Lidocaine and Increased Respiratory Resistance Produced by Ultrasonic Aerosols

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Respiratory resistance significantly increased from 5.0 to 8.0 cm H₂O/l/sec in anesthetized patients who were given ultrasonically nebulized water for 20 minutes via an endotracheal tube. Intravenous administration of lidocaine failed to reverse the provoked increase in resistance. In another group, respiratory resistance significantly increased from 5.8 to 7.5 cm H₂O/l/sec in response to nebulized water despite prior and concurrent intravenous administration of lidocaine. In a third group, initial respiratory resistance was 5.6 cm H₂O/l/sec and did not increase during a 20-minute challenge with intratracheally administered ultrasonically nebulized 2 per cent lidocaine. In a final group, resistance was increased from 5.0 to 6.9 cm H₂O/l/sec with nebulized water. When challenge was continued with nebulized 2 per cent lidocaine, resistance remained elevated for about 10–12 minutes. It then decreased and returned to its initial control value at about 17 minutes, despite continuing lidocaine aerosol administration.

Lidocaine, when administered intratracheally as an aerosol, both prevented and reversed provoked increases in respiratory resistance. Intravenously administered lidocaine was ineffective. Intratracheal administration of ultrasonically nebulized lidocaine might be another useful technique for management of bronchoconstriction in anesthetized patients. (Key words: Lung, bronchospasm; Anesthetics, local, lidocaine; Aerosols, lidocaine.)

Management of bronchospasm during anesthesia is largely empirical. Methods advocated for reversing bronchoconstriction in anesthetized patients are usually based on animal experiments or extrapolations from treatment of asthma in conscious subjects. There have been few objective studies of bronchoactive drugs during anesthesia in man. We reported that endotracheal administration of ultrasonic aerosols provokes increased respiratory resistance in anesthetized patients, and proposed that this might serve as a model for study of bronchoconstriction during anesthesia.1

Previous reports of observations made during clinical anesthesia suggest that intravenous administration of lidocaine can alter response to bronchial stimulation and modulate the cough reflex.2 Animal studies have shown that administration of aerosols containing local anesthetics produces reversible blockade of both afferent and efferent neural activity in airways without affecting the ability of smooth muscle to contract.3 It seemed likely that local anesthetics could influence bronchial mechanics during clinical anesthesia and might be useful for prevention or treatment of bronchospasm. We have, therefore, studied the effects of both intravenously administered and aerosolized lidocaine on the increased respiratory resistance provoked by endotracheal administration of ultrasonic water aerosol in anesthetized patients.

Methods

Subjects of the study were 22 consenting adult surgical patients free of bronchopulmonary disease who required general endotracheal anesthesia for abdominal surgery. They were premedicated with combinations of opiates, barbiturates, and diazepam in customary clinical doses. Anesthesia was induced with thiopental (200–400 mg.) and endotracheal intubation was accomplished with the aid of succinylcholine. Anesthesia was maintained with nitrous oxide supplemented with meperidine (2.5–3.0 mg/kg) and neuromuscular paralysis was established with d-tubocurarine (0.4–0.6 mg/kg).

Following surgical incision, five control
determinations of respiratory mechanics were made at three-minute intervals while patients were ventilated with unhumidified gas from the anesthesia system using methods previously described. To make a measurement, the respiratory system was inflated with a predetermined volume of gas and this volume was held in the respiratory system until pressure stabilized. Then passive exhalation into a waterless spirometer occurred. Transthoracic pressure during thoracic inflation was recorded using a pressure transducer; volume and flow during the subsequent passive exhalation were recorded from outputs of the transducers of the spirometer. Total respiratory compliance was calculated by dividing total volume exhaled (corrected to BTPS) by pressure during sustained thoracic inflation. The instant when flow was 0.5 l/sec was identified and volume remaining in the lungs at this point was measured. Division of this volume by compliance gave the transthoracic pressure required to produce a flow of 0.5 l/sec, from which total respiratory resistance was calculated. Resistance of the apparatus was subtracted from total measured resistance to obtain patient resistance.

All patients received ultrasonically generated aerosols of distilled water and/or 2 per cent lidocaine in distilled water administered into the lungs through clear plastic endotracheal tubes. This was provided by a Monaghan 670 Nebulizer set to aerosolize 2–3 ml/min of liquid into the inspiratory limb of the anesthesia system. With a respiratory pattern of slow, deep inspiration, dense mist could be observed moving down the endotracheal tube with each inspiration. The measurement sequence, performed at predetermined times during the studies, consisted of five measurements of respiratory mechanics at three-minute intervals. When lidocaine was used intravenously, subjects received 1 mg/kg as a single injection, followed by sustained infusion of 1–2 mg/min. Statistical evaluation of data was by t test for paired data.

Subjects were divided into four groups, as follows.

**Group I.** Control measurements → 20 minutes of water aerosol → measurement sequence during continued water aerosol administration → intravenous lidocaine → measurement sequence during continued water aerosol and intravenous lidocaine administration.

