics.

An argument frequently heard for the inclusion of vasoconstrictors in local anesthetic solutions is that the amount of endogenous epinephrine released in response to inadequate anesthesia or stress is much greater than that which reaches the circulation from a dental injection. Many recent studies, using lidocaine with epinephrine as experimental treatment and lidocaine without epinephrine as control, have not supported this argument.[18,20,21,27] These studies have used standard dental injections, usually supraperiosteal infiltration, posterior superior alveolar nerve block, and inferior alveolar nerve block. Studies of an alternative injection technique, the periodontal ligament injection, have also demonstrated significant effects on the cardiovascular system despite its use of reduced volumes when compared to standard techniques.[28] Since the periodontal ligament injection is essentially an intraosseous injection,[29] Smith and Pashley feel that the high pressures developed during these injections may force solutions into capillaries and venules so rapidly that the technique may mimic an intravascular injection.[30] Vasoconstrictors injected with the local anesthetic are rapidly absorbed into the circulation, regardless of the type of dental injection, and may cause significant cardiovascular system changes within minutes of the time of injection.

DRUG INTERACTIONS

Significant drug interactions may occur between vasoconstrictors injected with local anesthetic agents and either tricyclic antidepressants or β blockers. Tricyclic antidepressants inhibit the neuronal uptake of catecholamines, resulting in increased concentrations of catecholamines at the sympathetic neuroeffector junction. Yagiela et al[31] found that the cardiopulmonary response to epinephrine was not significantly affected in tricyclic antidepressant-treated dogs if the dose of epinephrine was less than 0.67 mg/kg. From these data a maximum limit of 0.05 mg of exogenous epinephrine was proposed for the patient on tricyclic antidepressants. Yagiela et al reported that the

action of epinephrine was increased in dogs concurrently administered the tricyclic antidepressant desiprimine two to four times and that the potency of levonordefrin and norepinephrine was increased seven to eightfold in these experimental animals.[31]

Beta blockers inhibit the vasodilation of arterioles by sympathomimetic drugs. This β-receptor blockade will allow the vasoconstricting α-adrenergic effects of epinephrine to predominate, since compensatory vasodilation cannot occur. Administration of epinephrine or even levonordefrin to a patient who is β blocked may result in a significant increase of blood pressure.[32] The more cardioselective (β_1) the blocker is the less chance there is for this interaction to occur.[33]

It is unclear whether inclusion of a vasoconstrictor in the local anesthetic solution alters the response to the local anesthetic agent if inadvertent intravascular injection occurs. Since epinephrine is used in the treatment of local anesthetic-induced cardiovascular collapse, it has been suggested that epinephrine-containing local anesthetic solutions are safer than the local anesthetic alone. Moore and Scurlock hypothesized that added epinephrine would counteract local anesthetic cardiovascular toxicity.[34] Bernards et al,[35] in a study to determine whether 1 : 200,000 epinephrine altered bupivacaine toxicity, administered bupivacaine with or without epinephrine intravenously to pigs until cardiovascular collapse occurred. Epinephrine had no effect on the dose of bupivacaine that caused cardiovascular collapse or the ability to resuscitate the animals. Epinephrine, however, decreased the dose of bupivacaine that produced cardiac dysrhythmias and seizures, although the plasma concentration of bupivacaine was identical in the two groups at onset of seizures. The authors felt that epinephrine produced a peripheral vasoconstriction that resulted in a reduced volume of distribution and led to exposure of the central nervous system to a higher concentration of bupivacaine. In this model of local anesthetic toxicity, epinephrine did not increase the margin of safety of the local anesthetic; it did not protect the animals against bupivacaine-induced cardiovascular collapse; nor did it make the animals any easier to resuscitate after collapse. Other animal studies have shown that epinephrine may potentiate the lethality of the local anesthetic when both drugs are administered intravascularly. Measurements of radioactive-labeled lidocaine have shown that epinephrine promotes entry of local anesthetics into brain tissues due to a greater proportion of cardiac output being directed to the brain.[36,37] Kambam and associates,[38] in a survival study of rats after cardiotoxic doses of 0.5% bupivacaine with or without 1 : 200,000 epinephrine, found that the addition of epinephrine potentiated the cardiotoxic effects of bupivacaine. Yagiela,[39] in a report concerning the influence of epinephrine on lidocaine toxicity, postulated that the potentiation of lidocaine toxicity by epinephrine could be due to either epinephrine-induced effects on the cardiovascular system, which alter the distribution of lidocaine, or a lidocaine-epinephrine interaction that directly enhances central nervous system or cardiovascular system toxicity.

