A Study of Intravenous Lidocaine as a Suppressant of Cough Reflex

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THE intravenous administration of local anesthetics for analgesia or as a supplement to general anesthesia has been the subject of numerous reports over a period of years.[1,2] Although several advantages have been claimed for the use of these agents it has been difficult to establish their particular contribution to general anesthesia. Since all drugs carry inherent liabilities, significant advantages should be demonstrable if these drugs are to be used as anesthetic supplements. The advantages most generally attributed to the intravenous use of lidocaine and other local anesthetics are analgesia,[2] anti-arrhythmic effect[3] and suppression of reflexes, such as the cough reflex.[4]

Observation during a previous study impressed the authors[4] that the suppression of the cough reflex was the most striking action of lidocaine when used as a supplement for general anesthesia. It was the purpose of this study to determine if the degree of cough suppression produced by the intravenous administration of this local anesthetic differed substantially from such drugs as meperidine and thiobarbiturate at dose levels which did not seriously depress respiration. The second portion of the study was designed to test the effect of lidocaine on the cough reflex during induction of nitrous oxide-ether anesthesia, since these respiratory reflexes are often troublesome during this induction.

Methods and Results

Since lidocaine, like other local anesthetics, does not produce general anesthesia it was necessary to study this drug action while maintaining anesthesia with another agent. In the first portion of the study, thiobarbiturate

was employed as the major agent and in the second portion diethyl ether. Preliminary observations indicated that the endotracheal tube was an effective and predictable stimulus of the cough reflex. When reflexes were suppressed to a point where the endotracheal tube caused no spontaneous cough, additional stimulus was produced by moving the tube three times through a distance of 1 inch. If no cough or irregularity in the respiratory pattern occurred as the result of this stimulus it was judged that a complete suppression of the cough reflex had occurred. In most instances visual observation was made of the cough and respiratory irregularities. However, in a portion of the studies a balloon was placed in the esophagus and connected to a pressure transducer to give pressure tracings which reflected the changes in intrathoracic pressure.[5] The minute volume determinations were made with a Wright respirometer.

THIOPENTAL, MEPERIDINE, LIDOCAINE COMPARISON

Three groups of ten patients were used to compare the effects of lidocaine, meperidine, and thiopental on the cough reflex. All patients were men ranging in age from 20 to 65 years, with a mean age of 39 years. Classification of physical status was either 1 or 2 and the average weight was 172 pounds. The scheduled operations included 19 orthopedic, five otolaryngological, two abdominal, two neurosurgical, and two miscellaneous operative procedures.

After the patient was selected for study, the test drug was selected at random with a limit of ten patients for each drug. Preanesthetic medication in all cases was 0.4 mg. scopolamine. An initial dose of thiopental of 4.4 mg./kg. of body weight was administered intravenously followed by ventilation with oxygen and intubation using 60 mg. succinylcho-
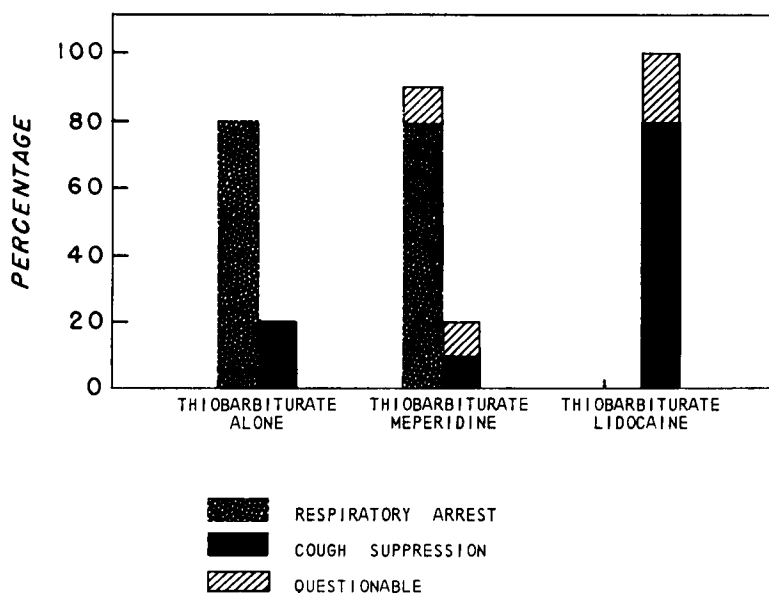
FIG. 1. A comparison of meperidine, lidocaine and thiopental as depressants of the cough reflex in relation to the depression of respiration.

