Nerve Impulse Conduction and Cutaneous Receptor Responses During General Anesthesia

Rudolph H. de Jong, M.D.,* and Roger A. Nace, B.S.†

The effects of ether, methoxyflurane, halothane and nitrous oxide on impulse generation and impulse conduction in the peripheral nervous system were studied in 16 cats. The compound action potential, generated by electrical stimulation of the femoral nerve, was recorded from the nerve's intact saphenous branch. Spike amplitude and integrated output of cutaneous touch receptors likewise were recorded from the saphenous nerve.

General anesthetics had no significant effect on conduction in myelinated (alpha and delta) fibers. Output from cutaneous receptors also was not greatly altered by inhalation anesthetics. Amplitude of non-myelinated (C-fiber) responses decreased slightly during halothane and nitrous oxide administration, and increased slightly when ether or methoxyflurane were given. However, the changes produced in C-fibers were insignificant, and probably of little practical consequence. Thus, inhalation anesthetics—in usual anesthetic concentrations—have no important effect on conduction in the peripheral nerve or on generation of impulses in cutaneous receptors.

The absence of motor responses to peripheral stimulation during anesthesia is usually attributed to depression of the central nervous system. Larrabee and Posternak have shown that anesthetic concentrations of barbiturates, ether and chloroform depress synaptic transmission in autonomic ganglia without affecting axonal conduction in sympathetic fibers. However, it is conceivable that general anesthetics could alter impulse conduction along cutaneous afferent pathways, or reduce the response of cutaneous receptors to natural stimulation. Hence general anesthetics might act by blocking afferent input either along the impulse conducting system or in sensory receptors. This investigation was done to determine whether currently used inhalation anesthetics affect function in the peripheral nervous system.

Methods

Experiments were performed on 16 healthy cats, weighing 2.7 to 4.1 kg., anesthetized intraperitoneally with pentobarbital (30-35 mg./kg.). The trachea was intubated under topical anesthesia. Esophageal temperature was maintained between 37° and 38° C. with a heating blanket. With the aid of surface landmarks, a catheter was advanced via the right femoral artery to the origin of the right common iliac artery. Arterial blood pressure and left fronto-occipital electroencephalogram (EEG) were recorded continuously on a penwriter. Five per cent glucose in lactated Ringer's solution was given intravenously at a rate of 7-10 ml./kg./hour.

The right femoral nerve in the groin and its saphenous branch near the ankle were separately exposed through small incisions, leaving at least 6 cm. of the nerve undisturbed and with circulation intact (fig. 1). At each site, the nerve was placed on bipolar electrodes and immersed in warm (37° C.) mineral oil saturated with 5 per cent CO₂ in oxygen by bubbling. The femoral nerve electrode delivered pulses of 0.1 msec. duration. The distal electrode recorded action potentials and cutaneous receptor impulses in the saphenous nerve. Following preamplification, nerve potentials were displayed simultaneously at fast (1 msec./cm.) and slow (20 msec./cm.) speeds on a dual-beam oscilloscope, and photographed on 35 mm. film.

The area of maximal response to stroking of hairs in the cutaneous receptor field (fig. 1) was stimulated at uniform intensity by a
rotating nylon brush. Receptor-generated potentials at rest and during 5 seconds of mechanical stimulation of the skin were displayed on the oscilloscope and photographed on film moving at 10 mm/sec. Simultaneously, the amplified output was fed to an integrating network and an audio-monitor.

Upon completion of the surgical procedure, neuromuscular conduction was blocked with gallamine (Flaxedil) and the lungs mechanically ventilated with air at a rate of 24 per minute and tidal volume of 12 mL/kg. Ether was given to 4 cats, methoxyflurane and halothane each to 5 cats and nitrous oxide to 2 cats in a nonbreathing system. Nitrous oxide was delivered as a 75/25 mixture with oxygen for 45 to 60 minutes. The volatile anesthetics, vaporized at known temperature in a Copper Kettle, were given in sufficient concentration to cause profound depression of cortical neurons (EEG levels 5 or 6; ether and methoxyflurane). For lack of reliable EEG indications of anesthetic activity, arterial hypotension (to 50 mm. of mercury) was chosen to indicate maximal permissible halothane concentration. Highest inflowing anesthetic concentrations were 15 per cent ether, and 3 per cent methoxyflurane or halothane. The inflowing anesthetic concentration was reduced to maintain EEG burst suppression of 2–5 seconds (ether, methoxyflurane) or arterial pressure of 60–75 mm. of mercury (halothane) for 45 to 90 minutes. The concentration was then further reduced to establish light surgical anesthesia (5 per cent ether, 0.5–1 per cent methoxyflurane, 1 per cent halothane) which was maintained for an additional 45 to 90 minutes. Subsequently, the animal was ventilated with oxygen till recovery of EEG and/or blood pressure.

One of the following procedures, to test nerve function, were done at completion of each experiment: (1) Pentobarbital (10–25 mg./kg.) or gallamine (3–5 mg./kg.) were injected intravenously, (2) 2 ml. of 95 per cent alcohol were injected into the arterial blood supply to the right leg, or (3) nerve responses were recorded for up to two hours after death.

Peak-to-peak amplitude of nerve action potentials (in microvolts) and conduction time (in milliseconds) were measured on magnified film. Conduction velocity, expressed in meters per second, was obtained by dividing conduction distance by conduction time. Amplitudes of alpha, delta and C responses were expressed as percentages of their respective control values. The stepwise linear regression relating anesthetic concentration or time to C-wave amplitude was calculated (BMD program 02R) and the data were plotted (XTAB program B-6) by a digital computer. Mean experimental values were compared with control amplitude (t-test; paired comparison).

