

Systemic Safety of Adrenaline (Epinephrine) in Dental Local Anaesthesia: A Review of the Evidence in Patients with Systemic Disease and Comorbidities

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Abstract

Objective: Adrenaline (epinephrine) is routinely combined with local anaesthetic agents in dentistry to prolong pulpal and soft-tissue anaesthesia, reduce systemic toxicity of the anaesthetic base, and improve haemostasis at the surgical site. Despite this, many clinicians restrict or avoid its use in patients with hypertension, ischaemic heart disease, arrhythmia, diabetes mellitus, thyroid disease and other systemic conditions, out of a belief that the drug poses a meaningful systemic cardiovascular or metabolic risk. This review examines the pharmacological and clinical evidence for the systemic safety of adrenaline-containing dental local anaesthetics in patients with common comorbidities.

Methods: A narrative review of the pharmacokinetic and pharmacodynamic literature on adrenaline, together with clinical trials, systematic reviews and evidence reports addressing the cardiovascular, endocrine and pharmacological safety of epinephrine-containing dental local anaesthetics, was undertaken using PubMed/MEDLINE, ScienceDirect, and the Agency for Healthcare Research and Quality evidence library. English-language systematic reviews, randomised and prospective clinical studies, and authoritative pharmacology references published up to 2024 were included.

Results: The mass of adrenaline delivered in one to two standard dental cartridges (0.009-0.036 mg at 1:100,000 or 1:80,000 concentration) is far below the therapeutic doses used for anaphylaxis or cardiac arrest (0.3-1.0 mg) and is rapidly inactivated by monoamine oxidase and catechol-O-methyltransferase, with a plasma half-life of only a few minutes. Systematic reviews in hypertensive and coronary disease patients report only small, clinically insignificant changes in blood pressure and heart rate, with no serious adverse cardiovascular events attributable to correctly administered epinephrine-containing anaesthesia. Controlled trials in heart failure, diabetes mellitus and coronary artery disease similarly demonstrate haemodynamic and metabolic stability. The principal, well-documented systemic hazard is a pharmacodynamic interaction with non-selective beta-adrenergic blocking agents, and true contraindication is limited to decompensated or uncontrolled endocrine disease such as unstable hyperthyroidism or pheochromocytoma.

Conclusion: When administered within recommended dose limits, using an aspirating technique and appropriate patient selection, adrenaline in dental local anaesthesia does not produce clinically meaningful systemic harm even in patients with common cardiovascular, endocrine or other systemic comorbidities. Withholding adrenaline in these patients is frequently more hazardous than its judicious use, because it results in inadequate anaesthesia and a larger, uncontrolled release of endogenous catecholamines in response to pain and stress.

Keywords

Adrenaline; Epinephrine; Local Anaesthesia; Dental Anaesthesia; Vasoconstrictors; Systemic Disease; Cardiovascular Safety.

1. Introduction

Local anaesthesia is the cornerstone of pain control in clinical dentistry, and adrenaline (epinephrine) is the most widely used additive to the local anaesthetic solution. As a potent agonist at both alpha- and beta-adrenergic receptors, adrenaline produces localised vasoconstriction at the site of injection. This action slows systemic vascular uptake of the anaesthetic base, prolongs pulpal and soft-tissue anaesthesia, reduces peak plasma concentrations of the anaesthetic agent (thereby lowering the risk of local anaesthetic systemic toxicity), and improves intra-operative haemostasis [1,2]. Adrenaline is also the physiological hormone released endogenously by the adrenal medulla during pain, anxiety and stress, meaning that every dental patient, treated or untreated, is already exposed to circulating catecholamines during operative procedures.

Despite the pharmacological rationale for its use, adrenaline-containing local anaesthetics are frequently withheld, or their use is reduced to plain solutions, in patients who present with hypertension, ischaemic heart disease, cardiac arrhythmia, congestive heart failure, diabetes mellitus, or thyroid dysfunction. This practice is driven by a longstanding, largely anecdotal, clinical impression that exogenous adrenaline injected during dental treatment can precipitate hypertensive crisis, myocardial ischaemia, arrhythmia or dangerous glycaemic instability in patients with systemic disease. Such concerns are understandable given adrenaline's potent physiological effects when administered intravenously in emergency medicine, but they conflate pharmacological dose and route with the trace quantities delivered submucosally during routine dental injections.