line intravenously. No topical anesthetic was employed, and the cuff of the endotracheal tube was not inflated. The patient's lungs were artificially ventilated until the first respiratory activity returned, at which time the test drug was given intravenously every minute until either complete cough suppression or respiratory arrest had been produced.

The test doses of thiopental and lidocaine were 1.1 mg./kg. of body weight and that of meperidine, 0.36 mg./kg. Assisted ventilation was instituted if a serious respiratory deficiency occurred. After the end point (respiratory arrest or cough suppression) had been reached, the patient was observed for a short period during which time additional drugs were given if cough was still active. After the study was discontinued the anesthetic administration was continued with nitrous oxide and other agents, including additional thiobarbiturate, meperidine, lidocaine or inhalation agent, as determined by the anesthetist. The doses used for the test drugs were selected from preliminary studies which indicated that the end point would occur with five to six doses on the average. The induction dose of thiopental averaged 340 mg. The average total doses at the end point for the three test drugs were: meperidine 160 mg., lidocaine 515 mg., and thiopental 475 mg. (in addition to the induction dose).

Results. The effectiveness of the drugs compared in this study is illustrated in figure 1. Both thiopental and meperidine produced respiratory arrest in a high proportion of the patients before the cough reflex was suppressed. In contrast, lidocaine suppressed cough in a high proportion of patients without producing respiratory arrest, a difference with a *P* value of .011 (Mainland's contingency table).[6] The questionable cases in the lidocaine series were patients who exhibited slight respiratory irregularity when the study had to be concluded because of the excessive duration of the study and the delay of scheduled operation. In one case in the meperidine series there was similar interference.

A difference between the patients given meperidine and those given thiopental not indicated by the graph was the vigor of the cough after respiratory arrest in a majority of the patients receiving thiopental. In the patients receiving meperidine only two had a cough of this degree, and in general, a more vigorous stimulation was required to elicit the cough. In five patients the cough persisted in a decreased form, even though several additional doses of meperidine were administered in the three- to five-minute period immediately following respiratory arrest. One patient in which cough disappeared with two additional doses of meperidine was noted to have a re-

turn of a weak cough with stimulation when respiration recommenced nine minutes later.

ETHER INDUCTION STUDY

In order to determine the effect of lidocaine on a different cough stimulus, lidocaine was administered during the induction of nitrous oxide-ether anesthesia using a double blind technique in which half of the patients received lidocaine and half received a placebo (saline). The induction was judged as either smooth or stormy and the time was noted from induction to quiet respiration. If the induction was stormy and unduly prolonged (ten minutes) the anesthesiologist could elect to use other agents, such as cyclopropane or lidocaine. Thirty patients were employed in this study in which ten inductions were performed by each of three anesthesiologists. A placebo or lidocaine was selected in a random manner except that the number of patients administered lidocaine and the placebo were equal in each anesthesiologist's group.

Seven males and 23 female patients were selected from the routine operative schedule. Ages ranged from 15 to 63 years with a mean age of 38. Physical status of these patients ranged from classes 1 to 3. Scheduled operations included 14 abdominal, seven perineal, four of the extremities, and five of head and neck.

