Effects of Lidocaine Infusion in Cats After Unilateral Labyrinthectomy

Steven M. Parnes, MD; Zorik Spektor, MD; Norman Strominger, PhD

• In the auditory/vestibular system, intravenous lidocaine hydrochloride administration has been reported to provide transient relief from severe tinnitus, reduce dizziness and emesis accompanying Meniere's disease, and sometimes improve audiometric thresholds in sensorineural hearing loss. In this study, the labyrinth was destroyed unilaterally in a series of cats. Animals constantly fell and demonstrated prominent contralateral nystagmus and a rotary motion of the head. Within four hours of a 4-mg/kg intravenous lidocaine hydrochloride injection, the cats were able to ambulate freely without falling. The nystagmus was reduced, and there was virtual absence of the rotary head motion. In contrast, the controls had persistent signs of vestibular disturbance. These results demonstrate that lidocaine infusion ameliorates the effects of unilateral labyrinthectomy in cats and thus may be a potential antivertiginous agent.

***(Arch Otolaryngol Head Neck Surg* 1988;114:653-656)**

Accepted for publication Aug 26, 1987.

From the Division of Otolaryngology (Drs Parnes and Spektor) and Department of Anatomy (Dr Strominger), Albany (NY) Medical College.

Read before the 89th Annual Meeting of the American Laryngological, Rhinological, and Otological Society, Palm Beach, Fla, May 7, 1986.

Reprint requests to Division of Otolaryngology, Albany Medical College, Albany, NY 12208 (Dr Parnes).

Lidocaine hydrochloride is a widely used local anesthetic. When administered intravenously (IV), the drug has significant multisystemic effects. It potentiates cardiac electrical stimulation threshold by increasing potassium conductance and therefore acts as an antiarrhythmic agent.[1] It affects the central nervous system (CNS) by reducing central pain and frequency of epileptic seizures.[2] At plasma levels of 5 mg/L and above, lidocaine produces feelings of dissociation, paresthesia, mild drowsiness, agitation, multiple twitching, convulsions, disorientation, and decreased hearing.[3,4]

The effects of IV lidocaine on the auditory and vestibular systems have been noted by a number of investigators. In 1937, Lewy[5] reported that IV lidocaine can be used safely in the treatment of tinnitus. Melding et al[6] demonstrated that IV lidocaine improves audiometric thresholds and suppresses tinnitus in patients with presumed damage or degeneration of the organ of Corti. In a double-blind, crossover study, Israel et al[7] found improvement in subjective tinnitus in 19 of 26 patients. In addition, IV administration of lidocaine has been reported to reduce dizziness, nausea, and vomiting.[8,9] An intratympanic injection of lidocaine was also effective in alleviating tinnitus and vertigo in patients with Meniere's disease.[10]

At the present time, information is scant regarding the effects of IV lidocaine on the mammalian vestibular apparatus. The purpose of this study was to evaluate the effectiveness of IV lidocaine for control of vertigo in cats after unilateral labyrinthectomy.

MATERIALS AND METHODS

A right labyrinthectomy was performed on 14 adult cats with an average weight of 2.5 kg. Anesthesia was achieved with IV thiamylal sodium followed by endotracheal intubation and halothane. The right tympanic bulla was approached laterally through a postauricular skin incision. Section and retraction of the sternocleidomastoid, digastric, and stylohyoid muscles provided the necessary exposure. An opening large enough to visualize the round window was drilled in the bulla. The labyrinth was then obliterated with a drill. The bulla was packed with absorbable gelatin sponge, and the incision was closed. The animals were then allowed to recover from anesthesia for 12 to 14 hours. One animal died of complications from anesthesia before surgery and was excluded from the study.

In the first part of the study, four cats received a 4-mg/kg of body weight IV injection of lidocaine hydrochloride. An-

