studies, but dose-related depressant effects have not been observed.††

In our studies and others,[10,11] patients liked going to sleep with midazolam maleate. It appears that midazolam maleate shares the salutary characteristics of the benzodiazepines, *i.e.*, sedation, hypnosis, anticonvulsive activity, muscle relaxation, benign effects on other organ systems, and a high therapeutic index. However, it is unique in its water solubility and is shorter-acting. We believe midazolam maleate may be a more satisfactory alternative to thiopental for induction of anesthesia than the available benzodiazepines.

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†† Investigational Drug Brochure, RO 21-3981, Roche Laboratories, June 1977.

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Cough Suppression by Lidocaine

THOMAS J. POULTON, M.D.,* AND FRANCIS M. JAMES, III, M.D.†

The intravenous administration of local anesthetic agents to supplement general anesthesia has been the subject of previous reports. Steinhaus and Howland[1] reported the use of lidocaine administered iv as an adjunct to nitrous oxide–thiobarbiturate anesthesia. They concluded that lidocaine decreased the activity of pharyngeal and laryngeal reflexes. Steinhaus and Gaskin[2] evaluated the effectiveness of lidocaine given iv in suppressing the cough reflexes of anesthetized patients whose tracheas were intubated. Lidocaine prevented cough in eight of ten patients stimulated by manual displacement of the endotracheal tube. They also reported lidocaine to be more effective than a placebo in producing smooth induction of anesthesia with diethyl ether. These studies were performed on anesthetized patients receiving other drugs that might have modified tussive activity. We have evaluated the antitussive effects of clinical doses of lidocaine given intravenously to awake human volunteers using a reliable technique of cough induction.[3–5]

Methods

Ten healthy volunteers 23 to 39 years old (six women and four men) were selected from among medical personnel. None had a history of cardiac or respiratory disease, and all had normal electrocardiograms. Eight subjects were nonsmokers; two smoked less than a pack of cigarettes daily. None of the subjects had a spontaneous cough, and none was taking antitussive medication. This protocol was approved by the Clinical Research Practices Committee, and each subject gave fully informed consent. Resuscita-

* Chief Resident in Anesthesia. Currently, Fellow in Critical Care Medicine, Department of Anesthesiology, University of Florida School of Medicine, Gainesville, Florida 32601.
† Professor of Anesthesia.
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Address reprint requests to Dr. James.

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tion equipment was present during all phases of this study.

Coughing was induced using a modification of a method previously described.[3,5] A contoured breathing mask with attached nebulizer‡ was fitted to the subject's face. The nebulizer, containing one of four concentrations of aqueous citric acid solution, was connected to a wall oxygen source§ by plastic tubing with an interposed Y-piece (fig. 1). Occluding the open port of the Y-piece directed gas flow through the nebulizer; opening the port of the Y-piece halted nebulizer output.

Oxygen flow was arbitrarily set at either 5 or 10 l/min and remained constant for all subsequent studies of each individual. The volunteer was seated comfortably in a quiet room and was instructed to breathe with the mouth open. After 1 min the aerosol was introduced during expiration to fill the mask with nebulized citric acid for the subsequent inhalation. Addition of the aerosol was stopped after five inhalations. Coughs (audible glottic closures) were counted for a 2-min period beginning with the first inhalation of citric acid. This constituted one trial. Following a 3-min rest period the trial was repeated. The results of two consecutive trials were summed and represented one test.

The study proceeded in three phases. First, cough threshold was determined by nebulizing 2 per cent citric acid (wt/vol) solution. When fewer than ten coughs were produced, a 5 per cent solution was substituted, followed in turn by 10 and 15 per cent solutions until a concentration that produced ten or more coughs during the test was found. This was defined as the threshold concentration for the subject. Then a cough baseline was established by determining the response of the subject to repeated challenges with the threshold concentration of citric acid. Each subject completed six tests as described above on each of six different days. Finally, the effect of intravenously administered lidocaine on the baseline cough response for each subject was evaluated. After insertion of an intravenous catheter and with the nebulizer mask positioned as described, lidocaine, 1.5 mg/kg, in a volume of 10 ml, or saline solution, 10 ml, was given iv over 1 min. Lidocaine and saline placebo were administered in a double-blind manner. One minute after completion of injection, the subject was challenged with two trials of five inhalations each of the threshold

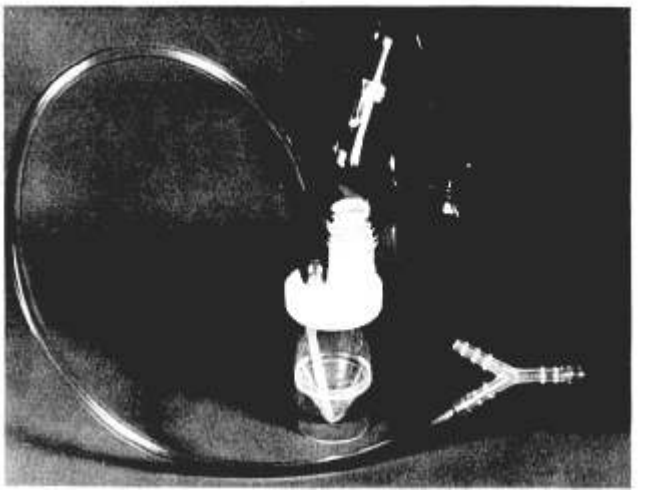

FIG. 1. Occlusion of the open port of the Y-piece directs oxygen flow through the nebulizer.

