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

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at www.sps.nhs.uk/articles/about-ukmi-medicines-qas/

Date prepared: August 2015

Summary

- A number of drug interactions that may potentially occur with local anaesthetic preparations are listed in the British National Formulary (BNF) and Summaries of Product Characteristics (SmPC). 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.
- 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 does not cover use of local anaesthetics in patients with medical conditions that may contraindicate or require caution in their use.

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 BNF, SmPC or product package leaflets for information on potential interactions. The list of interactions included in these resources can be disconcerting. It is sometimes difficult to interpret the advice in the BNF and SmPCs and apply it to the dental setting.

This Q&A explores the clinical significance of potential interactions between dental local anaesthetic preparations and other medicines as listed in the BNF and SmPCs. It does not cover use of local anaesthetics in patients with medical conditions that may contraindicate or require caution in their use.

Answer

Evidence of potential interactions with local anaesthetic dental preparations comes mainly from anecdotal case reports documented many years ago, when doses used were much higher than those 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/vasoconstrictor are used at high doses or for specific indications other than dental anaesthesia. Theoretical interactions are often included in SmPCs 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 agents e.g. lidocaine, are used for purposes other than local anaesthesia. As a treatment for arrhythmia, 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. Likewise, doses of adrenaline used in some areas of clinical practice are much higher than are administered for dental anaesthesia e.g. adrenaline 500micrograms IM is used for anaphylaxis and 1,000micrograms IV in 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 at the end of this document include all the interactions with local anaesthetics and vasoconstrictors as listed in the BNF and SmPC. 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 technique influence drug interactions?

As noted above, interactions between the local anaesthetic component in dental preparations is unlikely to occur; it is only adrenaline that may interact. The injection technique may influence this risk. 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, the preparations used for dental anaesthesia will not be administered into 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 [3]. Intraligamentary injection can result in rapid absorption into the systemic circulation. However, volumes used for this technique are very small (between 0.2 to 0.5ml; 2.5 and 6.25micrograms of adrenaline respectively) and levels reached are unlikely to result in clinically significant drug interactions. Caution may be 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 [4] to avoid inadvertent intravascular administration of local anaesthetic and adrenaline [2]. Correct administration of local anaesthetic leads to very low plasma concentrations compared to direct intravascular administration. This will minimise the likelihood of systemic side effects and drug interactions [4].
- Adhering to dosing recommendations in the product literature.

If a drug is not included in the following interaction tables, this indicates that NO interaction with a local anaesthetic or adrenaline is likely to occur.

Limitations

- The Q&A only addresses drug interactions with local anaesthetic dental 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 care. It does not address intra-osseous administration of local anaesthetics.

References


Q&A 152.4 What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry? August 2015

Available at www.sps.nhs.uk
What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry?


Bibliography/Further reading:
The following resources were used to compile the table of interactions:

Quality Assurance
Prepared by

Date this version written
August 2015

Checked by
Christine Randall. North West Medicines Information Centre, Liverpool.

Date of check
September 2015

Search strategy
- Embase: [LOCAL ANESTHETIC AGENT OR BUPIVACAINE OR LIDOCAINE OR LOCAL ANESTHESIA OR MEPIVACAINE OR ROPIVACAINE OR PRILOCAINE] and [DRUG INTERACTION] and [DENTISTRY]
- Medline: [ANESTHETICS, LOCAL OR BUPIVACAINE OR LIDOCAINE OR MEPIVACAINE OR ROPIVACAINE OR PRILOCAINE] and [DRUG INTERACTIONS] and [DENTISTRY]
- In-house databases/specialist dental resources

Q&A 152.4 What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry? August 2015
Available at www.sps.nhs.uk
What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry?

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.

Q&A 152.4 What is the clinical significance of potential drug interactions with local anaesthetic preparations used in primary care dentistry? August 2015 Available at www.sps.nhs.uk
Table 1: Interactions with local anaesthetics