The purpose of this review is to critically examine the pharmacokinetic, pharmacodynamic and clinical trial evidence concerning the systemic safety of adrenaline used in standard dental local anaesthetic concentrations (1:80,000 to 1:200,000), with particular reference to patients with common comorbidities. The central hypothesis of this review is that, at the doses and routes used in routine dental practice, adrenaline does not produce clinically significant systemic harm in the majority of medically compromised patients, and that the unnecessary avoidance of adrenaline-containing anaesthetics may itself pose a greater physiological risk than its judicious use, principally through inadequate pain control and the resulting surge in endogenous catecholamine release.

2. Materials and Methods

This is a narrative literature review. A structured search of PubMed/MEDLINE, ScienceDirect, the Cochrane Library and the Agency for Healthcare Research and Quality (AHRQ) evidence report database was conducted using the terms "epinephrine", "adrenaline", "local anaesthesia", "dental", "vasoconstrictor", "cardiovascular disease", "hypertension", "diabetes mellitus", "hyperthyroidism", "beta-blocker" and "systemic safety", individually and in combination. Articles were included if they were systematic reviews, randomised or prospective controlled clinical studies, authoritative pharmacology references (including manufacturer prescribing information and standard dental anaesthesia textbooks), or evidence-based practice reports published in English and addressing the cardiovascular, endocrine, or pharmacological safety of epinephrine-containing dental local anaesthetics in adult patients. Case reports without denominator data and non-peer-reviewed opinion pieces were excluded unless required to illustrate a specific, well-characterised drug interaction.

As this is a review of previously published data, no original human or animal experimentation was performed, and no institutional ethical approval or individual patient informed consent was required. Where clinical studies are cited, the ethical approval and consent procedures reported in the original publications are assumed to have met the standards applicable to the jurisdiction and journal of publication.

3. Results and Discussion

3.1 Pharmacological Rationale and Dose Comparison

A single dental cartridge contains 1.8 mL of solution. At a concentration of 1:100,000, this delivers 0.018 mg (18 micrograms) of adrenaline; at 1:80,000, approximately 0.0225 mg; and at 1:200,000, approximately 0.009 mg [3]. Even where two to three cartridges are used for a single procedure, the total dose administered submucosally rarely exceeds 0.05-0.07 mg. This is markedly lower than the doses employed therapeutically in emergency medicine: 0.3-0.5 mg intramuscularly for anaphylaxis,

and 1.0 mg intravenously for cardiac arrest [3]. The comparison is instructive because it is these emergency, systemically administered doses — not the trace submucosal doses used in dentistry — that are associated with the marked pressor and chronotropic effects clinicians tend to associate with adrenaline.

Malamed's classic teaching in dental local anaesthesia recommends a maximum dose of 0.2 mg of adrenaline for a healthy adult per appointment, reduced to no more than 0.04 mg (40 micrograms) — roughly two cartridges of a 1:100,000 solution — for a patient with clinically significant cardiovascular disease [1,4]. These recommended limits were derived precisely to keep the administered dose well below any threshold associated with adverse systemic effects, giving a substantial safety margin for routine restorative and surgical procedures, which typically require only one to two cartridges.

3.2 Pharmacokinetics: Rapid Systemic Inactivation

Adrenaline's brief duration of systemic action is central to its safety profile. Following parenteral administration, plasma adrenaline is cleared with an effective half-life of under five minutes [2]. It is extensively and rapidly metabolised, principally by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), enzymes that are abundant in the liver, kidney and other extraneuronal tissues, to the inactive metabolite vanillylmandelic acid [2]. The liver accounts for approximately 32% of the clearance of circulating exogenous adrenaline, the kidneys 25%, skeletal muscle 20%, and mesenteric organs 12% [2]. Because dental injections are given submucosally rather than intravenously, and because the co-administered vasoconstriction itself limits the rate of systemic absorption from the injection site, the peak plasma concentrations achieved during dental anaesthesia are far below those produced by intravenous emergency dosing, and the small quantity that does enter the circulation is metabolised within minutes. This pharmacokinetic profile — rapid, near-complete enzymatic inactivation with no significant accumulation over the timeframe of a dental appointment — provides the physiological basis for the absence of cumulative systemic toxicity, even when comorbid disease is present.

