CLINICALLY RELEVANT DRUG INTERACTIONS OF LOCAL ANAESTHETICS

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A biotransformation of local anaesthetics

The biotransformation of drugs after absorption is classified as phase I, generally resulting in the loss of pharmacological activity or enhancement of activity of some prodrugs. An example is hydrolysis of ester or amide linkage. Phase II conjugation reactions lead to formation of highly polar conjugates, which are rapidly excreted in the urine and faeces.

A metabolic conversion of local anaesthetics is enzymatic process, mediated by major catalyst family of enzymes, cytochrome P450 monoxygenase system. This enzyme system is mostly localized in liver, although every tissue has some specific metabolic activity. Other organs contributing to overall metabolic capacity are kidneys, gastrointestinal tract, skin and lungs. Within the cell, the drug metabolising activity is localised in the endoplasmic reticulum (phase I, hydrolysis) and in the cytosol (phase II, conjugation enzymes).

A drug interaction means a possibility that one drug may alter the intensity of pharmacological effects of another drug given concomitantly. The outcome may be enhanced or diminished pharmacological effect of one or both of the drugs, or appearance of a new effect, not observed with either drug alone.

Drug interactions

Pharmacodynamic drug interactions are interactions between two drugs at drug receptors, or additive or inhibitory effects due to actions at different sites in an organ. An example of nonreceptor drug interaction is effect of aspirin and heparin which, given concomitantly, may cause profound coagulation disorder by acting at different points of the coagulation cascade. Commonly used drug interaction at receptors site is that of neuromuscular blocking agents and anticholinesterase drugs.

Pharmacokinetic drug interactions are present as alterations of absorption, distribution, or elimination of one drug by another. Some of pharmacokinetic drug interactions are listed below:

1. Biotransformation (adrenaline and local anaesthetics: a delayed metabolism of local anaesthetic)
2. Distribution (adrenaline and local anaesthetics: prolonged action of local anaesthetic)
3. Absorption (binding to plasma proteins, enhanced toxic effects of local anaesthetics in hypoproteinaemia)
4. Excretion (an inhibition of excretion of procainamide by cinemetine and amiodarone)

A metabolism of local anaesthetics

An ester group of local anaesthetics, like tetracaine, is hydrolysed and inactivated mostly by cholinesterase in plasma and in the liver. The amide-linked local anaesthetics are metabolised by cytochrome P450 family (see table 1). One drug may be metabolised through more than one metabolic pathway, involving two or more enzymes, acting in the alternative or consecutive reactions. Enzymes involved in bupivacaine

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Table 1. Cytochrome enzymes involved in the biodegradation of local anaesthetics

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>CYP 1A2</th>
<th>CYP 2D6</th>
<th>CYP 3A4, 5, 7</th>
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<tr>
<td>Substrates</td>
<td>Ropivacaine</td>
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<td>Caffeine</td>
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<td>Carvedilol</td>
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<td>Ondansetron</td>
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<td>Tramadol</td>
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<td>Inhibitors</td>
<td>Amiodarone</td>
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<td>Cimetidine</td>
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<td>Fluoroquinolones</td>
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<td>Char-grilled meat</td>
<td>Carbamazepine</td>
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<td>Brusel sprouts</td>
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degradation into piperolyxidine (PPX), its major metabolite, are CYP2D6, which produced only small amounts of metabolite, and CYP3A4 which most efficiently metabolised bupivacaine into PPX.1 Cytochrome P450 family of enzymes is present in almost all human cells and tissues, but mostly in the endoplasmic reticulum in the liver. Therefore, caution is needed when local anesthetics are extensively used in patients with severe hepatic impairment. Another important issue that may alter biodegradability of local anesthetics is plasma protein deficiency, occurring in the cirrhosis, severe trauma, cancer, some inflammatory disorders, postoperatively, and in neonates.

Interactions of local anesthetics

Local anesthetics and adrenaline

Prolongation of action of local anesthetics by vasoconstrictors is commonly exploited in the clinical praxis. Skin blood flow changes confirmed by laser Doppler flowmetry after intradermal injection of ropivacaine in various concentrations showed an increase in skin blood flow after 1% ropivacaine, and reduction in flow after 0.5% and weaker concentrations compared to saline. Ropivacaine/epinephrine injections were followed by a lower skin blood flow compared to saline, but the flow was significantly larger compared to the effect of epinephrine alone at the 20-minute recording.2

Kihara et al. have found that plasma lidocaine concentrations were higher in patients receiving lidocaine alone for the first 30 minutes than in patients receiving lidocaine + epinephrine (5 pg mL−1) for continuous epidural anaesthesia. Lidocaine and its plasma metabolites were significantly higher in the group receiving lidocaine alone, but no significant difference was observed after 2 hours. In continuous epidural anaesthesia, addition of epinephrine to lidocaine solutions was thus ineffective after 2 hours for reducing the potential for systemic toxicity.3 There were some attempts to use adrenaline prior to local anaesthetic, and delay systemic absorption of the drug. After 1:20,000 adrenaline was administered into the epidural space 5 minutes before 20 ml bupivacaine 0.5%, a delay in the time to peak plasma concentration of bupivacaine was noted. However prolonged epidural block and increased efficacy were noted independently on timing of adrenaline, and priming with adrenaline showed minimal clinical advantage.4 Comparable effects on delay of maximal concentration, time to peak concentration, and terminal half-life were observed in children after caudal blockade by ropivacaine and adrenaline.5

