OBSERVATION

Systemic Toxicity From Topically Applied Lidocaine in Conjunction With Fractional Photothermolysis

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Background: Topical anesthetics, unlike injectable anesthetics, can be applied painlessly and can provide sufficient pain control to maintain patient comfort throughout a variety of laser procedures. Although the use of topical lidocaine is considered relatively safe, instances of cardiotoxic and neurotoxic adverse events have been reported to occur.

Observations: A 52-year-old woman underwent fractional photothermolysis for management of severe hypopigmentation and scarring of several years' duration. Shortly after termination of treatment to her face and neck, which required prolonged exposure to a 30% lidocaine gel compound both before and during surgery, she developed clinical signs and symptoms consistent with systemic lidocaine toxicity. The results of laboratory studies confirmed serum lidocaine levels within the toxic range. We postulate that the combination of the high concentration of topical lidocaine required to achieve sufficient anesthesia, together with the laser-induced disruption in epidermal barrier function, may have been responsible for this phenomenon.

Conclusions: Application of a 30% topical lidocaine gel to a limited area in conjunction with fractional photothermolysis may generate serum lidocaine levels high enough to elicit systemic toxicity. Laser surgeons should be alert to this phenomenon, particularly in patients with underlying hepatic, endocrine, cardiac, or central nervous system/psychiatric dysfunction; in patients with a low body mass index; and in patients who are taking medications that may interfere with hepatic lidocaine metabolism.

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THE CENTRAL NERVOUS AND cardiovascular systems are particularly susceptible to the action of local anesthetics. The sequence of events related to the central nervous system after a progressive increase of local anesthetic agents is as follows: paresthesias, dizziness or light-headedness, drowsiness, excitation, abnormal behavior, fasciculations, and tremors. Ultimately, in severe toxic reactions, clonic muscular contractions and convulsions occur.[1] The cardiovascular system is somewhat more resistant to the toxic effects of local anesthetics than the central nervous system. Cardiovascular toxicity usually manifests as tachycardia and hypertension. Ventricular arrhythmias and cardiac arrest are also known adverse effects. At high blood levels, most local anesthetics also act as direct myocardial depressants, which, coupled with their intrinsic vasodilator properties, may produce hypotension.[2]

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REPORT OF A CASE

A 52-year-old white woman presented to our clinic for management of severe hypopigmentation and scarring due to postsurgical infection and wound dehiscence that had occurred after she underwent a facelift by another physician several years earlier. She agreed to undergo fractional resurfacing. This new technology (Fraxel; Reliant Technologies, Palo Alto, Calif) relies on a 1550-nm diode-pumped erbium fiber laser delivered through an optically tracked microprocessor-controlled handpiece to produce an array of microscopic thermal zones (MTZs). Each of these zones is extremely thin (approximately 100 µm in diameter) and 400 to 700 µm deep, producing a column of thermal damage that results in collagen denaturation.[3] The procedure is painful and requires application of a 30% lidocaine gel both for reducing discomfort and for allowing easy gliding of the treatment handpiece along the skin.

After a tracking dye was applied according to company specifications, 30% lidocaine gel was applied to the entire face and neck anterior to the sternocleidomastoid muscle. One hour after application, treatment was performed at the following settings: forehead, 11 mJ, 250 MTZ/cm^2, 8 passes; face and neck, 13 mJ, 250 MTZ/cm^2, 4 passes; followed by 6 mJ, 250 MTZ/cm^2, 2 passes. Within less than 5 minutes of treatment termination, the patient became visibly agitated

and reported feeling light-headed and anxious. She also stated that she had palpitations and slight nausea as well as perioral paresthesias. Vital signs showed a blood pressure reading of 170/92 mm Hg (baseline, 130/70 mm Hg) with a pulse rate of 74/min (baseline, 70-80/min). She was taking no other medications and had a history of anxiety attacks. The patient's weight was 52 kg, and her body mass index (calculated as weight in kilograms divided by the height in meters squared) was 17 (normal range, 18.5-24.9). No other pretreatment medications had been administered, and nerve blocks had not been performed.

The remaining topical anesthetic gel was promptly washed off, and the patient was given 2 mg of lorazepam sublingually. A total of 1 L of lactated Ringer solution was infused intravenously over the following 2 hours, during which the patient was maintained in observation with continuous monitoring of her vital signs. Her symptoms began to improve shortly after institution of the above measures and had completely resolved at the time of her discharge 3 hours later.

Laboratory studies performed approximately 60 minutes from the onset of symptoms revealed a normal complete blood cell count and metabolic profile and an absence of amphetamines, cocaine, phencyclidine, barbiturates, opiates, propoxyphene, ethanol, and tetrahydrocannabinol. The patient's plasma lidocaine level was 1.5 µg/mL.