3.3 Cardiovascular Disease and Hypertension

Cardiovascular disease is the comorbidity most frequently cited as a reason to withhold adrenaline. The strongest evidence addressing this concern comes from systematic reviews. Bader and colleagues, in a systematic review commissioned by the Agency for Healthcare Research and Quality, examined the cardiovascular effects of epinephrine-containing local anaesthetics in hypertensive dental patients and found that use of epinephrine in uncontrolled hypertensive patients was associated with only small, non-significant increases in systolic and diastolic blood pressure, with no adverse outcomes reported in the studies reviewed [5,6]. A subsequent systematic review by Seminario-Amez and colleagues, evaluating the use of local anaesthetics with vasoconstrictor agents in patients with hypertension and coronary disease, concluded that the use of one to two cartridges of local anaesthetic containing 1:80,000, 1:100,000 or 1:200,000 adrenaline is safe in patients with controlled hypertension and/or coronary disease [7].

Even in more severe cardiac disease, the evidence is reassuring. The Tooth-HF trial, a prospective, double-blind, randomised study in patients with heart failure and reduced left ventricular ejection fraction, found that a lidocaine-adrenaline solution was safe and effective, produced no adverse cardiovascular events, and was in fact associated with better intra-operative pain control than plain lidocaine without adrenaline [8]. These findings support the pharmacological expectation that, at the doses used clinically, the dominant physiological driver of intra-operative cardiovascular change is the sympathetic response to pain and anxiety, rather than the pharmacological dose of adrenaline in the anaesthetic solution itself.

3.4 Endocrine Disease: Diabetes Mellitus, Thyroid Disease and Pheochromocytoma

Diabetes mellitus is the second most common comorbidity prompting clinicians to avoid adrenaline, owing to its known glycogenolytic and hyperglycaemic effects and its inhibition of pancreatic insulin release at pharmacological doses [2]. Clinical studies specifically designed to test this concern at dental doses, however, have not demonstrated clinically meaningful glycaemic instability. Tily and

Thomas compared glycaemic response to epinephrine-containing local anaesthesia between healthy and diabetic patients undergoing dental extraction and found no significant difference in pre- and post-operative blood glucose between the two groups, the only significant change occurring in diabetic patients who had omitted their pre-operative hypoglycaemic medication [9]. Comparable findings were reported by Hemanth Kumar and colleagues in diabetic patients undergoing third molar extraction, and by Diaconu and colleagues, who found articaine with 1:200,000 adrenaline to be comparably safe to plain mepivacaine with respect to glycaemic response in diabetic patients [10,11]. Taken together, these data indicate that adrenaline-containing local anaesthesia is safe in patients with controlled diabetes mellitus and does not clinically destabilise glycaemic control, provided that patients continue their usual hypoglycaemic therapy.

Thyroid disease and pheochromocytoma occupy a distinct category. Unlike hypertension, coronary disease and controlled diabetes, where the literature supports safety, uncontrolled or decompensated endocrine hyperfunction represents a genuine, if uncommon, contraindication. In uncontrolled hyperthyroidism, the tissue sensitivity to circulating catecholamines is pathologically heightened, and in pheochromocytoma, autonomous catecholamine secretion means that even small additional doses of exogenous adrenaline can theoretically provoke a disproportionate pressor response. The literature update by Seminario-Amez and colleagues explicitly states that in patients with decompensated diabetes mellitus, uncontrolled hyperthyroidism or pheochromocytoma, the use of vasoconstrictors is contraindicated, independently of the dose or anaesthetic technique used, whereas in medically controlled cardiovascular and endocrine disease, adrenaline-containing anaesthesia remains safe provided the total dose does not exceed 5.4 mL of a 1:100,000 solution (three cartridges), intravascular injection is avoided, and the patient is adequately anaesthetised and behaviourally managed throughout treatment [3]. This distinction is important: the systemic risk associated with adrenaline in dentistry is not a function of the presence of endocrine disease per se, but specifically of its being uncontrolled or decompensated.