Although clinically attractive, this drug combination needs a special attention to proper drug administration. An accidental intravascular injection of local anaesthetic solution containing adrenaline during the attempt of regional block caused increase in the mean arterial pressure, mean pulmonary artery pressure, and in pulmonary capillary wedge pressure which was not different from those observed following adrenaline alone.6

Local and general anaesthetics

Interactions of local and general anaesthetics are important in the view of conversion of one method to another, or combination of both techniques. MAC of inhaled anaesthetics may be altered in such clinical situation. MAC of halothane and isoflurane was decreased during infusion of lidocaine. A mechanism of this additive drug action is nonenzymatic because inhaled anaesthetics are metabolised through CYP 2E1.7 LOCH

Phenobarbital is well known inducer of CYP 3A enzyme group. The rates of formation of lidocaine metabolite monoethyl-glycinexilide (MEGX) were higher in the microsomes of the phenobarbital group than in those of the control group. This effect may lead to shorter duration, and anaesthetic effect in the patients receiving phenobarbital may be weaker.8 General anaesthetics fentanyl citrate, halothane, and ether did not have statistically significant effects on any of the CYP activities and overall metabolism of local anaesthetics. Lokh observed that a single dose of ketamine mildly inhibits the activity of CYP2D1 and CYP3A, and may have implications on effects of drugs metabolised by those enzymes.9 In vivo study of Ganenheit confirmed that ketamine significantly enhanced the total anaesthetic effect of bupivacaine and prolonged its elimination half-life in mice. A clinician should be aware of this inhibitory effect of ketamine on the metabolism of bupivacaine if two drugs are used together.10

The effects of two local anaesthetics

Local anaesthetics block Na+ channels and prevent the generation and conduction of nerve impulses. Since two anaesthetics may have different affinity for Na+ channels, there is a possibility for one drug to displace another from receptor binding site, reduce overall duration of action and decrease its toxicity after accidental overdose.
In the canine papillary muscle model a competitive antagonism between cocaine and lidocaine at a single sodium channel receptor was observed. Lidocaine improved a conduction velocity decreased by cocaine, but did not significantly change the effective refractory period. This effect may prove as beneficial in reversing cocaine-induced slowing of ventricular conduction.11

A hypothesis that lidocaine or phenytoin might be used for the treatment of bupivacaine overdoses compared in the isolated heart of rabbits with bupivacaine and with either phenytoin or lidocaine added to bupivacaine. Contrary to expected, QRS duration was significantly increased by adding phenytoin or lidocaine to bupivacaine. The effects of bupivacaine on intraventricular conduction were not improved after these drugs, and phenytoin or lidocaine should not be used for treating bupivacaine intoxication.12

The cardiotoxic effects of intracoronary ropivacaine were reduced by hypocapnic alkalosis. It may be a useful adjunct to standard resuscitative measure after inadvertent administration of amide local anaesthetic agents.13

**Drug inhibitors**

Ishoheit et al. studied the possible interaction of erythromycin and itraconazole with intravenous lidocaine.14 Compared with placebo and itraconazole, erythromycin significantly prolonged the elimination half-life of lidocaine from 2.5 to 2.9 and increased MEGX concentrations. Itraconazole is a stronger inhibitor of ropivacaine than clarithromycin. Both drugs inhibited the CYP3A4 mediated formation of (S)-2',6'-piperoxylidide from ropivacaine in a dose-dependent manner.15 The mean ropivacaine clearance was modestly decreased by ciprofloxacin inhibition of the CYP1A2-mediated formation of 3-OH-ropivacaine. At the same time, the CYP3A4-mediated formation of PLEX was increased. This increase in the metabolic degradation by alternative pathway may diminish the significance of enzyme inhibition, and should not be of any clinical significance in patients with normal liver and renal function. In susceptible patient populations the concomitant use of ciprofloxacin with ropivacaine might produce toxic symptoms.16

An oral ingestion of paracetamol or propranolol increased lidocaine concentrations after intramuscular administration of local anaesthetic. A percent of lidocaine bound in the tissue significantly decreased, too.17

Diltiazem is well known drug inhibitor. When given in combination with bupivacaine, plasma concentrations of bupivacaine attained were similar in the absence and presence of diltiazem, but toxicity was approximately two-fold increased by diltiazem. Lethal plasma concentrations of bupivacaine were significantly smaller after bupivacaine and dilatiazem, and death resulted from a progressive decrease in cardiac contractility and mean arterial pressure.19 A potentiation of the negative inotropic effect, diminished force and stroke velocity of slow action potentials in guinea pig myocardium were observed in the presence of nifedipine and bupivacaine.19