**Group II.** Control measurements → intravenous lidocaine (continued throughout remainder of study) → measurement sequence → 20 minutes of water aerosol → measurement sequence during continued water aerosol administration.

**Group III.** Control measurements → 20 minutes of 2 per cent lidocaine aerosol → measurement sequence during continued lidocaine aerosol administration.

**Group IV.** Control measurements → 20 minutes of water aerosol → measurement sequence during continued water aerosol administration → 2 per cent lidocaine aerosol for 20–30 minutes with measurement of respiratory mechanics every three minutes.

**Results**

Results are summarized in tables 1–4. Resistance values listed are the mean of five values obtained during a measurement sequence.

Endotracheal administration of distilled water aerosol to patients in Group I significantly increased respiratory resistance from 5.0 (SE 0.76) to 8.0 (SE 1.71) cm H$_2$O/l/sec ($P < 0.05$) (table 1). Resistance remained elevated at 8.5 (SE 1.89) following intravenous administration of lidocaine. Mean control respiratory resistance in patients of Group II was 5.8 (SE 0.68) cm H$_2$O/l/sec (table 2). Following intravenous administration of lidocaine, resistance was 6.0 (SE 0.64) cm H$_2$O/l/sec, an insignificant change. Twenty minutes of water aerosol given during continued infusion of lidocaine significantly increased resistance to 7.5 (SE 0.91) cm H$_2$O/l/sec ($P < 0.01$). Mean control respiratory resistance in Group III patients was 5.6 (SE 0.35) cm H$_2$O/l/sec (table 3). Following 20 minutes of 2 per cent lidocaine aerosol, resistance remained unchanged at 5.5 (SE 0.43) cm H$_2$O/l/sec. In Group IV patients, 20 minutes of water aerosol significantly increased respiratory resistance from 5.0 (SE 0.42) to 6.9 (SE 0.91) cm H$_2$O/l/sec ($P < 0.01$). Aerosol administration was then continued with 2 per cent lidocaine rather than water. Resistance remained elevated for about 10
minutes, then decreased to control values over 15–20 minutes following the start of the lidocaine aerosol.

Discussion

In previous studies we showed that administration of ultrasonically generated aerosols to anesthetized patients via an endotracheal tube consistently increased respiratory resistance.1 The increase was independent of composition of the mist, was not progressive, and persisted as long as aerosol administration was continued.8 Isoproterenol and halothane promptly decreased the provoked bronchoconstriction. Atropine, both intravenous and aerosolized, as well as ketamine failed to decrease artificially elevated resistance.17 In the present study, intravenously administered lidocaine failed either to prevent increases in respiratory resistance provoked by endotracheal administration of water aerosol or to reverse increased resistance once established. The dose of lidocaine selected for intravenous administration has been recommended for management of cardiac arrhythmias and is therefore known to be capable of exerting systemic effects.8 When administered as an aerosol directly into the airway, however, 2 per cent lidocaine was capable of both preventing provoked increases in resistance and reversing provoked elevations of respiratory resistance after they had occurred.

The mechanism involved in production of increased respiratory resistance by direct endotracheal administration of aerosols remains uncertain. Most previous studies of provoked bronchoconstriction in man have been done on conscious subjects breathing spontaneously through the upper airway. Under these circumstances, bronchoconstriction may be elicited by many different stimuli, including inert dust, smoke, chemical irritants, specific allergens, and bronchoactive drugs. In susceptible individuals, cold air and exercise are also effective stimuli. An important feature of studies in which the stimulus is administered through the intact upper airway is that atropine almost invariably both prevents and reverses bronchoconstriction.8 This indicates operation of a reflex mechanism. Receptors are probably stimulated by nonspecific irritants. Location and identity of these receptors have not been well documented in man. In dogs, irritant receptors are primarily distributed in the upper airway, trachea, and bronchi larger than 1 mm in diameter.10 The afferent limb of the reflex would involve the trigeminal, glossopharyngeal, and vagus nerves with the efferent limb in the vagus nerve.

There have been relatively few studies in man in which irritant materials have been administered directly into the lung via an endotracheal tube, thereby bypassing the upper airway. Cheney and Butler administered ultrasonically generated mists intratracheally to patients without histories of pre-existing respiratory disease. Respiratory resistance increased after 30 minutes and
remained elevated for the duration of mist administration. The increase in resistance was not progressive, and the magnitude of change was comparable to that reported in the present study.11 In another study, the same investigators found that aerosol delivered through the upper airway increased resistance in patients with pre-existing bronchopulmonary disease but not in subjects with normal respiratory systems. The increased resistance in patients with pulmonary disease was not prevented by atropine.12 The extent to which nebulized materials breathed through the nose or mouth penetrate below the larynx has been questioned. Asmundsson and associates studied the distribution of radioactive ultrasonic mist. They found that when 6 ml of the material had been nebulized, only 64 μl could be detected below the larynx.13 Arborelius and associates administered specific allergen directly into one lung of asthmatic subjects who had Carlen tubes in place. They reported that the resulting bronchoconstriction was confined to the lung that had received the allergen.14

These studies suggest that the response to inhalation of irritants through the intact upper airway is qualitatively different from that following direct delivery into the lower airway. In the former situation, most of the material is deposited above the larynx, and the bronchoconstrictive action is blocked or reversed by atropine, implying a reflex mechanism. When irritants or antigens are introduced directly into the lower airways, it is possible that most of the irritant receptors are bypassed. In this situation, direct irritation in small peripheral bronchi, not involving a reflex, seems to be the most likely mechanism for bronchoconstriction. The response may be unilateral and is neither blocked nor reversed by atropine. We postulate that bronchoconstriction following intratracheal administration of nebulized water is produced in this manner.

