Even 'safe' medications need to be administered with care

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SUMMARY

A 60-year-old man with a history of hepatic cirrhosis and cardiomyopathy underwent transoesophageal echocardiogram. He received mild sedation and topical lidocaine. During the recovery period the patient developed ataxia and diplopia for about 30 mins, a result of lidocaine toxicity. The patient was administered a commonly used local anaesthetic, a combination of 2% viscous lidocaine, 4% lidocaine gargle and 5% lidocaine ointment topically to the oropharynx. The total dose was at least 280 mg. Oral lidocaine undergoes extensive first pass metabolism and its clearance is quite dependent on rates of liver blood flow as well as other factors. The patient's central nervous system symptoms were mild and transient but remind us that to avoid adverse side effects, orally administered drugs with fairly high hepatic extraction ratio given to patients with chronic liver disease need to be given in reduced dosages. Even 'Safe' medications need to be carefully administered.

BACKGROUND

Lidocaine is the most frequently used local anaesthetic in medical practice and is available in a variety of formulations. There have been multiple case reports illustrating dangers and toxic effects of lidocaine ranging from ataxia and diplopia to seizures and death. Case reports of central nervous system (CNS) toxicity suspected to be a result of oral administration of lidocaine have been previously published. This case reminds us that even commonly used medications considered very safe need to be administered with care.

CASE PRESENTATION

The patient was examined in the emergency department shortly after resolution of his symptoms.

Physical examination revealed temperature of 98.4°F, irregular pulse of 66, blood pressure of 126/67 and respiratory rate of 16.

The patient was awake, alert and in no distress.

Ocular examination demonstrated no nystagmus and full extraocular motion. No diplopia was evident.

Lower extremities had 2+ swelling bilaterally. The gait was steady.

Medical history is significant for alcoholic liver cirrhosis, atrial fibrillation, non-ischaemic cardiomyopathy with ejection fraction of 45% and portal hypertension with gastric varices.

The patient works in maintenance. He lives with his elderly mother and is her care-taker. The patient does not smoke, stopped alcohol use

8 years before this episode and is not using illicit drugs.

Medications include warfarin 5 mg per day, metoprolol XL 50 mg daily, lisinopril 2.5 mg daily, docusate sodium 100 mg daily, potassium chloride 20 mEq per day and furosemide 40 mg each day.

INVESTIGATIONS

Transoesophageal echocardiogram showed no mass or thrombus in left atrium or left atrial appendage.

Laboratory examinations including liver function tests and electrocardiogram were negative.

OUTCOME AND FOLLOW-UP

The patient was admitted to the hospital for observation and underwent successful atrial fibrillation ablation within 24 h. He did well following the procedure and remains well after 3 months.

DISCUSSION

The patient's estimated lidocaine dose was at least 280 mg from a combination of 2% viscous lidocaine, 4% lidocaine gargle and 5% lidocaine ointment topically to the oropharynx.

Lidocaine is the most frequently used local anaesthetic in medical practice and is available in a variety of formulations.^{1 2} Lidocaine works by directly bonding to intracellular Na⁺ channel and blocking the excitatory Na⁺ current.³

Lidocaine is almost completely metabolised by dealkylation in the liver by CYP3A4.⁴ The initial metabolite is monoethylglycinexylidide (MEGX). It is pharmacologically active, has a half-life of longer duration than that of lidocaine but is not as effective in blocking the sodium channel. This substance is then broken down into inactive glycine xylidide.⁴

Metabolic clearance of lidocaine is complex and has a high first-pass extraction. Impaired metabolism due to cirrhosis is multifactorial. The primary disorder is the reduction of functional hepatocytes. In addition, portal blood flow is distorted resulting in portal-systemic shunting. Hepatic lipid deposition also causes impaired metabolism.^{5 6}

With the first passage of lidocaine through the normal liver, 65–70% is extracted with the remainder going to systemic circulation unchanged.⁷ Lidocaine's extraction ratio which is medium to high depends greatly on liver flow. The formation of MEGX is related to hepatic blood flow as well as the activity of cytochrome P450.⁸