The method of induction of anesthesia included an initial dose of thiopental to produce unconsciousness followed by succinylcholine intravenously, 40–60 mg., and intubation. A circle absorption system was employed with a flow of 2 liters/minute of nitrous oxide and 1 liter/minute of oxygen. Ether was vaporized with a no. 8 Heidbrink vaporizer; the concentration was increased as rapidly as possible until satisfactory surgical anesthesia was reached. The test drug, 2 per cent lidocaine or placebo, was injected in 2.5 ml. increments within a period of three minutes and in an amount approximating, but not exceeding, that of the thiopental. The induction doses of thiopental ranged from 125 to 375 mg., and consequently the test drug was administered in similar dosages, 100 to 340 mg. Lidocaine dosage averaged 245 mg. or 12.2 ml. of a 2 per cent solution, whereas the average placebo dosage was 14.5 ml.

TABLE 1

	Number Patients	Smooth Inductions	Minutes to Quiet Resp.	Number Requiring Suppl. Agent
Control	15	3 (20%)*	9.5†	9‡
Lidocaine	15	13 (86%)*	5.6†	2‡

* $P < .01$.
† $t = 3.40$. $P < .01$ if $t > 2.76$.
‡ $P < .05$.

Results. The results of this study are shown in table 1. The proportion of smooth inductions in the series receiving lidocaine was significantly higher [6] than in the placebo group. The average time to quiet induction for the placebo group was almost double that of the lidocaine group. This difference was also highly significant, as shown by the *t* test. There was even a significant difference between the number of cases requiring supplemental agents in the control series as compared to lidocaine group.

A graphic demonstration of the change in the cough reflex during the induction of anesthesia in a 48 year old woman is presented in figure 2, which shows tracings of pressure changes in esophagus and chest movements recorded with the use of a strain gauge arch. After induction with 320 mg. of thiopental and intubation with the aid of succinylcholine, 50 mg., the patient regained the first respiratory movements at 0 time. Nitrous oxide–ether anesthesia was started as previously described and the lidocaine administration was commenced at time one minute. The tracing at two and one-half minutes revealed a markedly irregular respiratory pattern, however, by four minutes the lidocaine injection had been completed and the pattern became less irregular. In the third portion at six minutes the regular pattern of respiration is broken only momentarily, even when the standard stimulus of the three movements of the endotracheal tube was instituted. A minute volume measured at that point was 7.7 liters/minute.

Discussion

The problem of evaluating the cough reflex suppressant property of anesthetic drugs is complicated by the fact that almost all central
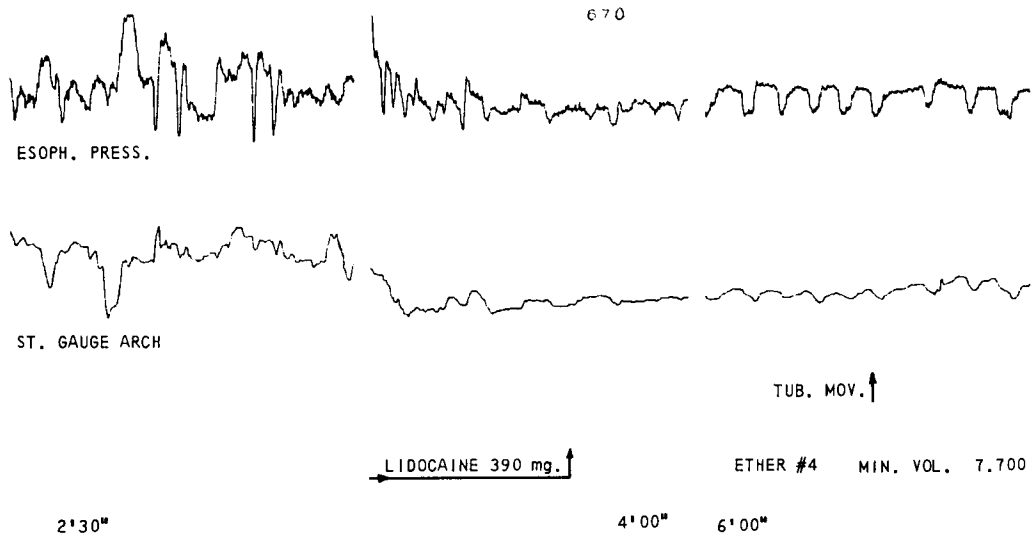
FIG. 2. Esophageal pressure and chest movement tracings of a patient during induction with diethyl ether and the administration of lidocaine intravenously.