HEMOSTASIS

Vasoconstrictors are added to local anesthetic solutions to provide hemostasis at surgical sites. A 1 : 50,000 concentration of epinephrine is sometimes used for this purpose, although many studies have shown that this is not the concentration of epinephrine that provides optimal vasoconstriction balanced with potential for cardiovascular system toxicity. For example, studies of epinephrine's effects on cutaneous blood flow have indicated that no measurable difference exists between equal volumes of 1 : 50,000, 1 : 100,000, and 1 : 200,000 solutions.[40] Harrington and Carpenter,[41] in a study using a laser Doppler device to follow dynamic changes in skin perfusion after infiltration of 1% lidocaine with graded concentrations of epinephrine, found that the lidocaine alone caused an increase in local blood flow of two to three times baseline. Five min after infiltration of 1% lidocaine plus epinephrine (1 : 50,000, 1 : 100,000, 1 : 200,000 1 : 400,000), the vasodilating effect of lidocaine was effectively counterbalanced by each of these concentrations. Concentrations of 1 : 800,000 and 1 : 1,600,000 were not reliably effective at 5 and 10 min. Periodontal flap surgery may be an exception, however, in that the 1 : 50,000 concentration might be superior to more dilute solutions of epinephrine. According to a study by Buckley et al,[42] blood loss with 2% lidocaine plus 1 : 100,000 epinephrine injected locally for hemostasis is more than double that when 2% lidocaine with 1 : 50,000 epinephrine is used.

Ropivacaine

Ropivacaine, a new long-acting local anesthetic, has been demonstrated to cause vasoconstriction when used alone. Kopacz et al[43] evaluated both bupivacaine and ropivacaine, with and without added epinephrine, for effects on local cutaneous blood flow after subcutaneous infiltration in pigs. Solutions of 0.25% and 0.75% ropivacaine reduced blood flow by 52% and 54%, respectively. Solutions of 0.25% bupivacaine increased blood flow by 90%, and 0.75% bupivacaine increased blood flow by 82%. Ropivacaine may prove to be a useful agent in dentistry. If its vasoconstricting effect decreases its vascular uptake and prolongs its action, ropivacaine could be used alone, thereby eliminating potential side effects from systemic absorption of epinephrine.

Reduction in Neuronal Blood Flow

Vasoconstrictors affect the blood supply to the nerves in the area of injection, in addition to their effects on nonnervous tissues in the area. Myers and Heckman[44] found that the blood supply to rat sciatic nerve was reduced 78% when 2% lidocaine with 1 : 100,000 was applied to tissues surrounding the nerve. Application of 1% lidocaine without vasoconstrictor reduced blood flow to the nerve by 19%. Myers and Heckman believed that epinephrine may have a pathogenic role in those relatively rare reports of neurologic deficit following local anesthetic procedures. Partridge[45] in a study of the effects of lidocaine and epinephrine on rat sciatic blood flow, demonstrated similar reductions in nerve blood flow to those reported by Myers and Heckman. Partridge also reported a synergistic reduction in blood flow when lidocaine and epinephrine were combined. Two percent lidocaine alone decreased nerve blood flow by 18%; application of 5 μg/mL epinephrine alone decreased blood flow by 20%. The combination of lidocaine and epinephrine reduced nerve blood flow by 60%. Bupivacaine, which is a more potent vasodilator than lidocaine, also reduced nerve blood flow. A 0.25% bupivacaine solution decreased nerve blood flow by 35%, 0.5% bupivacaine by 25%, and 0.75% bupivacaine by 15%.

