

## Lidocaine as an Analgesic for Experimental Pain

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The purpose of this study was to evaluate the analgesic contribution of intravenously administered lidocaine and to correlate it with blood levels of the drug. In a double-blind manner, 14 healthy male volunteers received saline solution or lidocaine, 0.2 per cent, at three increasingly greater rates of infusion on two separate days. Experimental pain was produced by means of the submaximal tourniquet-induced ischemia test of Beecher and Smith. The times to the onset of ischemic (threshold) and unbearable (tolerance) pain were recorded for three control trials to two tests for the same end points during each infusion rate. Between the two ischemic trials, while the test solution continued to be infused, venous blood samples were drawn and analyzed for lidocaine by gas chromatography. No statistically significant difference in analgesia between the control and lidocaine values for threshold or tolerance was observed at blood levels from 1 to 3  $\mu\text{g/ml}$ . The data suggest that lidocaine at these blood levels produces sedation but not analgesia. (Key words: Analgesia: measurement. Anesthetics, local: lidocaine. Pain: experimental.)

INTRAVENOUSLY ADMINISTERED local anesthetic drugs have been reported to produce systemic analgesia and to be useful adjuncts for general anesthesia. However, no correlation of blood levels and analgesic effectiveness has been reported. Recently, Himes, DiFazio, and Burney<sup>1</sup> showed that blood levels of lidocaine as high as 3  $\mu\text{g/ml}$  decreased the MAC for nitrous oxide in man by 15 to 30 per cent. The purpose of this study was to correlate blood concentrations of lidocaine with its analgesic effectiveness in a controllable model.

### Materials and Methods

Subjects of the study were 14 healthy male volunteers, with no known history of neurologic or vascular disease. Informed consent was obtained from every subject. The submaximal tourniquet-induced ischemia test of Beecher and Smith<sup>2</sup> was used to produce experimental pain. This involved the exsanguination of an upper extremity by the application of an Esmarch bandage, followed by the inflation of a tourniquet on the upper arm to 250 torr. After one minute of ischemia,

the subject was asked to squeeze a hand-held rubber ball at the rate of one compression/sec for 60 sec. The arm was then placed at the supine subject's side and the times to the onset of pain (threshold) and unbearable pain (tolerance) were recorded with a stopwatch. Using a table of random numbers to decide the sequence of administration, subjects received lidocaine, 0.2 per cent (2 g lidocaine in 1,000 ml lactated Ringer's solution) or saline solution intravenously in a double-blind manner on two different test days (at least three days apart). The EKG was monitored continuously. At least three ischemic trials were performed on each test day prior to beginning any infusion, and served as the controls for that day. A 10-20-min recovery period during which perfusion was established by deflating the tourniquet preceded the next trial. Following the control trials, a 20-gauge catheter was placed in a vein at the foot or ankle for infusion of the test solution. A 16-gauge catheter, connected to a heparin drip, was placed in the contralateral arm for blood sampling, and a control venous blood sample was obtained.

A calibrated infusion pump was used to deliver the test solution at three rates that corresponded to 15, 30, and 60  $\mu\text{g/kg/min}$  lidocaine in a 70-kg subject. At the beginning of each infusion period, and 15 min later, a bolus dose of test solution, corresponding to 50 mg lidocaine, was given. Forty-five minutes after the start of each infusion rate, the first ischemic trial was performed. The infusion was continued during the subsequent recovery period, and a 5-ml venous blood sample was obtained. The second ischemic trial was then completed, and the plasma level of lidocaine increased by giving the priming doses and increasing the infusion rate. The infusion rates were not randomized, in an attempt to keep the subjects blind to the test solution as long as possible and to achieve constant blood levels of the drug. All blood samples were analyzed for lidocaine by gas chromatography.<sup>3</sup>

The means of the times to threshold and tolerance for the three control trials on each day were calculated. These were compared with the averaged time of the same two endpoints measured in the two ischemic trials during each of the three infusion rates. The latter results were then expressed as percentages of the control values for the same day. Differences between the control and test values and between the lidocaine and saline solution data were determined using Student's *t* test and analysis of variance for all groups.

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### Results

The times to threshold (onset of pain) and tolerance (unbearable pain) measured after the three different 45-min infusion periods with saline solution were not significantly different, demonstrating the consistency of the control group (fig 1). Lidocaine produced no significant change from control in threshold or tolerance for the tourniquet-induced ischemic pain at any of the blood levels of lidocaine achieved (fig. 2).

With increasing blood levels, the subjects showed several side effects. At level 1 (less than 1  $\mu\text{g/ml}$ ), 50 per cent of the subjects reported lightheadedness. In the range of 1 to 2  $\mu\text{g/ml}$  (Level 2), this incidence of lightheadedness remained, and tinnitus or perioral numbness were mentioned by 30 and 35 per cent of the subjects, respectively. By Level 3 (2–3  $\mu\text{g/ml}$ ), 85 per cent of the subjects reported drowsiness or were sleeping, and noticed tinnitus, perioral numbness, and slurred speech. No major drug-induced complication was encountered in this study.