COMMENT

Topical anesthetics, unlike injectable anesthetics, can be applied painlessly and can provide sufficient pain control to maintain patient comfort throughout a variety of laser procedures.[4] Although the use of topical lidocaine is considered relatively safe, instances of cardiotoxic and neurotoxic adverse events have been reported. In January 2005, a 22-year-old woman, in excellent health, experienced convulsions, lapsed into a coma, and subsequently died after applying a topical gel containing 10% lidocaine, 10% tetracaine, and an unknown amount of phenylephrine to both legs under occlusion.[5] At autopsy, she was determined to have suffered anoxic brain damage as a result of lidocaine toxicity. In January 2002, a similar incident resulted in the death of a healthy 25-year-old woman who had applied a cream containing 6% lidocaine and 6% tetracaine under occlusion to both legs prior to laser hair removal.[6] Tetracaine is thought to cause systemic toxic effects at much lower plasma concentrations than lidocaine, although the toxic effects of coadministered local anesthetics are thought to be at least additive (http://www.rxlist.com/cgi/generic4/synera_ad.htm).

Central nervous system toxicity may be seen at plasma lidocaine levels as low as 1 to 5 µg/mL.[7] Levels in this range commonly lead to clinical signs, including tinnitus, dysgeusia, light-headedness, nausea, and diplopia. Treatment of patients showing these signs and symptoms include removal of lidocaine and careful observation and supportive measures. It should be noted that serum lidocaine levels in our patient were measured approximately 1 hour after the onset of symptoms. Given the half-life of lidocaine in the bloodstream, peak levels may have been as high as 3 µg/mL. Plasma lidocaine levels in the 5- to 12-µg/mL range can cause nystagmus, slurred speech, hallucinations, muscle tremors, and seizures. Management centers around maintenance of a patent airway and ventilation as well as administration of benzodiazepines. Plasma lidocaine levels above 20 µg/mL are associated with coma and respiratory arrest.[7]

Lidocaine is mostly eliminated through hepatic metabolism, and only a small fraction is eliminated unchanged.[8] CYP1A2 is the main enzyme responsible for the metabolism of lidocaine, but CYP3A4 plays a more important role at higher lidocaine concentrations.[9] CYP1A2 inhibitors such as ciprofloxacin may lead to reduced lidocaine clearance, resulting in higher peak concentrations and area under the curve in serum.[10] The serum lidocaine level has also been demonstrated to be elevated in individuals with compromised liver function compared with controls.[11]

The mechanism of action of lidocaine in the central nervous system is not fully understood, but its administration is associated with increased activity in limbic structures.[12] Lidocaine can lead to both excitation and depression of the central nervous system. Initially, the excitation can be attributed to lidocaine preferentially blocking inhibitory cortical synapses of the central nervous system. However, at higher concentration, lidocaine blocks actions of both inhibitory and excitatory neurons, leading to generalized central nervous system depression.[13] It is possible that our patient's history of anxiety attacks made her more susceptible to the central nervous system effects of systemically available lidocaine. Also, the patient's low body mass index may have facilitated the development of elevated serum lidocaine levels.[14]

Percutaneously applied lidocaine must penetrate the stratum corneum to exert its effect.[15] However, disruption of the stratum corneum markedly enhances transepidermal absorption. Singer et al,[16] for instance, have shown that disruption of the stratum corneum with a low-fluence erbium-YAG unit (fluence, 3.5 J/cm^2; pulse width, 600 microseconds; and spot diameter, 6 mm) before application of 4% lidocaine cream decreases the time necessary to obtain cutaneous anesthesia from 60 minutes to 5 minutes. Percutaneous absorption follows a dose-response curve and increases with temperature.[17] It is known that fractional photothermolysis creates countless zones of epidermal disruption, and tissue heating is a direct consequence of absorption of laser energy by water, the device's selective chromophore.[3] These phenomena may help explain the symptoms that were observed in our patient, as well as the timing in the onset of symptoms immediately after treatment. Despite the findings presented herein, it should be noted that fractional resurfacing in conjunction with 30% lidocaine topical anesthesia has an excellent safety record. In fact, the procedure has been performed in our office almost 1000 times, and clinical symptoms of lidocaine toxicity have been observed in only 1 other instance, involving treatment of the entire back for acne scarring.

In conclusion, application of a 30% topical lidocaine gel to a limited area in conjunction with fractional photothermolysis may generate serum lidocaine levels high enough to elicit systemic toxicity. Further studies are war-

ranted to explore the pharmacokinetics of this agent in this unique and expanding clinical setting. In the meantime, laser surgeons should be alert to this phenomenon, particularly in patients with underlying hepatic, endocrine, cardiac, or central nervous system/psychiatric dysfunction; in patients with a low body mass index; and in patients who are taking medications that may interfere with hepatic lidocaine metabolism.

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