nervous system depressants have this property to some degree. Since drugs must be evaluated for both therapeutic effectiveness and adverse action, one approach to the evaluation of cough suppression can be obtained by the degree of respiratory depression which is produced by the dose of the drug which completely suppresses cough. The first portion of this study was planned to determine if there was a gross difference between the cough suppressant action of lidocaine and an opiate such as meperidine, which has been commonly employed for the control of cough during general anesthesia. Thiopental, which is recognized as a relatively poor suppressant of these respiratory reflexes, was included since it was used as the induction agent. The comparison of the three drugs shown in figure 1 would indicate that a gross difference exists between lidocaine and meperidine when employed to suppress cough during general anesthesia.

Although respiratory depression was assessed grossly by observing the cessation of respiration, the difference between meperidine and lidocaine was highly significant. In no instance did respiratory arrest occur with lidocaine in contrast to nine out of ten trials with meperidine. It was interesting that two patients had a suppression of cough by thiopental even though this drug is generally recognized as a poor suppressant of these reflexes.

An impression was gained that the activity of the cough reflexes varied considerably even in this group of relatively young, vigorous and healthy patients. As previously mentioned, the cough was noticeably vigorous in patients receiving thiopental for suppression of this reflex. Meperidine, on the other hand, more commonly depressed both respiration and the cough reflex.

It should be noted that this comparison involves a relatively limited period and that no conclusions can be drawn concerning the action of these drugs for longer time periods. It is possible that the sites of action for the respiratory depression and the suppression of cough are not identical, in which case the access of the drug to site of action may vary. Satisfactory clinical use of meperidine as a suppressant of cough may be in part due to the lack of vigorous cough stimulation (endotracheal tube movement) in ordinary clinical circumstances or a relatively more intense effect of this drug with longer time period. It should also be emphasized that this drug comparison is made in the presence of another drug (thiopental), and consequently the resultant effect may be an interaction of two drugs.

In the induction study, the irritant effect of diethyl ether was added to the endotracheal tube as a stimulus of the cough reflex. It

should be emphasized that no attempt was made to increase the concentrations of ether gradually. The amount of test drug given was determined by the amount of thiopental administered so that patient variation to drugs could be taken into account to some degree. Both the overall judgment of the induction as to its smoothness and the time required to produce quiet respiration indicated that there was a highly significant difference between the saline control and lidocaine. The option of administering additional agents when induction was markedly delayed further indicated that lidocaine depressed reflexes of the upper respiratory tract. Figure 2 illustrates a typical case in which quiet respiration follows the lidocaine administration. The minute volume of 7,700 ml./minute would argue that an adequate respiration volume could be maintained under these circumstances. Tracings from other patients in this study show a graded depression of the cough reflex from minimal to complete suppression with minute volume readings in a normal range.

The possibility of some degree of respiratory depression following lidocaine cannot be determined from these studies. In a study by Siebecker and co-workers [7] lidocaine was administered during deep ether anesthesia and obvious respiratory depression resulted. The major difference in this earlier study was the great depth of anesthesia attained (plane 3) at the time of lidocaine administration. One explanation for the augmented respiration during the deeper planes of ether anesthesia is given as a reflex stimulation of the respiratory tract due to the anesthetic agent.[8] If the respiratory stimulation produced by this reflex effect is blocked by lidocaine the respiratory depression or arrest noted in the study by Siebecker and co-workers could be easily explained.