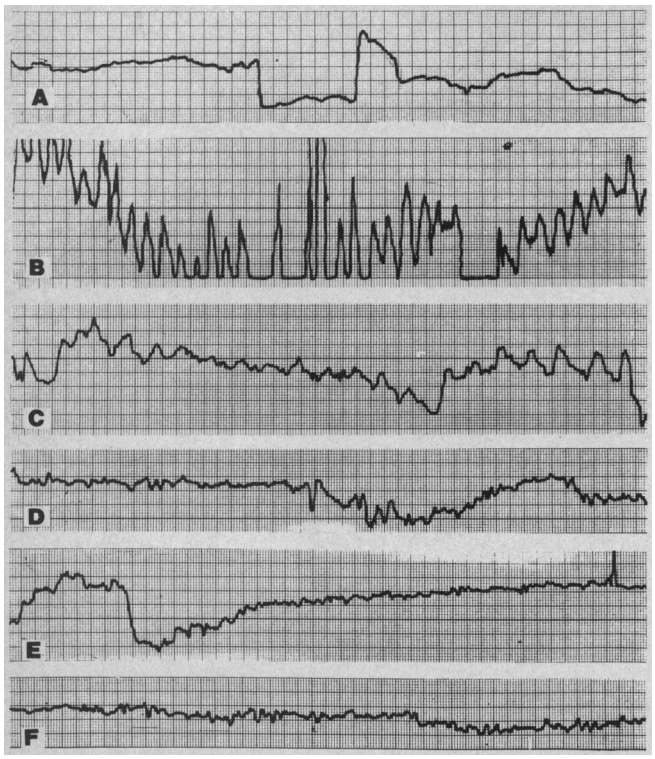

Fig 1.—Electronystagmographic (ENG) recordings obtained on experimental animal. A, Baseline ENG recorded on healthy cat, demonstrating spontaneous eye movements. B, ENG recording obtained 14 hours after right labyrinthectomy. Lidocaine hydrochloride (4 mg/kg) was administered immediately after this recording. C, D, E, and F, ENG recordings obtained on same cat 75 minutes, 150 minutes, 3½ hours, and 4½ hours after injection.

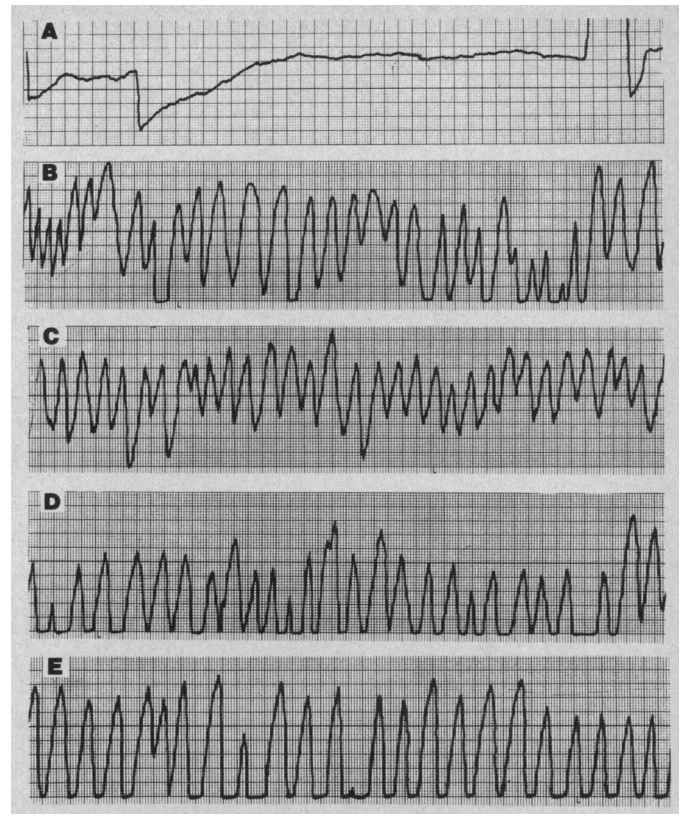

Fig 2.—Electronystagmographic (ENG) recordings obtained on control animal. A, Baseline ENG on healthy cat. B, C, D, E, Recordings obtained 14, 16, 18, and 20 hours, respectively, after right labyrinthectomy.

other four animals received an equivalent injection of saline and served as controls. Two cats (one experimental and one control) were observed simultaneously just before injection and then for at least four 15-minute periods at one- to two-hour intervals. At each observation, the general orientation, behavior, and presence of nystagmus were recorded by three independent observers who were unaware of which cat received the lidocaine. The animals then were perfused with normal saline and 10% formaldehyde solution. The temporal bones were removed and examined under a dissection microscope, which confirmed the completeness of the unilateral labyrinthectomy.

