What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry?

Prepared by a UK Medicines Information (UKMi) team for NHS healthcare professionals
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Background

The amide local anaesthetics most commonly used for dental procedures in primary care are lidocaine, prilocaine, articaine and mepivacaine. The majority of local anaesthetic dental cartridges also contain a vasoconstrictor; either adrenaline (epinephrine) or felypressin.

Dentists commonly refer to the British National Formulary (BNF), Summary of Product Characteristics (SPC) or product package leaflets for information on potential interactions. The list of interactions included in these resources can be disconcerting and difficult to interpret and apply to the dental setting.

This Medicines Q&A explores the clinical significance of potential interactions between dental local anaesthetic preparations and other medicines as listed in the BNF and SPCs. It does not address use of local anaesthetics in patients with medical conditions that may contraindicate or require caution in their use, for example Parkinson's, cardiovascular or thyroid disease.

Answer

Evidence used to predict interactions between local anaesthetics used in dental practice and other medicines often comes from anecdotal reports documented many years ago, when doses used were higher than recommended today. Reports of serious drug interactions associated with currently recommended doses of local anaesthetics and vasoconstrictors in the dental setting are exceedingly rare (1).

Interactions listed in the BNF are usually only relevant when local anaesthetics, with or without vasoconstrictors, are used at high doses or for specific indications other than dental anaesthesia. Theoretical interactions are often included in SPCs if they have previously occurred with medicines that have similar pharmacological actions. Although many of the listed interactions are either theoretical and may not have been seen in dental practice or are relevant to much higher doses used for different indications, the manufacturer has an obligation to include this information in the product literature.

Some local anaesthetics e.g. lidocaine, are used for purposes other than local anaesthesia i.e. cardiopulmonary resuscitation and ventricular arrhythmias (2). When used to treat arrhythmias, lidocaine is used in doses of up to 1,750mg intravenously over 24 hours (2). Many of the interactions listed in the BNF apply to these higher doses. Adrenaline is also used clinically at much higher doses than when administered for dental anaesthesia e.g. adrenaline 500micrograms IM is used for anaphylaxis and 1,000micrograms IV for cardiac arrest (2). To put these doses into context, a 1.8ml lidocaine 2% with adrenaline 1:80,000 dental cartridge contains 36mg of lidocaine and 22.5micrograms of adrenaline and a 2.2ml cartridge contains 44mg of lidocaine and 27.5micrograms of adrenaline (2).

Do local anaesthetics and vasoconstrictors used for dental procedures result in drug interactions?

The tables in the appendix include all the interactions with local anaesthetics and vasoconstrictors as listed in the BNF and SPCs. The relevance of each interaction for the dental practitioner is put into context and any precautions required are addressed.

The local anaesthetics (lidocaine, prilocaine, articaine and mepivacaine) do not cause clinically significant interactions at doses used in dentistry. Of the available vasoconstrictors (felypressin and adrenaline), only adrenaline is listed as interacting with other drugs.

Can injection route, dose and technique influence drug interactions?

As noted above, interactions between the local anaesthetic component in dental preparations are unlikely to occur; adrenaline however may interact.

Route of administration

Drug interactions are more likely to occur when a drug is successfully absorbed into the systemic circulation. Correct administration of dental local anaesthetic leads to very low plasma concentrations compared to direct intravascular administration. This will minimise the risk of systemic side effects and drug interactions (3,4).

Dose administered

Many interactions are dose-related, if the dose of the added drug is low, the effects on the original drug will be reduced accordingly (5). Documented interactions involving lidocaine are often as a result of very high doses of lidocaine being given i.e. when indicated for ventricular arrhythmias and not usually associated with low doses administered in the dental setting.