‡ Mini-Neb® by Inspiron, Upland, California.
§ Oxequip, Model 1497, Flowmeter, Chicago, Illinois.

TABLE 1. Cough Responses to Threshold Concentration of Citric Acid Aerosol before and after Lidocaine and Placebo Administration

	Citric Acid (Per Cent)	Number of Coughs/Test*								Cough Response after Treatment	
		Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Mean	SD	Placebo	Lidocaine (1.5 mg/kg)
Subject 1	10	39	34	30	30	31	32	33	3	38	13
Subject 2	15	26	35	36	35	39	36	35	4	31	17
Subject 3	15	59	53	62	51	59	49	56	5	31	0
Subject 4	15	29	35	26	27	27	28	29	3	22	1
Subject 5†	15	11	14	13	14	13	10	13	2	8	2
Subject 6	5	24	35	29	28	38	35	32	5	22	7
Subject 7	5	21	24	25	26	30	28	26	3	3	1
Subject 8†	5	17	18	17	15	17	17	19	4	15	0
Subject 9	5	24	29	25	27	28	31	27	3	31	8
Subject 10	15	26	36	31	33	28	34	31	4	34	10
GROUPED MEANS								30 ± 11		24 ± 11	9 ± 9‡

* One test = two trials of five consecutive inhalations.
† Smoker.
‡ Significantly lower than mean baseline cough response ($P < 0.01$).

concentration. Forty-five minutes after the first injection the procedure was repeated with the remaining solution.

Data are reported as means ± 1 SD. Means of grouped data were analyzed using the Student t test. $P < 0.01$ was considered significant.

Results

Although there was much variation in threshold concentrations (range 5–15 per cent) and mean baseline cough responses (range 13–56 coughs/test), individual subjects responded consistently (table 1). Every subject had a stable response to the cough stimulus at the time of lidocaine administration. Standard deviations for mean baseline responses were low, ranging from 1.6 to 5.3.

Subjective responses to the intravenous injection of lidocaine were uniform. All subjects experienced tinnitus, and eight of ten also reported lightheadedness or circumoral paresthesias. None lost consciousness or experienced other ill effects. All ten subjects correctly identified the orders in which they had received the test solutions. Injection of lidocaine, 1.5 mg/kg iv, produced readily apparent decreases in the established cough responses in all subjects. There was a significant difference between the mean cough responses during baseline determinations and after lidocaine administration. There was no significant difference between the mean baseline value and the mean response following placebo for the group as a whole ($t = 2.14$).

Discussion

Bickerman *et al.*[3,4] and Berkowitz *et al.*[5] found citric acid aerosol inhalation to be a reliable method for evaluating the cough threshold. Our experience confirms this. All subjects had stable, reproducible cough responses to citric acid.

The conclusions of earlier studies were compromised by the concurrent administration of other drugs that might have possessed antitussive activity. Nevertheless, the importance of preventing cough during recovery from anesthesia for certain neurosurgical and ophthalmologic procedures has made the prophylactic intravenous administration of lidocaine a common practice. Our finding that intravenously administered lidocaine had a significant effect in decreasing the cough responses of awake unmedicated subjects tends to support this practice. The dosage used, 1.5 mg/kg, was less than that used in previous studies, and was not associated with significant adverse effects.

The double-blind design of this study was compromised somewhat by the subjective effects of lidocaine perceived by every subject. Preliminary studies, however, demonstrated it to be impossible for subjects voluntarily to suppress coughs induced by inhalation of the threshold concentration of citric acid. The two subjects (Subjects 5 and 7) who had striking decreases of coughs following both placebo and lidocaine appeared to hyperventilate. We believe that their increased inspiratory flow rates resulted in dilution of the citric acid aerosol by entrainment of air (through mask side ports).

The mechanism by which lidocaine suppresses cough is unknown. Depression of brain-stem function by lidocaine has been shown to occur,[6] and may be responsible. An alternate but less attractive hypothesis is that lidocaine may act by anesthetizing peripheral cough receptors in the trachea and hypopharynx.

We conclude that lidocaine clearly depresses the cough response in doses not associated with significant central nervous system toxicity. Further studies to elucidate the dose–response relationship and to evaluate the effectiveness of lidocaine in the treatment of pathologic cough seem warranted.

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