In the second part of the experiment, electronystagmography (ENG) recordings were conducted on five cats that had labyrinthectomies and one normal cat. Four cats (including one normal animal) received 4-mg/kg IV injections of lidocaine, and the remaining two cats with labyrinthectomies received saline. The animals were immobilized by wrapping their bodies in sheets, and ENGs were recorded before labyrinthectomy, after the labyrinthectomy, and at one- to two-hour intervals for six to eight hours after the injection of lidocaine. The ENGs were recorded with an ICS (Instrument Control Systems) recorder by means of surface electrodes applied to shaved lateral canthal areas and central supranasal area for each animal. The ENG recordings for each animal were compiled and compared.

RESULTS

The three independent observers accurately and consistently selected the cat that had received the IV lidocaine. Before the administration of the drug, the animals demonstrated signs of significant vestibular impairment. They were disoriented and incapable of changing positions without falling. They could not make purposeful movements, but when such were attempted they invariably moved in a circular pattern. A constant rolling motion of the head, unusually broad stance of front and hind limbs, and horizontal nystagmus directed toward the unoperated-on side were present in all animals.

Within one to two hours after the administration of IV lidocaine, all experimental cats demonstrated a significant improvement. They were able to exhibit purposeful movements without falling; they were able to navigate around obstacles and climb back into their cages; their stances improved and the rolling head motion had decreased noticeably while the nystagmus was still present. The most marked change in the animals' behavior occurred within one to three hours after the injection of lidocaine, with stabilization within four to six hours. Over the next several hours, a slight deterioration of their condition was noted. However, during the entire period of observation, the animals' condition was better than it had been immediately before the injection.

The four control cats, which received injections of saline, showed virtually no improvement within the first 24 hours after the labyrinthectomy. Only on the second day did the

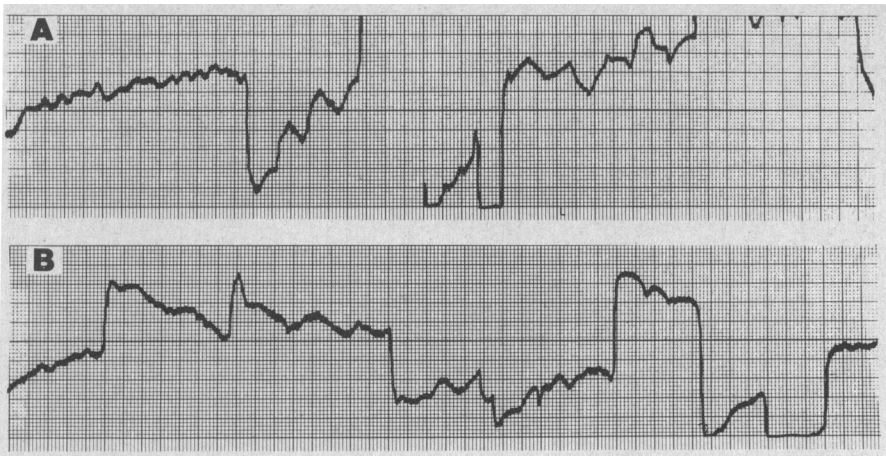

Fig 3.—Electronystagmographic recordings obtained on control and experimental animals 60 hours after right labyrinthectomy. A, Experimental animal that received 4 mg/kg of lidocaine hydrochloride. B, Control animal.

animals begin to demonstrate signs of gradual adaptation to their vestibular impairment.

The second part of the study centered on the use of ENGs as an objective measurement of the effect of lidocaine. Before surgery, the ENG recordings on the six cats including the cat without labyrinthectomy that received lidocaine demonstrated only spontaneous eye movement. After the operative procedure on five animals, spontaneous nystagmus with a fast component directed to the unoperated-on side was noted. Calibration was not attempted, but gain was kept constant to minimize variability. Neither object nor voice stimulation was able to produce a gaze fixation at that time. The three experimental animals that received lidocaine demonstrated a significant change in ENG recordings that lasted up to four hours and then began to revert back to preinjection tracings. There was a significant decrease in the amplitude of the slow-wave component within one to three hours after the injection. Two cats exhibited values of 25% or less from preinjection levels (Fig 1), while the third approximated 50% of the preinjection level. Moreover, the animals were able to fix their gaze on an object or to a voice stimulus for several seconds at a time. In contrast, the ENG recordings obtained on control animals (labyrinthectomy, IV saline) showed no change from the postlabyrinthectomy tracings (Fig 2), nor were the animals able to fixate on object or voice stimulus.