Technique

The injection technique may influence the risk of interactions. In general dental practice, local anaesthetic preparations are usually administered by one of three techniques; infiltration, regional block or by intraligamentary injection. Infiltration and regional block anaesthesia are not associated with significant systemic absorption. When these techniques are used, dental local anaesthetics will not reach the systemic circulation unless inadvertent intravascular administration occurs (3). Even in the unlikely event of a full cartridge of adrenaline-containing local anaesthetic being injected intravascularly, the plasma concentrations of adrenaline are unlikely to exceed plasma concentrations of adrenaline naturally produced by the body under stressful situations or when performing light physical exercise (4). Intraligamentary injection can result in rapid absorption into the systemic circulation. However, volumes used for this technique are very small (roughly 0.2ml i.e. 2.5micrograms of adrenaline per tooth) and plasma levels of adrenaline reached are unlikely to result in clinically significant drug interactions (4). Caution is required if more than one tooth is being anaesthetised by intraligamentary injection as higher levels of adrenaline may be achieved.

Dental practitioners can minimise risk of drug interactions by:

- Using an aspirating syringe (3,4) to avoid inadvertent intravascular administration of local anaesthetic and adrenaline (2).
- Adhering to dosing recommendations in the product literature.

If a drug is not included in the interaction tables (in the appendix), this indicates that no interaction with a local anaesthetic or adrenaline is documented in either the BNF or SPC.

Summary

- Drug interactions that may occur with local anaesthetic preparations are listed in the BNF and SPCs. Many are theoretical or are associated with higher doses of local anaesthetic preparations than those used for dental procedures in primary care.
- Reports of serious interactions between medicines and local anaesthetic preparations occurring in dental practice are exceedingly rare.
- Reports of interactions between medicines and vasoconstrictors (adrenaline) may require additional monitoring.
- Practitioners can minimise the risk of interactions by using an aspirating syringe, which reduces the likelihood of local anaesthetic being administered directly into a blood vessel.
- Adhering to dosage recommendations in the product literature will also minimise risk.
- This Q&A includes tables (see appendix) that discuss all the interactions with local anaesthetics and vasoconstrictors listed in the BNF and SPCs. The relevance of each interaction for the dental practitioner is put into context and any precautions required are addressed.
- This Q&A does not cover use of local anaesthetics in patients with medical conditions that may contraindicate or require caution in their use.

Limitations

- The Q&A only addresses drug interactions with dental local anaesthetic preparations and does not include information about interactions between medical conditions and local anaesthetics or vasoconstrictors.

- This document relates to infiltration, intraligamentary and regional block anaesthesia, as these are the techniques used in primary dental care. It does not address intra-osseous administration of local anaesthetics.

- Interactions between local anaesthetic agents used at higher doses in non-dental setting have not been addressed.

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Search strategy

1. Embase: "(exp "DRUG INTERACTION"/ AND exp DENTISTRY/) AND (exp "LOCAL ANESTHETIC AGENT"/ OR exp BUPIVACAINE/ OR exp LIDOCAINE/ OR exp "LOCAL ANESTHESIA"/ OR exp MEPIVACAINE/ OR exp ROPIVACAINE/ OR exp PRILOCAINE/ OR exp EPINEPHRINE/ OR exp FELYPRESSIN/ OR exp COCAINE/)"

2. Medline: "((exp "DRUG INTERACTIONS"/ AND exp DENTISTRY/) AND (exp "ANESTHETICS, LOCAL"/ OR exp BUPIVACAINE/ OR exp LIDOCAINE/ OR exp MEPIVACAINE/ OR exp ROPIVACAINE/ OR exp PRILOCAINE/ OR exp EPINEPHRINE/ OR exp FELYPRESSIN/ OR exp COCAINE/)) [Languages English]"

3. In-house databases/specialist dental resources

Clinical expert comments incorporated from (contacted in 2009):

- Dr John Meechan, Senior Lecturer in Oral and Maxillofacial Surgery, Newcastle University.
- Professor Crispian Scully, Professor of Oral Medicine, Pathology and Microbiology, University of London.
- Professor Munir Pirmohamed, Department of Clinical Pharmacology and Therapeutics, University of Liverpool.
- Dr Lesley Longman. Consultant/Hon. Senior Lecturer in Restorative Dentistry. Clinical Lead for Sedation and Special Care Dentistry. Liverpool University Dental Hospital and School of Dentistry.
- Dr Nikolaus Palmer. PhD BDS MFGDP (UK) General Dental Practitioner, Research Associate Mersey Deanery, Honorary Lecturer University of Liverpool.

