Lidocaine Toxicity with Tumescent Liposuction

A Case Report of Probable Drug Interactions

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We report a case of mild lidocaine toxicity. A reduced rate of lidocaine metabolism following tumescent liposuction may result from an inhibition of cytochrome P450 3A4 (CYP3A4) by sertraline (Zoloft) and flurazepam (Dalmane).

When two or three drugs are each substrates for the same enzyme, there is the possibility for an adverse drug reaction when used simultaneously. Lidocaine is rapidly and almost exclusively eliminated by CYP3A4. The newer antidepressant selective seratonin reuptake inhibitors (SSRI) such as sertraline are metabolized by the hepatic enzymes CYP3A4 and CYP2D6. The bezodiazepines such as midazolam (Versed) and diazepam (Valium) are also metablized by the CYP 3A4 isoenzymes. The specific cytochrome P450 enzyme responsible for the metabolism of flurazepam has not been identified.

Since 1994 there has been a rapid expansion of information about the specificity of hepatic microsomal enzymes of the cytochrome P450 family for the metabolism of different drugs. This new information permits a knowledgeable clinician to anticipate some adverse drug interactions.

Surprisingly high doses of lidocaine are well tolerated when delivered subcutaneously by the tumescent technique. For several years 60-mg/kg doses of lidocaine for tumescent liposuction has been the de facto, unpublished, recommended maximum safe dose. Until now there have been no reports of untoward consequences.

The safety of such high doses has yet to be well documented by rigorous pharmacologic studies involving a large number of patients. One study with 10 patients concluded that tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction.[1] We have personally performed tumescent liposuction on more than 400 patients using lidocaine doses in the range of 50–60 mg/kg without evidence of lidocaine toxicity.

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Case Report: Lidocaine Toxicity

Our patient was a 39-year-old female weighing 80 kg, on whom we performed two tumescent liposuction surgeries. Five years earlier, a breast cancer was treated by chemotherapy, radiation, and bone marrow transplantation. She had a long history of treatment with sertraline (Zoloft) 200 mg daily for anxiety disorder, panic attacks, and mild depression. Sertraline was not discontinued prior to either surgery.

The first surgery, liposuction of the hips and outer thighs, was uneventful. Perioperative sedation consisted of 10 mg PO zolpidem tartrate (Ambien). The dose of tumescent lidocaine totaled 59 mg/kg (lidocaine 800 mg/L, epinephrine 0.65 mg/L, sodium bicarbonate 10 meq/L) in 0.9% NaCl at 37°C. Liposuction produced of 2,700 mL of supranatant fat, and 250 mL of infranatant blood-tinged anesthetic solution.

One month later she returned for liposuction of the inner thighs, inner knees, and buttocks. Perioperative sedation on this occasion was 30 mg PO of flurazepam (Dalmane), instead of the zolpidem that was used for the first surgery. Between 11:20 a.m. and 13:00 p.m. she received 58 mg/kg of tumescent lidocaine (lidocaine 900 mg/L, epinephrine 0.65 mg/L, bicarbonate 10 meq/L) in 0.9% NaCl at 37°C. The liposuction was uneventful, yielding 1,800 mL of supranatent fat and 650 mL of infranatent blood-tinged anesthetic solution. She was discharged at 17:20 p.m. alert and fully ambulatory.

Ten hours after completion of the tumescent infiltration of lidocaine, the patient awoke, experiencing nausea, vomiting, unsteady gate, mild confusion, and dysarthria. Physical examination in a local emergency room revealed anxiety, short-term memory impairment, and slight pallor; otherwise, the neurologic and cardiovascular findings, the ECG, and routine laboratory studies were unremarkable. Blood drawn at 23:48 p.m. had a plasma lidocaine concentration of 6.3 mg/L by immunoassay (IA), and confirmed by gas chromatography (GC) to be 6.1 mg/L. Lidocaine plasma levels greater than 6 mg/L are associated with an increased risk of toxicity. Admitted to hospital for overnight observation, she was discharged the next morning after a

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06:45 a.m. lidocaine level was 2.9 mg/L by IA, and confirmed at 3.0 mg/L by GC.