The actions of aerosolized lidocaine demonstrated in the present study are attributed to a direct action of the drug on bronchial smooth muscle. Systemic administration of lidocaine does not appear to provide a sufficient concentration at the effector site to relax the contracted bronchial smooth muscle. Dain and associates studied effects of bupivacaine aerosols on broncomotor responses in dogs. They found that the drug blocked afferent and efferent reflexes but did not interfere with the ability of bronchial smooth muscle to contract in response to histamine aerosol.3 Direct action of lidocaine, postulated as an explanation for findings in the present study, could represent a species difference. It could also represent a difference in inten-

| Table 3. Responses of Subjects in Group III to Aerosolized Lidocaine |
|------------------------|---------|---------|
| Age (Years)            | Control | Lidocaine |
| Patient 13             | 41      | 6.0     | 5.8     |
| Patient 14             | 26      | 4.7     | 4.2     |
| Patient 15             | 21      | 4.8     | 4.7     |
| Patient 16             | 35      | 5.8     | 6.1     |
| Patient 17             | 18      | 6.5     | 6.4     |
| **MEAN**               |         | 5.6     | 5.5     |
| **SEM**                |         | 0.35    | 0.43    |

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| Table 4. Total Respiratory Resistances (cm H2O/sec) in Group IV at Intervals after Start of Aerosolized Lidocaine When Resistance Had Been Previously Elevated by Water Aerosol |
|-----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                 | Control | Water Mist | 5      | 8      | 11     | 14     | 17      | 20      | 23      | 27      | 30      |
| Patient 18      | 4.5     | 5.4      | 5.0    | 3.9    | 4.0    | 4.3    | 3.9     | 3.3     | 7.3     | 8.3     | 4.6     |
| Patient 19      | 6.6     | 10.5     | 10.1   | 10.3   | 9.0    | 8.0    | 7.5     | 7.2     | 7.3     | 3.7     | 4.6     |
| Patient 20      | 4.8     | 6.0      | 5.7    | 8.3    | 5.8    | 5.5    | 4.7     | 5.4     | 4.7     | 4.6     | 4.5     |
| Patient 21      | 3.1     | 6.7      | 7.0    | 6.7    | 7.2    | 6.9    | 5.3     | 5.8     | 5.8     | 5.8     | 4.5     |
| Patient 22      | 4.2     | 6.1      | 5.8    | 5.5    | 5.1    | 5.0    | 4.1     | 4.5     | 4.6     | 5.8     | 4.5     |
| **MEAN**        | 5.0     | 6.8      | 6.7    | 6.8    | 6.2    | 5.9    | 5.1     | 5.2     | 5.2     | 5.2     | 4.5     |
| **SEM**         | 0.42    | 0.91     | 0.90   | 1.11   | 0.86   | 0.67   | 0.64    | 0.66    | 0.66    | 0.66    | 0.66    |

* Significant increase from control value ($P < 0.01$).
sities of responses to an inert mist as opposed to a large dose of a bronchoactive drug. Dain and associates selected bupivicaine because of its high lipid solubility. We used lidoca-
aine because of the extensive clinical experience with its intravenous use as well as availability of a preparation appropriate for intravenous use in man. Aerosolized lidoca-
aine might be another useful measure for management of bronchospasm during anesthesia or in other patients being managed with an endotracheal tube. The relatively pro-
longed administration of lidocaine necessary for relief of established bronchoconstriction found in the present study may be a potential disadvantage of the method. It is possible that a more fat-soluble local anesthetic agent might act more rapidly. A clinical trial of lidocaine and evaluation of other local anesthetics as well seem justified.

We use bronchoconstriction provoked by aerosols as a model for the study of bronchoactive drugs in anesthetized patients because it is a safe, reproducible technique that can be applied in a planned and controlled manner. There are other stimuli that elicit bronchoconstriction during anesthesia. An example of a pharmacologic stimulus is the increase in respiratory resistance that occurs in susceptible patients in association with d-tubocurarine. It is also reasonable to postulate that reflex bronchoconstriction occurs during anesthesia. An example of this might be bronchoconstriction following insertion of an endotracheal tube in a susceptible patient. It remains to be determined whether drugs with bronchodilating properties are equally effective under all circumstances. Further studies of factors influencing bronchomotor tone during anesthesia in man should be done.

References

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