3.5 Drug Interactions: Non-Selective Beta-Adrenergic Blockers

The most pharmacologically significant and best-documented systemic hazard associated with dental adrenaline is not a direct effect of the drug on diseased tissue, but a receptor-level interaction with non-selective beta-adrenergic blocking agents such as propranolol and nadolol. When beta-1 and beta-2 receptors are pharmacologically blocked, adrenaline's vasodilatory beta-2 action in skeletal muscle vasculature is lost, leaving its alpha-1 mediated vasoconstriction unopposed; the result can be a marked rise in blood pressure with reflex bradycardia [12,13]. Ichinohe and colleagues demonstrated experimentally that propranolol reduces the plasma clearance of adrenaline and shifts its haemodynamic profile toward an alpha-dominant, pressor-predominant state, even at plasma concentrations comparable to those achieved during dental local anaesthesia [13]. Hersh and Giannakopoulos, reviewing this interaction specifically in the dental context, concluded that although clinically significant reactions are rare, they are dose-related, more likely with inadvertent intravascular injection or the use of multiple cartridges, and that cardioselective beta-blockers such as metoprolol and atenolol do not appear to produce the same hypertensive response [12]. This interaction is the one area in which the practising dentist should exercise specific caution: confirming which class of beta-blocker a patient is taking, using an aspirating technique, and limiting the total dose of adrenaline administered, rather than avoiding adrenaline altogether in every cardiac patient.

3.6 Why Endogenous Stress Response Is the Greater Risk

A frequently overlooked aspect of this topic is that dental pain and anxiety themselves provoke a substantial release of endogenous adrenaline and noradrenaline from the adrenal medulla and sympathetic nerve terminals. Inadequate anaesthesia resulting from the deliberate omission of adrenaline, and the consequent breakthrough pain during operative procedures, can generate endogenous catecholamine surges that are considerably larger, less predictable, and less controllable than the small, fixed dose delivered in the anaesthetic cartridge [1,6]. From a systemic safety standpoint, this means that the well-intentioned avoidance of adrenaline in an anxious cardiac or hypertensive patient may paradoxically increase, rather than decrease, the cardiovascular load placed on that patient during treatment. Adequate anaesthesia, achieved efficiently with an adrenaline-

containing solution, is therefore not only a comfort measure but a component of cardiovascular risk management in the dental chair.

3.7 Practical Recommendations for Safe Use

The evidence reviewed above supports a pragmatic, rather than an avoidance-based, approach to the use of adrenaline in medically compromised dental patients:

- (i) Limit the total dose administered per appointment — for patients with significant cardiovascular disease, no more than 0.04 mg (approximately two cartridges of a 1:100,000 solution) is recommended [1,4].
- (ii) Use an aspirating syringe technique before every injection to avoid inadvertent intravascular deposition, which is the scenario most strongly associated with adverse pressor responses [12].
- (iii) Confirm current medications, particularly non-selective beta-blockers, and adjust the dose and injection technique accordingly rather than substituting a plain solution by default [12,13].
- (iv) Ensure diabetic patients have taken their usual hypoglycaemic medication and eaten normally before treatment [9].
- (v) Reserve true avoidance of adrenaline for patients with decompensated or uncontrolled endocrine disease (uncontrolled hyperthyroidism, pheochromocytoma, unstable diabetes) and for recent (within one month) myocardial infarction or uncontrolled severe hypertension, in line with standard contraindication guidance [3,14].
- (vi) Prioritise profound, comfortable anaesthesia as a means of minimising the endogenous stress-catecholamine response, which for most patients represents a greater physiological burden than the pharmacological dose of adrenaline itself [6].

4. Conclusion

The weight of pharmacological and clinical trial evidence indicates that adrenaline, used at the concentrations and doses standard in dental local anaesthesia, is not a clinically significant systemic hazard for the great majority of patients with comorbid disease. The mass of drug delivered is a small fraction of therapeutic emergency doses, it is cleared from the circulation within minutes by ubiquitous enzymatic pathways, and controlled clinical studies in hypertensive, coronary, heart failure and diabetic patients consistently demonstrate haemodynamic and metabolic stability with its use. Genuine, evidence-based caution is warranted in a narrow set of circumstances — principally uncontrolled or decompensated endocrine disease, recent myocardial infarction, severe uncontrolled hypertension, and concurrent therapy with non-selective beta-adrenergic blockers — but these represent the exception rather than the rule among patients presenting for routine dental care. For the majority of patients with well-controlled systemic disease, the judicious use of adrenaline-containing local anaesthetic, within recommended dose limits and using a careful aspirating technique, is not only systemically safe but is likely to reduce overall cardiovascular risk by providing the profound anaesthesia that limits the far less predictable rise in endogenous catecholamines associated with intra-operative pain and anxiety. Blanket avoidance of adrenaline on the basis of comorbidity alone is not supported by the current evidence and may be clinically counterproductive.

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7. Conflict of Interest

The author declares no financial, professional, institutional or personal conflict of interest relating to the subject matter of this review.

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