Discussion

To the best of our knowledge, this is the first documented case of tumescent liposuction totally by local anesthesia where a standard dose of lidocaine, widely recognized as safe, has led to potentially toxic plasma lidocaine concentrations. It demonstrates the possibility of serious interactions between tumescent lidocaine and commonly used oral medications. Both sertraline and flurazepam have the potential for significantly reducing lidocaine clearance via inhibition of CYP3A4 and thereby increasing plasma lidocaine concentrations above the threshold for toxicity. It is unclear whether or not our patient's prior treatment for breast cancer affected her ability to metabolize lidocaine.

Perhaps sertraline and flurazepam had an additive effect on reducing the rate of lidocaine metabolism. During the first surgery, when the patient had taken sertraline but not flurazepam, there were no symptoms of lidocaine toxicity. It is possible that lidocaine plasma concentrations were elevated asymptomatically. Flurazepam has been taken by the majority of our tumescent liposuction patients and, other than the present patient, none have ever had evidence of elevated lidocaine blood levels.

Cytochrome P450 System

The cytochrome P450 (CYP450) family of enzymes is essential for most drugs eliminated by hepatic metabolism.[2] The "P450" designation is derived from the fact that these enzymes have 450 nm as the wavelength of maximum absorption in the reduced state in the presence of carbon monoxide. Based the homology of amino acid sequences, the CYP450 enzymes a have been categorized into families, subfamilies and individual enzymes.[3]

Microsomes are the microvesicles formed from fragments of endoplasmic reticulum after liver tissue has been homogenized and centrifuged. These enzymes located in the endoplasmic reticulum are referred to as microsomal enzymes. Metabolic drug interactions are usually studied in vitro using liver tissue.

Cytochrome P450 evolved over billions of years as an important means of converting potentially harmful concentrations of lipid soluble nutrients and environmental substances into more easily eliminated water soluble compounds. In humans there are 12 known families of CYP450 isoenzymes, of which only five are important in drug metabolism: 3A4, 1A2, 2C9, 2C19, and 2D6.

When two drugs, both requiring the same enzyme for metabolism, are given concurrently, there is a potential for an adverse drug interaction. Many factors determine the relative effects of one drug on the metabolism of another drug. Drug concentration and relative enzyme affinity determine metabolic drug interactions.

There is a significant degree of interpatient variability with respect to the enzymatic activity of the cytochrome P450 isoenzymes. This makes it difficult to predict the probability of any specific drug interaction.[4]

Hepatic Metabolism of Lidocaine

Lidocaine is rapidly eliminated by hepatic metabolism.[5] The liver metabolizes 70% of the lidocaine that enters the hepatic circulation at any given moment. When 1 L of blood passes through the hepatic circulation of a healthy volunteer, more than 700 mL of the blood is completely cleared of its lidocaine content.[6] Lidocaine is said to have a hepatic extraction ratio of 0.7. With such a high hepatic extraction ratio of 0.7, lidocaine metabolism is said to be flow rate limited. In other words, the rate of lidocaine metabolism usually depends on the rate of blood flow to the liver.

Table 1. Cytochrome P450 3A4 Inhibitors[49]

amiodarone
benzodiazepines
midazolam
triazolam
cimetidine
clarithromycin
chloramphenicol
cyclosporin
danazol
dexametasone
diltiazam
erythromycin
fluconazole
itraconazole
isoniazid
ketoconazole
methadone
methylprednisolone
metronidazole
miconazole
nicardipine
nifedipine
pentoxifylline
propofol
propranolol
quinidine
SSRI antidepressants
tetracycline
terfenidine
thyroxine
verapamil
antiseizure medications
carbamazepine
valproic acid
verapamil

At typical therapeutic plasma concentrations of lidocaine, metabolism of lidocaine is so efficient that lidocaine does not seem to cause any substrate inhibition of the enzyme CYP3A4 Lidocaine clearance can be reduced by any drug that inhibits CYP3A4 enzymes, such as erythromycin or ketoconazole. Similarly any condition that reduces hepatic blood flow, such as decreased cardiac output associated with congestive heart failure, or shock will decrease lidocaine clearance. The β-blocker drugs, such as propranolol decrease lidocaine by both mechanisms, propranolol inhibits CYP3A4 and is decreases cardiac output and therefore hepatic blood flow.[7] Patients with cirrhosis of the liver have a reduced lidocaine clearance; however, in renal insufficiency, lidocaine clearance is normal.