<table>
<thead>
<tr>
<th>Drug interaction as listed in the BNF or SmPC</th>
<th>Clinical relevance at doses used in dentistry</th>
<th>Nature of interaction</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthetics, local</td>
<td>None</td>
<td>Lidocaine used as an anti-arrhythmic at high doses in combination with other local anaesthetics may result in myocardial depression or increase the risk of ventricular arrhythmias.</td>
<td>2</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>None</td>
<td>Lidocaine used as an anti-arrhythmic at high doses given with other anti-arrhythmics agents may result in myocardial depression. Increased myocardial depression when anti-arrhythmics given with prilocaine however a clinically significant interaction is unlikely at doses used in dentistry. The manufacturer of articaine advises caution when administering this to any patient receiving an anti-arrhythmic agent however a clinically significant interaction is unlikely at doses used in dentistry.</td>
<td>2,5</td>
</tr>
<tr>
<td>Antibacterials: sulphonamides</td>
<td>None</td>
<td>Increased risk of methaemoglobinaemia when high doses of prilocaine given. This risk is increased if patient has other factors such as concomitant sulphonamide (e.g. co-trimoxazole). There are no case reports of methaemoglobinaemia occurring in the dental setting in patients using this combination.</td>
<td>1,2,6</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>None</td>
<td>Increased risk of ventricular arrhythmias if high doses of lidocaine are given with antipsychotics that prolong QT interval.</td>
<td>2</td>
</tr>
<tr>
<td>Antivirals: only fosamprenavir, darunavir, atazanavir, lopinavir, saquinavir.</td>
<td>None</td>
<td>These agents appear to increase plasma concentrations of lidocaine and potentially increase cardiotoxicity. However this is not expected to be clinically relevant at doses used in dentistry.</td>
<td>2,7</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>None</td>
<td>Lidocaine given at high doses in combination with beta-blockers may cause myocardial depression. Lidocaine clearance is reduced by propranolol and possibly nadolol. Risk of toxicity may increase when lidocaine is given in high doses.</td>
<td>2,8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>None</td>
<td>The action of lidocaine is antagonised by hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics. This is not expected to be clinically significant if the patient has a normal potassium level.</td>
<td>2</td>
</tr>
<tr>
<td>Ulcer-healing drugs: cimetidine only</td>
<td>None</td>
<td>Plasma concentrations of lidocaine can be increased by cimetidine (increased risk of toxicity when high doses of lidocaine are used). This same effect is not seen with other ulcer-healing drugs.</td>
<td>2,8</td>
</tr>
<tr>
<td>Sedatives</td>
<td>None</td>
<td>Midazolam has been reported to cause a modest reduction in serum lidocaine levels but not mepivacaine levels. However this is not expected to be clinically relevant at doses used in dentistry.</td>
<td>8</td>
</tr>
<tr>
<td>Drug interaction as listed in the BNF or SmPC (listed under ‘Sympathomimetics’)</td>
<td>Clinical relevance at doses used in dentistry</td>
<td>Nature of interaction</td>
<td>Relevant references</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Beta-blockers (non-cardioselective): propranolol, nadolol, timolol, sotalol, pindolol.</td>
<td>None if ≤2 cartridges of an adrenaline-containing solution are used. If more than two cartridges are required an adrenaline-free solution should be used.</td>
<td>Increased risk of severe hypertension and bradycardia when adrenaline given with non-cardioselective beta-blockers. Response to adrenaline may also be reduced. The severity of the interaction appears to be dose-related. Local anaesthetics used in dental surgery contain very low concentrations of adrenaline and only small volumes are given, so an interaction is unlikely. Adrenaline and nadolol may cause increased local vasoconstriction, resulting in lidocaine persisting for longer.</td>
<td>1,2,8,9,10</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Avoid using local anaesthetics containing adrenaline in patients who abuse cocaine, unless it is certain they have not used cocaine for ≥24 hours.</td>
<td>Cocaine and adrenaline both have sympathomimetic effects. Combined use increases these effects and the risk of arrhythmias.</td>
<td>8</td>
</tr>
<tr>
<td>Clonidine</td>
<td>None</td>
<td>Possible risk of hypertension when adrenaline given with clonidine. However not expected to be clinically relevant at doses used in dentistry.</td>
<td>2</td>
</tr>
<tr>
<td>Diuretics</td>
<td>None if ≤2 cartridges adrenaline-containing solutions are used.</td>
<td>Concurrent use of potassium-depleting diuretics and adrenaline-containing local anaesthetics has resulted in hypokalaemia.</td>
<td>7,9</td>
</tr>
<tr>
<td>Dopaminergics: entacapone</td>
<td>Limit dose to one cartridge.</td>
<td>Serum levels and therefore effects of adrenaline possibly enhanced by entacapone. No cases of adverse interactions with entacapone have been reported in the dental setting however caution in vasoconstrictor dosing is required.</td>
<td>1,2</td>
</tr>
<tr>
<td>Dopaminergics: rasagiline</td>
<td>None</td>
<td>Concomitant use of sympathomimetics with rasagiline should be avoided. However, the interaction is not clinically relevant in dentistry. The sympathomimetics referred to are those present in decongestant medications containing ephedrine or pseudoephedrine.</td>
<td>2,11</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitor antidepressants (MAOI)</td>
<td>None if ≤2 cartridges of adrenaline-containing solution are used. However the manufacturer of Scandanest Special and Septanest contraindicates use of these agents in patients taking tricyclic or MAOI antidepressants. This advice is over cautious and the BNF and manufacturers of other adrenaline-containing local anaesthetics do not include the same contraindications.</td>
<td>Co-administration of higher doses of adrenaline and MAOI antidepressants may produce severe prolonged hypotension or hypertension.</td>
<td>2,5,11,12</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Increased risk of hypertension and arrhythmias when high doses of adrenaline are given with tricyclics. However, local anaesthetics containing adrenaline should be used with caution with tricyclics.</td>
<td>1,2</td>
<td></td>
</tr>
<tr>
<td>Serotonin and noradrenaline reuptake inhibitors (SNRI): e.g. duloxetine, venlafaxine.</td>
<td>None if ≤2 cartridges of adrenaline-containing solution are used.</td>
<td>Co-administration of higher doses of adrenaline and SNRIs or phenothiazines may produce severe prolonged hypotension or hypertension.</td>
<td>9,13</td>
</tr>
</tbody>
</table>

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.