Hepatic blood flow is reduced in hepatic cirrhosis. With changes in the microcirculation from cirrhosis, the permeability of the sinusoids is decreased. Thus, after oral administration of lidocaine in cirrhotics, hepatic uptake is delayed.^{7–9}

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Serum level of alanine transaminase is not a reliable indicator in determining which patients will have deficient metabolism of lidocaine and therefore, should not be used to judge whether patients are at risk of lidocaine toxicity even if administered therapeutic doses of lidocaine.⁸

Chronic liver disease causes impaired drug metabolism more commonly than acute liver dysfunction.¹⁰

Orally administered drugs with fairly high hepatic extraction ratio given to patients with chronic liver disease need to be given in reduced dosages.¹¹ Thus, oral lidocaine, which was given to our patient, undergoes extensive first pass metabolism and its clearance is quite dependent on rates of liver blood flow as well as other factors.¹²

The metabolism of lidocaine in the liver is dependent on CYP34A. If concomitant medications used by the patient inhibit the functioning of CYP34A, toxic levels of lidocaine will result even if the patient is given therapeutic amounts.¹³ CYP34A is a drug metabolising enzyme that breaks down over 120 medications in man, and thus leads to innumerable drug interactions.¹³

There have been multiple case reports illustrating dangers and toxic effects of lidocaine ranging from ataxia and diplopia to seizures and death.^{14–21} Case reports of CNS toxicity suspected to be a result of oral administration of lidocaine have been previously published.¹²

During bronchoscopy, lidocaine is administered via a nebuliser as well as topically to the nasal passageway through the bronchoscope. This allows for patient comfort during the procedure and prevents cough reflex. It has been reported that 80 ml of topical lidocaine, a total of 3 g of topical lidocaine, given during bronchoscopy led to generalised seizure. The absorption of lidocaine is quite rapid from the upper airway, trachea, bronchi and alveoli. Blood concentrations peak 20–40 mins after it is administered topically. The total dose should not be greater than 4–5 mg/kg. Excessive doses given rapidly during bronchoscopy can be dangerous and must be avoided.¹⁵

Grand mal seizures have also been reported following transpharyngeal spraying of 10% lidocaine. A patient who had been administered a total of 800 mg of lidocaine from multiple doses in preparation for awake intubation experienced a tonic-clonic grand mal seizure.¹⁶

Use of lidocaine 10% spray during bronchoscopy without systemic sedation has also resulted in transitory ataxia. A 58-year-old man with a long history of alcohol dependence received nasal analgesia with 10% lidocaine spray and went on to have a staggered walk. Likewise, a 66-year-old woman who received topical lidocaine in 2% of the oropharynx for transoesophageal echocardiography experienced aphasia, bilateral dysmetria, loss of balance and abnormal movements 20 mins after lidocaine administration.¹⁷

Ophthalmic complications following dental anaesthesia have also been reported. They are rare and most commonly transient. The majority of the cases resulted from upper jaw anaesthesia, during middle superior alveolar block. Some, however, have followed a mandibular block. Diplopia secondary to lateral rectus palsy is the most frequent complication. Other patients have developed ptosis, mydriasis, Horner syndrome and visual loss. The causes of the transient deficits have been postulated to be secondary to diffusion of the anaesthetic to the orbit from the pterygomaxillary fossa, injection inadvertently into the orbit via the inferior orbital fissure or flow of the medication to the middle meningeal

artery following erroneous injection in the superior alveolar artery.¹⁸

Pain relief after median sternotomy using interpleural injection of lidocaine with epinephrine has been effective following bilateral lung surgery. A study measuring plasma levels of lidocaine at several intervals after injection and analgesic assessment was published in 1992. Lidocaine was used by the authors because of its rapid onset of action in decreasing pain. There were adverse effects in patients who received repeat injections resulting in peak levels of lidocaine of 5.3–6.2 µg/mm. Patients had muscular tremor and incoherent speech followed by drowsiness after multiple injections of lidocaine. Even after one dose, rapid initial peak plasma levels of lidocaine followed by slow decrease in level to 70% after 180 mins, led to toxic signs. The authors cautioned that after one dose of interpleural injection of lidocaine, a peak level of 3.3–5.1 µg/mm may be reached rapidly followed by slow decay so that repeat administration may cause cumulative toxicity.¹⁹