The metabolism of lidocaine by CYP3A4 is a sensitive means for evaluating hepatic function. Determining the amount of the lidocaine metabolite monoethylglycine-xylidide (MEGX) produced in a patient's liver has been used as a measure the degree of liver dysfunction and to predict the survival in critically ill patients.[8] Lidocaine metabolism is used to evaluate the enzymatic activity in a bioartificial liver.[9]

CYP3A4

The most abundant of all human cytochrome P450 enzymes, the isoenzyme cytochrome P450 3A4, is responsible for the metabolism of more drugs, and a broader range of drugs, than any other hepatic enzyme. CYP3A4 metabolizes a wide variety of drugs such as lidocaine, antidepressants, carbamazepine[10] (Tegretol), nifedipine (Procardia),[11] methadone,[11] and alfentanil.[12,13]

Certain drugs will augment the enzymatic activity of CYP3A4. Rifampicin induces CYP3A4 and augments the metabolism of lidocaine[14] and triazolam (Halcion).[15] An infusion of heme arginate induces CYP3A4 and augments lidocaine metabolism in patients with varigate porphyrial.[16]

Whereas CYP3A4 is inducible by some drugs, the CYP2D6 is not inducible but it can be inhibited by certain drugs.[17] Potent in vitro inhibitors of both CYP3A4 and CYP2D6 include sertraline (Zoloft), fluoxetine (Prozac), fluvoxamine (Luvox), and paroxetine (Praxil), all of which are selective seratonin reuptake inhibitors (SSRI).[18] All of the available newer antidepressants, including the SSRIs, and as well as nefazodone (Serzone), an antidepressant unrelated to SSRI, inhibit cytochrome P450 3A4, and are associated with clinically significant drug interactions.

The use of SSRI drugs is becoming more ubiquitous. Antidepressant medications are widely prescribed, and may be taken by prospective liposuction patients. For example, fluoxetine at 20 mg per day is used in the treatment of premenstrual dysphoria.[19]

Similarly, alprazolam (Xanax) has also been found to have a role in the treatment of severe premenstrual syndrome (PMS).[20] It is plausible that potential tumescent liposuction patients might be taking a combination of fluoxetine and alprazolam. The combination of an SSRI and a benzodiazepine might inhibit lidocaine metabolism, in a fashion analogous to the present case.

Drug Interactions and CYP3A4

There is a growing number of examples of drug interactions that are mediated by inhibition or induction of CYP3A4. Drug interactions mediated by CYP450 3A4 can have devastating consequences. For example, the nonsedating antihistamines terfenadine (Seldane), and astemizole[21] (Hismanal), as well as cisapride (Propulsid), used to treat nocturnal heart burn due to gastroesophageal reflux disease, are metabolized by cytochrome P450 3A4. However, ketoconazole (Nizoral), itraconazole (Sporanox), erythromycin, and clarithromycin (Biaxin) are potent inhibitors of P450 3A4 and block the metabolism of terfenadine, astemazole, and cisapride. The resulting elevation of plasma terfenadine, astemazole, or cisapride can cause fatal QT prolongation and torsades des pointes–type ventricular tachycardias.

Erythromycin inhibits the ability of CYP3A4 to metabolize midazolam. This interaction can result in a prolonged coma.[22]

Not all macrolide antibiotics inhibit CYP3A4. Azithromycin (Zithromax) and dirithromycin (Dynabac) are eliminated by a combination of hepatic metrabolism and biliary excretion. There are no reports of the effects of azithromycin or dirithromycin inhibiting CYP 3A4, however, clinical pharmacologic studies have shown that these drugs do not cause elevated terfenidine (Seldane) blood levels.

Methadone is extensively metabolized by CYP3A4 Fluvoxamine (Luvanox), a new SSRI antidepressant, is a potent mixed type inhibitor of methadone metabolism. Conversely, the metabolism of nifedipine (Procardia) by CYP3A4 is potently inhibited by methodone.[11]

The apparent decrease of CYP3A4 enzymatic activity with advancing age,[23] might simply be secondary to changes in liver blood flow, size, or drug binding and distribution with age.[24] Dietary factors, such as grapefruit juice, can inhibit CYP450 3A4 found in intestinal mucosa.

Fluoxetine (Prozac) via its metabolite norfluoxetine inhibits CYP3A4 and impairs the metabolism of warfarin (Coumadin).