Sixty hours after labyrinthectomy, both the control and experimental cats demonstrated relatively similar decreases in slow-wave amplitude of the nystagmus (Fig 3) as well as similar gait and posture. They still exhibited some slight head tilt to the right, but there was no rolling motion. Locomotion was much improved, but a tendency to circle persisted.

COMMENT

In the course of this study, several important observations were made. We noted that labyrinthectomy produced uniform vestibular impairment characterized by loss of locomotor function, postural changes, lateral nystagmus, and rolling motion of the head. Although all animals had these disturbances, each of them displayed a particular impairment to a different degree. For example, some cats could not change position at all; others were able to make several steps before falling. This observation is significant since it indicates that in cats, just as in humans, a specific anatomic and physiologic impairment produces a set of identical symptoms, each displayed with variable intensity.

As a result of this observation, the comparison of different animals relative to each other before or after the administration of lidocaine would have been invalid. Therefore, each animal was evaluated individually; that is, the condition of each cat after the injection of the drug was compared with its condition after the labyrinthectomy. Depending on the animal, the most obvious improvement appeared during a one- to three-hour interval after injection. The degree of disability before surgery did not correlate with the degree of improvement after the lidocaine treatment. Intravenous lidocaine invariably improved the animal's condition; however, the degree of improvement and the time between when it was most obvious varied from animal to animal. After the peak effect of the drug had been reached, the animal's condition stabilized and no further improvement was seen. In the ensuing 12 to 24 hours, the animal's condition worsened, but it never reverted to the immediate post-labyrinthectomy state.

In the second set of experiments, to establish a more objective evaluation criterion, we elected to record and compare ENGs. The recordings obtained on each animal demonstrated a decrease in the frequency and amplitude of nystagmus after the administration of lidocaine. The maximum change occurred during the period of one to three hours after the injection. This directly correlates with the behavioral changes observed in the animals.

Igarashi et al[11] reported that intensity of nystagmus after the loss of one labyrinth differed considerably among individual animals. Our findings support these observations. There was an obvious variability in the tracings obtained after surgery and after treatment with lidocaine. Therefore, as with the behavioral observations, only the recordings obtained on a specific cat may be objectively compared.

We concluded that unilateral labyrinthectomy resulted in a vestibular impairment that was most severe in the first 24 hours. During the following several days, the sensorineural adaptation mechanisms acted to improve the animals' condition. If the animals received IV lidocaine during the first day, a dramatic improvement and stabilization of their condition was seen. Relatively speaking, this improvement was equivalent to that

seen in controls 60 hours after the labyrinthectomy.

Intravenous lidocaine produced a uniform amelioration of the vestibular impairment effects in cats. At the present time, it is not known whether lidocaine itself or its metabolites are responsible for the therapeutic qualities and side effects. Lidocaine is metabolized in the liver by mixed-function oxidases by dealkylation to monoethylglycine and xylidide. The former metabolite has antiarrhythmic activity, while the latter has almost none. However, the latter compound retains significant local anesthetic and toxic properties.[3,4] Lidocaine has a half-life of 90 to 100 minutes, and lidocaine-produced side effects such as sleepiness and dizziness may be mediated by its metabolites.[12] The possibility that lidocaine's effect on the CNS is via the metabolites was further supported by the observation that it takes 60 to 90 minutes to produce its maximum effect on auditory brain-stem response latencies and an even longer time for this effect to subside.[13] Our study provides more evidence in support of this theory, since we observed the maximum effects of the drug during the 60- to 180-minute interval.

The evidence of the effects of IV lidocaine on the CNS is indisputable. The question to be answered is what cellular mechanisms are responsible for such effects. Ward and Honrubia[14] reported reversible decreases in the cochlear microphonics and eighth-nerve action potentials after perfusion of scala tympani with dilute lidocaine. Similarly, Rahm et al[15] reported a reduction in the magnitude of cochlear electrical response during topical administration of the drug. In evaluating the auditory brain-stem response during systemic infusion of lidocaine, Javel et al[13] determined that lidocaine increases axonal and synaptic conduction times, evidenced by increased latent periods in auditory brain-stem response waves in cats. This information was tested on human subjects by Ruth et al,[16] and a prominent change in the wave V amplitude and latency was noted.