### Discussion

Reports that local anesthetic drugs could be safely applied as adjuncts to general anesthesia and that postoperative analgesia occurred subsequently to such use stimulated this investigation. While past clinical studies have failed to determine blood concentrations of local anesthetic required to produce analgesia, a recent report from this institution quantitated the use of lidocaine as an anesthetic adjunct. Blood levels of lidocaine as high as 3  $\mu\text{g/ml}$  resulted in a decrease in the nitrous oxide MAC in man, a decrease in the halothane MAC in dogs, and a decrease in the cyclopropane MAC in rats of 15–40 per cent, with a ceiling effect of a decreased MAC found upon increasing blood and cerebrospinal fluid concentrations. While a mechanism of action for the decrease in MAC was not postulated, an analgesic action of lidocaine was considered, since several reports describe analgesia after intravenous administration of lidocaine.

Gilbert *et al.*<sup>4</sup> reported the successful use of intravenously administered lidocaine for the relief of pain secondary to advanced malignant disease, and DeClive-Lowe *et al.*<sup>5</sup> emphasized postoperative analgesia with a lack of side effects in 77 per cent of patients when lidocaine to as much as 750 mg/hr was given intravenously intraoperatively. In a later study, DeClive-Lowe *et al.*<sup>6</sup> stated that 90 per cent of surgical patients given lidocaine intravenously intraoperatively showed some postoperative analgesia, and suggested a central sedative effect of the drug. Bartlett and Hutaserani<sup>7</sup> compared postoperative analgesic requirements and

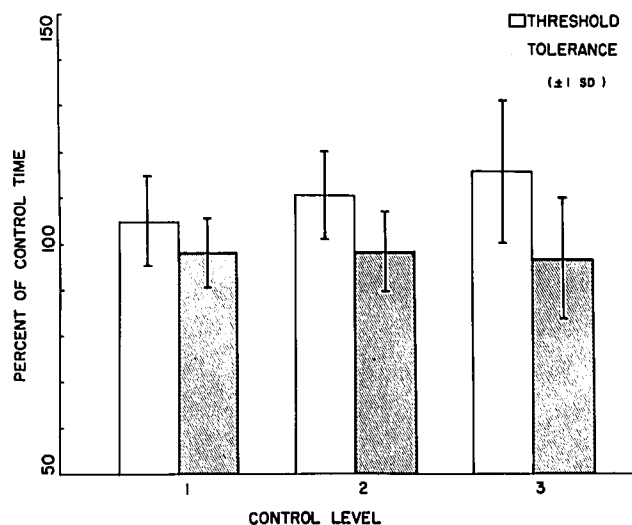


FIG. 1. The means for threshold and tolerance times with saline solution are expressed as percentages of the control times.

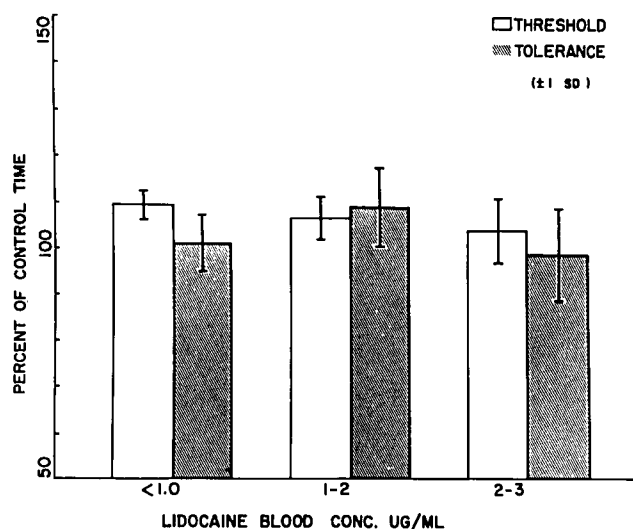


FIG. 2. The means for threshold and tolerance times with the three lidocaine infusion rates are expressed as percentages of the control times and resultant blood concentrations of lidocaine in  $\mu\text{g/ml}$ .

subjective pain characterizations in 600 patients, half of whom had received an anesthetic supplemented with intravenously administered lidocaine. In the first 24 hours after operation, 83 per cent of the patients receiving lidocaine experienced less pain compared with 25 per cent of controls.

Our study has investigated the analgesic effects of intravenously administered lidocaine on experimental pain, and we report blood levels of the drug. The submaximal tourniquet-induced ischemia test (as modified by Smith *et al.*<sup>2</sup>), used in this study, has been shown

dependably to identify analgesia produced by morphine,<sup>2</sup> aspirin,<sup>8,9</sup> and other analgesics. While we readily acknowledge that experimental pain is different from the unremitting, psychologically significant pain found in a clinical setting, the tourniquet-induced ischemia test represents the best approximation of the two for correlating the responsivenesses to analgesic agents. The pattern of an analgesic response characteristic of the tourniquet-induced ischemia test for analgesic drugs, *i.e.*, a maximal change in tolerance, was not seen in the present study after intravenous administration of lidocaine. The significant side effects that occurred with blood levels as high as 3  $\mu\text{g}/\text{ml}$  have been enumerated, and imply a central site of action. Although the clinical impression was that lidocaine was an analgesic, our data suggest that the *modus operandi* of low-dose lidocaine (at levels of drug that have been shown to decrease anesthetic requirements in man and animals) is predominantly one of sedation and not analgesia.

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