Sertraline and Other SSRI

The majority of the newer antidepressants of the SSRI type, including sertraline, are associated with clinically significant drug interactions mediated by the inhibition of cytochrome P450 enzymes.[25] Sertraline can inhibit both CYP2D6 and CYP3A4.

The usual oral dose of sertraline ranges from 50 to 200 mg once daily. Based on an elimination half-life ($t_{1/2}$) of 26 hours, steady-state plasma sertraline levels are achieved after 7 days of once-daily dosing in patients with healthy hepatic metabolism. Conversely, in patients who have a healthy liver, 1 week is required for the body's content of sertraline to be 98% eliminated after discontinuing the drug. In patients with mild cirrhosis, more than 2–3 weeks is required for sertraline to be eliminated. In vitro, sertraline shows inhibition of cytochrome P450 3A4 isoenzyme. But sertraline need not necessarily affect the metabolism of all drugs that are metabolized by CYP3A4. In vivo, sertraline does not seem to affect the metabolism of diazepam.[26]

Sertraline is tightly bound to plasma proteins, and may competitively displace other protein-bound drugs such as lidocaine, increasing the amount of free (unbound) drug, and increasing the potential for toxic reactions.

After discontinuing Zoloft, it might be prudent to wait 7–14 days before starting any drug known to have potential adverse cytochrome P450 (metabolic pathway) interactions. SSRIs are known to interact with monoamine oxidase inhibitors (MOAI) to produce fatal reactions. Fatal drug interactions have even occurred in patients who have discontinued an SSRI and were then started on an MAOI.

Benzodiazepines

The specific cytochrome P450 isoenzyme that is responsible for the metabolism of flurazepam has not been identified (personal communication, Roche Laboratories). The half-life of flurazepam in plasma is 2–3 hours, but its major active metabolite (*N*-desalkylflurazepam) has a half-life of 47–100 hours.

Benzodiazepines are metabolized by several different microsomal enzymes. Approximately 75% of the available benzodiazepines are significantly metabolized by CYP3A4. Cytochrome P450 3A4 metabolizes alprazolam.[27] (Xanax), triazolam[28] (Halcion), diazepam[29,30] (Valium), midazolam[31] (Versed), and other benzodiazepines. Plasma concentrations of these benzodiazepines increase when they are administered with drugs that inhibit CYP3A4, including most newer SSRI antidepressants.[25] There can be a considerable variation in the rate of metabolism of midazolam and triazolam among healthy volunteers.

The antipsychotics clozapine (Clozaril), and the antifungal ketoconazole (Nizoral), all noncompetitively inhibit midazolam metabolism. The metabolism of midazolam (Versed) is significantly decreased by the inhibition of CYP3A4 by Ketoconazole (Nizoral), itraconazole (Spoaranox), and fluconazole (Diflucan).[32] The antipsychotic olanzapine has little effect on midazolam metabolism.[34] Fluoxetine (Prozac) appears to impair the metabolism of alprazolam (Xanax) but not clonazepam (Klonopin).[34]

Nefazodone (Serzone), an antidepressant, is a competitive inhibitor CYP3A4 in the metabolism of alprazolam (Xanax)[27] and triazolam (Halcion [personal communication, Roche Laboratories]).[27] In contrast, the metabolic clearance of lorazepam (Ativan) depends on conjugation rather than hydroxylation, and thus it is not inhibited by nefazodone (personal communication, Roche Laboratories).

Fluoxetine (Prozac) may impair the metabolism of both diazepam (Valium), and warfarin (Coumadin). However fluoxetine does not impair lorazepam (Ativan), or oxazepam (Serax).[35]

Although the SSRI fluoxetine does not affect the metabolism of triazolam (Halcion),[36] the combination of the tricyclic antidepressant amitriptyline and triazolam has been associated with a fatality.[37]

Based on the present experience we now recommend lorazepam as the benzodiazepine of choice. A 2–4-mg oral dose of lorazepam produces more consistent and longer lasting anxiolysis, sedation, and anterograde amnesia that is comparable with 10–20 mg of diazepam.[38,39] Lorazepam appears to increase respiratory drive and attenuate the respiratory depression associated with meperidine.[40] Lorazepam is the only benzodiazepine that is not metabolized by cytochrome P450 enzymes, and therefore is less susceptible to adverse drug interactions. In its initial metabolic reaction lorazepam is conjugated to lorazepam-glucuronide, which has no CNS activity, and excreted in the urine. Available in 0.5-, 1-, and 2-mg tablets, lorazepam at 2 mg is equivalent in peak effectiveness to 10 mg of diazepam.