One possible mechanism of action of lidocaine may be based on blocking CNS sodium ion channels.[17] Our data showed a decrease in frequency and amplitude of the nystagmus after a systemic injection of lidocaine. This information supports the hypothesis of Javel and associates[13] that lidocaine increases nerve impulse conduction times. This explanation is plausible because unilateral labyrinthectomy destroys a delicate balance of information delivered to the vestibular nuclei from the sensory organs. Effectively, only one vestibular apparatus sends the afferent impulse. Intravenous lidocaine or its metabolites alter the sodium-potassium permeability in axons and synapses, which causes an increase in the conduction time, thus directing the symmetric input of information toward the equilibrium. This, subsequently, may produce the apparent changes in the ENG recordings and improve the animals' clinical condition.

At the present time, the usefulness of this information is most apparent in the treatment of Meniere's disease and other vestibular disturbances. Several investigators have used lidocaine for this purpose IV[5,7-9] and intratympanically,[10] with reported success. Our work supports the available information on such treatment. It also establishes an animal model that will allow us to understand further the actions of lidocaine and safely use it in clinical practice.

We would like to acknowledge the assistance of Richard Clark in obtaining the ENG records and the assistance of Sally Matern in the preparation and typing of the manuscript. We would also like to thank Barbara Frering for her patience and kindness in handling the animals.

References

1. Arnsdorf MF, Bigger JT Jr: Effect of lidocaine hydrochloride on membrane conductance in mammalian cardiac Purkinje fibers. *J Clin Invest* 1972;51:2252-2263.

2. Bernhard CG, Bohm E: On the central effects of xylocaine with special reference to its influence on epileptic phenomena. *Acta Physiol Scand* 1954;31(suppl 114):5-6.

3. Ritchie JM, Greene NM: Local anesthetics, in Goodman LS, Gilman AG, Rall TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co Inc, 1985, chap 15, pp 302-321.

4. Bigger JT, Hoffman BF: Antiarrhythmic drugs, in Goodman LS, Gilman AG, Rall TW, et al (eds): *ThePharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co Inc, 1985, chap 31, pp 748-783.

5. Lewy RB: Treatment of tinnitus aurium by the intravenous use of local anesthetic agents. *Arch Otolaryngol Head Neck Surg* 1937;25:179-183.

6. Melding PS, Goodey RJ, Thorne PR: The use of intravenous lignocaine in the diagnosis and treatment of tinnitus. *J Laryngol* 1978;92:115-121.

7. Israel JM, Connelly TJ, McTigue ST, et al: Lidocaine in the treatment of tinnitus aureium. *Arch Otolaryngol Head Neck Surg* 1982;108:471-473.

8. Gejrot T: Intravenous xylocaine in the treatment of attacks of Meniere's disease. *Acta Otolaryngol* 1963;80(suppl 188):190-195.

9. Gejrot T: Intravenous xylocaine in the treatment of attacks of Meniere's disease. *Acta Otolaryngol* 1976;82:301-302.

10. Fradis M, Podoskin L, Ben-David J, et al: Treatment of Meniere's disease by intratympanic injection with lidocaine. *Arch Otolaryngol Head Neck Surg* 1985;111:491-493.

11. Igarashi M, Collins WE, Schroeder DJ: Effects of calorizations and repeated unidirectional angular accelerations on the nystagmus of unilaterally labyrinthectomized cats. *Acta Otolaryngol* 1977;83:252-257.

12. Boyes RN, Scott DB, Jebson PJ, et al: Pharmacokinetics of lidocaine in man. *Clin Pharmacol Ther* 1971;12:105-116.

13. Javel E, Mouney DF, McGee J, et al: Auditory brain-stem responses during systemic infusion of lidocaine. *Arch Otolaryngol Head Neck Surg* 1982;108:71-76.

14. Ward PH, Honrubia V: The effects of local anesthetics on the cochlea of the guinea pig. *Laryngoscope* 1969;79:1605-1617.

15. Rahm WE Jr, Strother WF, Crump JF, et al: The effects of anesthetics upon the ear: IV. Lidocaine hydrochloride. *Ann Otol Rhinol Laryngol* 1962;71:116-123.

16. Ruth RA, Gal TJ, DiFazio CA, et al: Brain-stem auditory-evoked potentials during lidocaine infusion in humans. *Arch Otolaryngol Head Neck Surg* 1985;111:799-802.

17. Strichartz GR: The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. *J Gen Physiol* 1973; 62:37-57.