More extensive studies are needed to define accurately the effect of lidocaine on respiration at the dose levels required to suppress the cough reflex. From the study of DeKornfeld and Steinhaus [9] it appears that the depression of respiration produced by lidocaine differs in its dose-effect curve from that found with the opiates. Relatively slight decrease in minute volume was produced by lidocaine until a dosage was reached which produced

respiratory arrest of short duration following which there was almost complete recovery.

From these studies it would appear that lidocaine (and presumably other local anesthetics) might be employed to control the cough during general anesthesia. The usefulness of a drug for this purpose would require a weighing of the advantages of cough suppression with the possible disadvantages of circulatory depression. Since local anesthetic agents have been demonstrated to be cardiovascular depressants they obviously should not be employed for this purpose when circulatory depression is considered to be a particular hazard, as in the case of the poor risk patient. It would also be necessary to weigh the hazard of cough suppression in the postoperative period as regards the problem of aspiration and respiratory complications. The poor risk patient, especially in the older age groups, has less active respiratory reflexes, as shown by Pontoppidan and Beecher,[10] and consequently should not require drugs for this purpose. On the other hand, the extensive toxicity studies of Bromage and Robson [11] reported blood levels following epidural, intramuscular and intravenous administration of lidocaine which would indicate that the doses used in study should be well tolerated by the average patient. These authors also suggest that systemic absorption from topical and regional techniques may account for some clinical effects observed following various regional procedures, such as analgesia and the depression of respiratory reflexes.

Summary

A comparison of lidocaine and meperidine as depressants of the cough reflex during general anesthesia revealed that the local anesthetic could completely suppress cough without severe respiratory depression, whereas the opiate caused respiratory arrest in a high percentage of patients before this reflex was depressed. In a study which added the irritant effects of diethyl ether to those of the endotracheal tube during induction, the administration of lidocaine resulted in significantly shorter and smoother inductions when compared to a saline placebo. These studies suggest that the local anesthetics are representatives of a qualitatively different type of central

nervous depression which may offer a practical therapeutic approach to the control of the cough reflex and related reflexes of the upper respiratory tract during general anesthesia.

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POSTPARTUM HEADACHES   A series of 307 parturients receiving general anesthesia was compared to a series of 514 patients receiving spinal anesthesia for delivery. Spinal anesthesia was administered using 22 gauge, or most often 25 to 26 gauge needles, and postpartum activity was not restricted. General anesthesia usually was with nitrous oxide and ether. There was a 3 per cent incidence of spinal and an equal incidence of nonspinal headache among those patients receiving spinal anesthesia. There were no severe headaches. Of the patients receiving general anesthesia 9.6 per cent developed postpartum headache, one of which was severe. When fine needles and careful technique are used in administering spinal anesthesia to parturients, the incidence of postpartum headache is no higher than in patients who receive general anesthesia. (*White, C. W., and others: Anesthesia and Postpartum Headache, Obstet. Gynec. 20: 734 (Dec.) 1962.*)

PARACERVICAL BLOCK   To produce uterosacral or paracervical block about 5 ml. of local anesthetic solution is injected at three and nine o'clock just under the mucosa of each vaginal fornix. A long metal guide is used to facilitate placement of the needle when the cervix is dilated over half way but is still accessible. Relief of the pain of uterine contraction is usually immediate and complete. Most deliveries are spontaneous, and the uterus contracts well after delivery. When combined with pudendal and possibly ilio-inguinal block, paracervical block provides a method of obstetrical anesthesia which is simple, safe, and effective. Reports totaling more than 1,500 cases fail to reveal any major complications attributable to this procedure. (*McGowan, G. W.: Uterosacral or Paracervical Block for Obstetrical Anesthesia, Western J. Surg. 70: 307 (Nov.–Dec.) 1962.*)