Lidocaine and CYP3A4

Lidocaine is principally metabolized by the CYP3A4. CYP3A4 oxidizes a diversity of substrates including drugs, carcinogens, and steroids.[41] CYP3A4 alters lidocaine by a sequential process of oxidative *N*-dealkylation, first by oxidative deethylation of the amino nitrogen yielding mono-ethyl glycine xylidide (MEGX). Next, an additional oxidative reaction removes the residual eythyl group from MEGX, yielding glycine xylidine (GX).[42]

By competitive inhibition or by enzyme induction, drugs can either inhibit or accelerate lidocaine metabolism. Sertraline (Zoloft) has been shown to have some

inhibition of cytochrome P450 3A4 in vitro although the clinical significance of this has not been established. The combination of lidocaine and the antiarrhythmic amiodarone[43] (Cordarone), both metabolized by CYP3A4, is associated with bradycardia and seizures.[44] Antiepileptic drugs appear to compete with lidocaine for CYP3A4 and slow lidocaine metabolism.[45] Although the clinical significance is not clear, in rat liver microsomes lidocaine and propranolol exhibit mutual metabolic inhibition.[46]

Drugs that inhibits enzymatic activity of CYP 3A4 have the potential for elevating the plasma concentrations of lidocaine. In the setting of tumescent liposuction where patients' lidocaine blood levels are typically in the low therapeutic range between 1 and 3.5 mg/L, anything that causes a diminution of lidocaine metabolism can result in lidocaine levels above the 6-mg/L threshold for potential toxicity.

Recommended Maximum "Safe" Doses of Tumescent Lidocaine

Our present recommendation for maximum allowable doses of tumescent lidocaine in healthy, young female patients is as follows: 45 mg/kg for thin patients, 55 mg/kg for average patients, and 60 mg/kg for overweight patients.

Doses as high as 80–90 mg of tumescent lidocaine might be safe in a majority of patients, however, the true risk of toxicity is unknown. Administering such high doses, without well-documented toxicology studies based on large numbers of patients, is cavalier at best. Serial liposuction procedures separated by 1 week or more are safer than 1-day heroic mega-liposuction sessions utilizing imprudent doses of lidocaine. The fundamental philosophy of tumescent liposuction is "safety first and convenience second."

Maximal lidocaine doses must be reduced in certain situations. In patients who are taking drugs that interfere with lidocaine metabolism, such as the newer SSRI antidepressant sertraline (Zoloft), lidocaine doses must be reduced by at least 30–40%.

It is our clinical impression that obese patients tolerate higher mg/kg doses of lidocaine better than relatively thin patients. There is a higher incidence of lidocaine toxicity among coronary care unit patients weighing less than 70 kg.[47] Thus, thin patients may have a smaller volume of distribution, and a slower clearance for lidocaine. In other words, given identical mg/kg doses of lidocaine, thinner patients will have greater peak plasma lidocaine concentration than obese patients.

Males, whose percentage of body fat is usually 10–20% less than females, have a smaller volume of distribution for lidocaine and therefore the maximum allowable dose should be reduced by 10–20%.

Younger patients tolerate more lidocaine than older patients. This is attributed to the decrease in cardiac output, and the consequent decrease in hepatic perfusion associated with advancing age. Thus, older patients should be given smaller doses of tumescent lidocaine.

The present case illustrates the possibility of an unanticipated toxic drug interaction. A lidocaine dose that would be safe under normal circumstances might be toxic as a result of unanticipated drug interactions. Because patients do not always provide an accurate clinical history, one cannot rely on a history for eliminating the possibility of an adverse drug interaction. One needs to be cautious and conservative when using more than 35 mg/kg of lidocaine for tumescent liposuction.

Drugs that potentially interfere with lidocaine metabolism should be discontinued at least 2 weeks before using tumescent technique for local anesthesia when high doses of lidocaine are anticipated. If it is not reasonable to discontinue a drug that might interfer with lidocaine metabolism, then the surgery should be limited to smaller total doses of lidocaine.

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