Appendix 1. Table 1. Interactions with local anaesthetics

Drug interaction as listed in the BNF or SPC[1]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Anaesthetics, local Bupivacaine Chloroprocaine Levobupivacaine Oxybuprocaine Proxymetacaine Ropivacaine Tetracaine Please note these are local anaesthetics for non-dental use.	Lidocaine used as an anti-arrhythmic at high doses (i.e. 1,750mg intravenously over 24 hours compared to 36mg contained in a 1.8ml dental cartridge) in combination with other local anaesthetics may result in myocardial depression or increase the risk of ventricular arrhythmias. Combined use of local anaesthetics at total doses that significantly exceed combined maximum recommended doses can cause classic local anaesthetic toxicity reactions: CNS excitation, convulsions, respiratory depression and cardiac arrest. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,6,7
Anti-arrhythmics Adenosine Amiodarone Disopyramide Dronedarone Flecainide Mexiletine Propafenone Vernakalant	*Lidocaine* When used at anti-arrhythmic doses (1,750mg intravenously over 24 hours) and given with other anti-arrhythmic agents, myocardial depression may occur. *Prilocaine* When used for spinal anaesthesia, increased myocardial depression has been reported when anti-arrhythmics are given with prilocaine. *Articaine* Manufacturer of articaine advises caution when administering this to any patient receiving an anti-arrhythmic agent. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,7-9

[1] Clinically significant interactions are unlikely when local anaesthetics are administered in the dental setting; interactions are often specific to intravenous use of anaesthetics following systemic absorption.

Drug interaction as listed in the BNF or SPC[1]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Antibacterials (sulphonamides) Co-trimoxazole Sulfadiazine	High doses of prilocaine can lead to methaemoglobinaemia. This risk increases with concomitant use of sulfonamides e.g. co-trimoxazole. There are no case reports of methaemoglobinaemia occurring in the dental setting with this combination.	None, a clinically significant interaction is unlikely at doses used in dentistry.	1,2,8, 10
Antipsychotics Amisulpiride, Aripiprazole, Asenapine, Benperidol, Cariprazine, Chlorpromazine, Flupentixol, Fluphenazine, Haloperidol, Loxapine, Lurasidone, Olanzapine, Quetiapine, Promazine, Sulpiride, Trifluoperazine, Zuclopenthixol	Lidocaine used as an anti-arrhythmic at high doses (i.e. 1,750mg intravenously over 24 hours compared to 36mg contained in a 1.8ml dental cartridge) in combination with antipsychotics that prolong QT interval may result in increased risk of ventricular arrhythmias. There is no reference of this potential interaction in specialist interaction or psychiatry resources. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,7
Antivirals Atazanavir, Darunavir, Fosamprenavir, Lopinavir, Ritonavir, Saquinavir, Tipranavir	These agents appear to increase plasma concentrations of lidocaine via CYP3A4 inhibition, potentially causing bradycardia, hypotension and pins and needles. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,5,7, 11
Benzodiazepines Clonazepam, Diazepam, Flurazepam, Lorazepam, Lormetazepam, Midazolam, Nitrazepam, Oxazepam, Temazepam	Midazolam has been reported to cause a modest reduction in serum lidocaine levels but not mepivacaine levels. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,5