Intraoperative Versus Delayed Bleeding

Potential problems associated with the use of a vasoconstrictor in surgical procedures are rebound, or delayed, postoperative bleeding and impaired wound healing. Sveen,[8] in a study of the effects of adding vasoconstrictor to the local anesthetic solution, found no postoperative hemorrhage in a control group of patients who had oral surgical procedures performed with local anesthetic without added vasoconstrictor. Control patients received injections of 3% mepivacaine, and experimental subjects received injections of 2% lidocaine with 1 : 80,000 epinephrine. Patients who received no vasoconstrictor had an approximately twofold increase in intraoperative blood loss (31.5 ± 13.3 mL versus 14.1 ± 7.1 mL). Although intraoperative bleeding was noted by the surgeon to impede the surgical procedure in 79% of the patients who did not receive vasoconstrictor, the surgical times were not significantly affected. Eighty-one percent of patients in the vasoconstrictor group experienced delayed-onset postoperative bleeding; 83% of these patients also had delayed extraction site healing. Studies of blood loss during and after full mouth extraction surgery reported similar results. Meyer and Allen[9] found reduced intraoperative bleeding and increased postoperative bleeding when vasoconstrictor was used.

Gores et al[46] measured blood loss in patients having multiple dental extractions and alveoplasty. Patients were divided into two groups; one group had significant flap reflection and the other group did not. The groups were further subdivided into those having surgical procedures performed under general anesthesia plus local anesthesia with 3% piperocaine with 1 : 56,000 epinephrine and those having general anesthesia alone. Intraoperative blood loss for surgical procedures with minimal flap reflection was 109 mL (range 5 to 166) for the local anesthesia/vasoconstrictor group, and 179 mL (61 to 280) for the no local anesthesia group. Intraoperative blood loss for those procedures with extensive flap reflection was 201 mL (72 to 401) for the local anesthesia/vasoconstrictor group, and 401 mL (191 to 771) for the no local anesthesia group. As in Sveen's study, the use of vasoconstrictor did not reduce the average operating time. Although control of hemorrhage is said to be necessary for optimum performance of many periodontal and oral surgical procedures, it appears that many surgeons are able to perform procedures without being delayed by increased intraoperative blood loss.

An important factor in the use of vasoconstrictors to control intraoperative bleeding is the technique and location of administration of the agent. Infiltration of the vasoconstrictor near or in the surgical site is required. Nerve block anesthesia at a distant site will be less effective in control of bleeding from a surgical wound.[47]

USE IN GENERAL ANESTHESIA

Another important consideration in use of vasoconstrictors is concurrent administration of general anesthesia. Some general anesthetic inhalation agents sensitize the heart to the effects of catecholamines; halothane is a particularly potent sensitizing agent. The maximum recommended dose of epinephrine over 10 min in the adult patient under halothane general anesthesia is 0.10 mg, and the maximum recommended dose over 60 min is 0.30 mg. Maximum recommended doses of epinephrine in patients under enflurane general anesthesia are the same as those for halothane. Maximum recommended doses of epinephrine for patients under isoflurane anesthesia are 0.30 mg over 10 min and 0.90 mg over 30 min.[4,48–50]

CONCLUSION

The pharmacologic principle of using the lowest dosage possible to produce the desired action, and to minimize the potential for toxicity, should be applied to the use of vasoconstrictors in local anesthetic agents. The optimal concentration of vasoconstrictor will vary, depending

upon the local anesthetic agent selected, the duration of anesthesia needed, the site of injection and its vascularity, and the requirement for intraoperative hemostasis and the extent of hemostasis desired.

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