Deaths have been related to liposuction as well. Repeated doses of lidocaine in solution infused subcutaneously followed by fat aspiration through microcannulas have been performed as a common surgical technique. During this technique, tumescent liposuction, repeated large doses of lidocaine have been administered, reported to be as high as 10–88 mg/kg. The maximum recommended dose is 4.5 mg/kg. This excessive infusion of lidocaine in solution may have led to toxic serum levels and deaths of previously healthy persons during cosmetic surgery.¹⁴

Other reports have been published of patients administered topical lidocaine during transoesophageal echocardiogram leading to systemic absorption and CNS effects. This lidocaine toxicity was related to congestive heart failure as well as diminished hepatic function.²¹

Besides use of recommended dosage guidelines there are other factors that clinicians should keep in mind during administration of this ubiquitous medication to ensure greater patient safety. It is necessary to focus on the anatomy of the site of absorption of lidocaine, the rapidity of absorption from the tissues at that site as well as the initial dose. The frequency of doses and cumulative total dosage must also be kept in mind. Concomitant medications taken by the patient, such as metoprolol, which can lower blood flow to the liver must be considered. If the patient is taking medications that inhibit CYP34A, this will result in slower breakdown of lidocaine. About half of all medications being administered to patients now, including simvastatin, colchicines and diltiazem, inhibit CYP34A.¹³

It is, therefore, incumbent on clinicians to investigate the risk factors of metabolic derangement and concomitant medications adequately in each patient prior to administering lidocaine. Even initial doses considered to be in the therapeutic range may result in toxicity if the metabolism of this anaesthetic is impaired.^{11 12 21 12}

The mild CNS manifestations of overdose of this medication are lightheadedness, confusion, dizziness, drowsiness and double vision. More serious manifestations are tremors, convulsions, unconsciousness and arrest. The first sign of toxicity may be drowsiness, followed by unconsciousness and respiratory arrest. Allergic reactions are extremely rare but manifestations include urticaria, oedema and anaphylactoid reactions.²²

Several points about this case provide opportunities to enhance patient safety. First, the frequent safe use of lidocaine

decreases concern about toxicity and may lead to excessive administration. Second, translating from per cent dose to milligram equivalents may be challenging in everyday busy clinical practice. Finally, the pharmacokinetics of lidocaine metabolism is complex but have to be kept in mind.

In our patient decreased hepatic blood flow from cardiomyopathy and reduced ejection fraction, hepatic cirrhosis and use of metoprolol impaired clearance of lidocaine. In addition, the bioavailability of lidocaine through mucus membranes with diminished first pass metabolism because of hepatic fibrosis and inhibition of CYP3A4 increased systemic absorption of the drug. These factors led to lidocaine toxicity with CNS effects.

Unfortunately, clinical guidelines for dose adjustments in patients with hepatic dysfunction comparable with the specific guidelines in patients with renal dysfunction, based on creatinine clearance, are not readily available. Clinicians must be judicious in administering this common medication. Lidocaine, although considered 'Safe' may result in toxic levels if given unwisely.

Learning points

- ▶ A single application of 5% lidocaine ointment should not exceed 300 mg of lidocaine hydrochloride.
- ▶ If 5% lidocaine ointment is used concomitantly with other products containing lidocaine, the total dose requires careful monitoring.
- ▶ Adverse effects of using 5% lidocaine ointment most commonly occur secondary to overdosage and rapid absorption.
- ▶ Application to large areas of abraded skin may also lead to systemic absorption and toxicity.
- ▶ The pharmacokinetics of lidocaine metabolism is important. If there is poor hepatic flow, structural pathological changes to the liver, loss of mass, known steatosis or evidence of impaired microsomal metabolic activity, then the possibility of slowed breakdown of lidocaine should be considered. Evidence of congestive heart failure is also a risk factor for lidocaine toxicity.

Competing interests None.

Patient consent Obtained.

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