Drug interaction as listed in the BNF or SPC[1]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Beta-blockers Acebutolol Atenolol Betaxolol Bisoprolol Celiprolol Esmolol Levobunolol Metoprolol Nadolol Nebivolol Pindolol Propranolol Timolol	Lidocaine used as an anti-arrhythmic at high doses (i.e. 1,750mg intravenously over 24 hours compared to 36mg contained in a 1.8ml dental cartridge) in combination with beta-blockers may result in myocardial depression. Lidocaine clearance is reduced by propranolol and possibly nadolol. Risk of toxicity may increase when lidocaine is given in high doses, much greater than doses used in a dental setting. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,5,7, 11
Cimetidine	Oral cimetidine may increase plasma concentrations of lidocaine administered intravenously or via epidural. This same effect is not seen with other ulcer-healing drugs. No reports of significant interactions in doses used in dentistry found.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,5
Diuretics Acetazolamide Amiloride Bendroflumethiazide Bumetanide Chlortalidone Co-amilofruse Co-amilozide Co-flumactone Co-tenidone Co-triamterzide Furosemide Hydrochlorothiazide Indapamide Spironolactone Torasemide Xipamide	The action of intravenous lidocaine is antagonised by hypokalaemia. Diuretics e.g. acetazolamide, loop diuretics or thiazides and related diuretics, can cause hypokalaemia. No reports of significant interactions when lidocaine is administered in the dental setting found. This interaction is specific to intravenous use of lidocaine.	None, a clinically significant interaction is unlikely at doses used in dentistry.	2,7

Table 2. Interactions with adrenaline (epinephrine)

Drug interaction as listed in the BNF or SPC (listed under 'Sympathomimetics')[2]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Beta-blockers (non-cardioselective) Nadolol Pindolol Propranolol Sotalol Timolol	Increased risk of severe hypertension and bradycardia when adrenaline is given with non-cardioselective beta-blockers. Response to adrenaline may also be reduced. The severity of the interaction appears to be dose-related, serious blood pressure rises and severe bradycardia has occurred in patients given 300micrograms of adrenaline. Local anaesthetics used in dental surgery contain very low concentrations of adrenaline and only small volumes are given, so an interaction is unlikely. A maximum of two cartridges of adrenaline-containing solution are recommended. However in certain situations more cartridges may be administered if required, for example in specialist settings. Where more cartridges are used heart rhythm monitoring is also recommended.	None, if a maximum of two cartridges of adrenaline-containing solution are used. If more than two cartridges are used or if the procedure is short and haemostasis is not required, an adrenaline-free solution should be used.	1,2,3,5, 11,13, 15-20
Catechol-O-methyl transferase (COMT) inhibitors Entacapone Opicapone Tolcapone	Dopaminergics affect the action of catechol-O-methyl transferase (the enzyme that initiates exogenous adrenaline metabolism); concomitant use may result in increased adrenaline levels.	Although there are no data regarding interactions in a dental setting, recommend limiting to a maximum of one cartridge.	1,2,5, 16,18
Cocaine	Cocaine and adrenaline both have sympathomimetic effects. Combined use increases these effects and the risk of arrhythmias.	Avoid using local anaesthetics containing adrenaline in patients who abuse cocaine, unless it is certain they have not used cocaine for 24 hours or more.	1-5, 10,20

[2] Sympathomimetic drugs stimulate the sympathetic nervous system. Symptoms of sympathomimetic toxicity include: hypertension, tachycardia, diaphoresis, agitation, tremors, seizures, hyperthermia, and dilated pupils (12).
Sympathomimetic toxicity can be monitored by monitoring BP and heart rate. Re-monitoring these vital signs at 5-10 minutes after administration of adrenaline-containing anaesthetic is strongly suggested.