**Benzodiazepines**

Benzodiazepines are mostly used as sedative premedication before local anaesthesia. The sedative/hypnotic interaction between the administration of intravenous midazolam and intramuscular lidocaine or bupivacaine was observed in women undergoing gynecological surgery. Both bupivacaine and lidocaine enhanced the effect of midazolam and intensified it from the sedative into the hypnotic range.20 Another drug from this group, diazepam was proven to be safe for children undergoing surgery under caudal block with a mixture of lidocaine and bupivacaine. Diazepam eased no pronounced modifications in bupivacaine protein binding when used concomitantly.21

**Systemic toxic reaction**

Siegmund described a toxic lidocaine level with seizures and reduced lidocaine clearance 65 h after amiodarone was added to the treatment regimen. The underlying mechanism was altered hepatic metabolism of lidocaine caused by amiodarone inhibition.22

An abuse of first local anaesthetic cocaine is usually followed by several toxic manifestations. Those were expressed at significantly lower concentrations when cocaine was used in combination with ethanol.23 The investigations of underlying mechanisms of such actions revealed that cocaine acts through sodium channel receptors.24 Measurements of dopamine transporter activity showed that cocaine, dimethacaine and procaine inhibited dopamine uptake in vitro in the dose-dependent manner, and reversibly increased endogenous dopamine efflux from the striatal area of rats. Amide containing local anaesthetics prilocaine, etidocaine, procainamide, and lidocaine inhibited dopamine uptake in vitro minimally.25

[24] The addition of cocaine decreased the action potential duration and increased phase 0 of the action potential in the canine papillary muscle model. Lidocaine displaced cocaine from the sodium channel receptor through competitive binding. It improved the conduction velocity decreased by cocaine, but did not significantly change the effective refractory period. This competition at the sodium channel receptor may be beneficial in the reversing cocaine-induced slowing of ventricular conduction and some other toxic symptoms.11

Enhanced toxicity was observed when local anaesthetics were used in combination with cytostatics. Lidocaine enhanced bleomycin-induced cytotoxicity and DNA damage. The inhibition of DNA repair processes may be responsible for the toxicity and DNA damage when lidocaine is added to bleomycin.Clinically achievable concentrations of local anaesthetic procaine enhanced doxorubicin cytotoxicity in vitro resulting in marked tumour growth inhibition. Incubating temperature of 40°C enhanced all effects of procaine and doxorubicin on cell growth.26

A combination of local anaesthetic and corticosteroid was proved to be efficient. The local anesthetics are able to enhance corticosteroid betamethasone-17-benzoate penetration through human skin to a different extent. Lidocaine was the most effective, possibly enhancing the drug solubility and the diffusion coefficient due to membrane fluidization.27

**Coagulation**

Local anaesthetics were suspected to induce some coagulation disorders. The most investigated was inhibition of platelet aggregation. This should be important in view of damage to vessels of local anaesthetic given for intravenous regional anaesthesia after intravenous injection. The effects of prothrombinic epidural blood patch in the presence of local anaesthetic should be reduced. Although local inhibition of platelet aggregation was not confirmed by a thromboelastography,28 it may arise from interactions with other drugs or herbal preparations.

**Gingo biloba** extract exerts its effect through its influence on prostaglandin metabolism and antagonism of platelet aggregating factor. The inhibition of platelet activating factor raises the greatest concern for the perioperative period. An acute retrobulbar haemorrhage in a 65 year old patient was observed after 5 ml 2% lidocaine and 5 ml 0.75% bupivacaine was inserted in the inferotemporal region of her left orbit by 25 gauge...
needle of 25 mm length. Haematological investigations showed a normal blood count, prothrombin and partial thromboplastin times. Renal and liver function tests were normal, too. The only risk factor was *Gingko biloba* extract tablets 40 mg three times a day she used for the past two years.28

**Conclusion**

Drug interactions of local anaesthetics should always be considered. Instead of being deleterious some of those could be used in clinical setting to reduce doses of drugs or to improve efficiency of one or both drugs given concomitantly. A special attention should be paid to impaired reactions in patients with liver diseases, those using some of drugs known to inhibit drug metabolism, receiving anticancer chemotherapeutics and critically ill patients.

**REFERENCES**


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**IMPLANTABLE SYSTEMS FOR PAIN THERAPY**

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Two different therapies are provided by means of the Medtronic implantable systems: neurostimulation and intrathecal drug delivery (IDD). The advantages of implantable systems are:

- Relief of chronic, intractable pain
- Improve ability to perform activities of daily living: improve quality of life
- Targeted delivery generally means fewer side effects than other therapies
- Screening test optimizes outcome for each patient
- Therapy non-invasively adjustable to meet changing patient needs

There is little if any discussion in the literature on which patient is more likely to benefit from neurostimulation vs. IDD.

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