Drug interaction as listed in the BNF or SPC (listed under 'Sympathomimetics')[2]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Diuretics Acetazolamide Amiloride Bendroflumethiazide Bumetanide Chlortalidone Co-amilofruse Co-amilozide Co-flumactone Co-tenidone Co-triamterzide Furosemide Hydrochlorothiazide Indapamide Spironolactone Torasemide Xipamide	Use of potassium-depleting diuretics (acetazolamide, loop and thiazides) and adrenaline-containing local anaesthetic increases the risk of adrenaline-induced hypokalaemia. A maximum of two cartridges of adrenaline-containing solution is recommended.	None, if a maximum of two cartridges of adrenaline-containing solutions are used.	3,11,13, 18,20
Monoamine oxidase inhibitor antidepressants (MAOI) Isocarboxazid Phenelzine Tranylcypromine	Co-administration of higher doses of intravenous adrenaline, when used to treat cardiac arrhythmias, and MAOI antidepressants may produce severe prolonged hypotension or hypertension. The manufacturers of *Scandonest Special, Septanest, Artikent, Isonest, Bartinest and Orabloc* contraindicate their use in patients taking MAOI antidepressants[3]. This advice is over cautious and the BNF and manufacturers of other adrenaline-containing local anaesthetics do not include the same contraindications. The interaction is unlikely to be of clinical significance in the dental setting, however caution is advised and a maximum of 2 cartridges is recommended.	None, if a maximum of two cartridges of adrenaline-containing solution are used.	2,5,9, 10,14, 16,17, 20-24
Phenothiazines Chlorpromazine[4] Prochlorperazine Trifluoperazine	Co-administration of higher doses of intravenous adrenaline and phenothiazines may produce severe prolonged hypotension or hypertension. Although there are limited data regarding interactions in a dental setting, caution is advised and a maximum of two cartridges are recommended. Additional monitoring for sympathomimetic toxicity may be appropriate.	None, if a maximum of two cartridges of adrenaline-containing solution are used.	14, 21-23

[3] Prescribers should be aware that when using medicines outside their product licence this alters their professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.
[4] Chlorpromazine is a phenothiazine that can be used as an antipsychotic (as listed in table 1) or as an anti-emetic (2).

Drug interaction as listed in the BNF or SPC (listed under 'Sympathomimetics')[2]	Nature of interaction	Clinical relevance at doses used in primary care dentistry	Refs
Rasagiline	Concomitant use of sympathomimetics with rasagiline should be avoided. The sympathomimetics known to interact with adrenaline are those present in decongestant medications e.g. ephedrine or pseudoephedrine. No reports of significant interactions with adrenaline when administered in the dental setting found.	None, this interaction is not clinically relevant in dentistry.	2,5,25
Serotonin and noradrenaline reuptake inhibitors (SNRI) Duloxetine Venlafaxine	Co-administration of higher doses of intravenous adrenaline and SNRIs may produce severe prolonged hypotension or hypertension. Although there are limited data regarding interactions in a dental setting, caution is advised and a maximum of two cartridges is recommended. Additional monitoring for sympathomimetic toxicity may be appropriate.	None, if a maximum of two cartridges of adrenaline-containing solution are used.	12, 20-22, 26
Tricyclic antidepressants (TCA) Clomipramine Dosulepin Imipramine Lofepramine Nortriptyline Trimipramine	Co-administration of higher doses of intravenous adrenaline, when used to treat cardiac arrhythmias, and TCAs may increase the risk of hypertension and arrhythmias. The manufacturers of *Scandonest Special, Septanest, Artikent, Isonest, Bartinest and Orabloc* contraindicate their use in patients taking MAOI antidepressants[5]. This advice is over cautious and the BNF and manufacturers of other adrenaline-containing local anaesthetics do not include the same contraindications. The interaction is unlikely to be of clinical significance in the dental setting, however caution is advised and a maximum of two cartridges is recommended.	None, if a maximum of two cartridges of adrenaline-containing solution are used.	1,2,5, 10,11, 14,16, 17,20, 24

[5] Prescribers should be aware that when using medicines outside their product licence this alters their professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.