Results

Controls. The compound action potential recorded from the saphenous nerve consisted of three distinct groups of waves. Responses were identified, according to their conduction velocity, as representing alpha fibers (86.7 ± 4.8 m./sec.), delta-fibers (20.3 ± 0.7 m./sec.), and C-fibers (1.33 ± 0.02 m./sec.). These values agree closely with those obtained by others.2, 3, 4

The resting activity of cutaneous receptors responding to touch and movement of hair consisted of a continuous discharge of sharp spikes of 20–50 μV. amplitude. The resting rate of firing remained constant as long as
blood pressure was greater than 40-50 mm. of mercury. Stroking the skin within the cutaneous receptor field sharply increased the firing rate and increased the amplitude of the discharge by 50 to 300 per cent.

For technical reasons, receptor discharges could be integrated electronically only with higher amplitude spikes (obtained in six experiments). Integrator output was used to provide a measure of both spike amplitude and frequency. Receptor output during cutaneous stimulation was 4 to 17 times greater than resting baseline level.

**Experimental Findings.** Amplitude of alpha and delta waves was not significantly changed, even when EEG and/or blood pressure were profoundly depressed. Alpha potentials remained within ± 5 per cent and delta potentials within ± 10 per cent of control value, irrespective of anesthetic concentration.

Inhalation anesthetics had a more pronounced effect on amplitude of the C-wave, which ranged between 60 and 150 per cent of control value. The computed regression line relating amplitude to concentration consistently showed (not illustrated) a falling trend of C-wave amplitude with increasing anesthetic concentration. But the correlation was not significant \( P \geq 0.1 \). The regression of amplitude on time showed a small rising trend in C-wave amplitude as time progressed. But the correlation was not significant \( P > 0.1 \), except for ether \( P < 0.05 \).

A significant change in mean pooled experimental C-wave amplitude was seen only with ether \( P < 0.05 \); it amounted, however, to no more than a 5 per cent increase (table 1). The results with ether (fig. 2) are noteworthy since older reports have described a profound depressant effect of ether in vitro. Corresponding findings were obtained for the other anesthetics (figs. 3 and 4).

The resting level of receptor spike potentials during anesthesia varied within 20 per cent of control value; in view of the

### Table 1. Experimental Values

<table>
<thead>
<tr>
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<th>Ether</th>
<th>Methoxyflurane</th>
<th>Halothane</th>
<th>Nitrous oxide</th>
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<tbody>
<tr>
<td>C-wave Amplitude (percent control ± S.D.)</td>
<td>104.6 ± 12.0</td>
<td>99.7 ± 16.0</td>
<td>98.2 ± 8.5</td>
<td>98.2 ± 8.5</td>
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<tr>
<td>Concentration (percent)</td>
<td>11.3</td>
<td>1.5</td>
<td>2.1</td>
<td>75.0</td>
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Mean experimental C-wave amplitude for n observations. Average inflowing anesthetic concentration is shown in last column.

**Fig. 2.** Scattergram of C-wave amplitude (percentage control) versus inflowing concentration of ether. Open squares represent mean amplitude for each concentration. The downward trend of amplitude with increasing ether concentration was not significantly different from control.

**Fig. 3.** Scattergram of C-wave amplitude (percentage control) versus inflowing concentration of methoxyflurane. Open squares represent mean amplitude at the specific concentration. The downward trend of amplitude with increasing methoxyflurane concentration was not significantly different from control.
Fig. 4. Scattergram of C-wave amplitude (percentage control) versus inflowing concentration of halothane. Open squares represent mean amplitude at the specific concentration. The decrement in amplitude with increasing halothane concentration was borderline significant ($P < 0.1$), though obviously small.

low initial amplitudes, this was an unimportant change. Receptor responses to cutaneous stimulation (which excites delta and faster-conducting C-fibers) also were not obviously affected by anesthetics. The integrated output from cutaneous receptors fluctuated considerably between $-30$ and $+50$ per cent. There was a small rise in output— independent of anesthetic concentration— with time, which persisted after recovery from the anesthetic.

Circulation to Nerve. The lack of appreciable changes in nerve and receptor responses made it necessary to ascertain whether bloodborne anesthetic actually reached the nerve. Intact arterial circulation was conclusively demonstrated by the almost instantaneous extinction of nerve potentials when alcohol was injected into the artery supplying the right leg.

The effect of severe hypotension on nerve responses was checked by inducing circulatory arrest. The alpha potential started to fall within 20 to 30 minutes and disappeared at 75 minutes. The delta potential fell to 50 per cent of control at 30 minutes and disappeared at 40 to 45 minutes. The C-fibers were much more resistant to anoxia; their action potentials remained unchanged for up to 60 minutes, and were still 40 per cent of control after 120 minutes. The integrated cutaneous receptor response fell to one-half within 10 minutes of circulatory arrest, and disappeared in 40 to 60 minutes. Finally, neither pentobarbital nor gallamine, given intravenously, altered nerve responses.

Discussion

We have shown that ether, methoxyflurane, halothane and nitrous oxide depress neither impulse conduction in a peripheral nerve (including non-myelinated axons) nor cutaneous receptor activity. Early studies $^5,^7$ indicated that ether produced a profound depolarizing conduction block in invertebrate nerve. Subsequently, on mammalian nerve, ether was found to produce conduction block in vivo only if given in near lethal doses.$^8$ This observation was substantiated for ether, as well as for chloroform and pentobarbital, by Larrabee and Posternak.$^1$ These authors found that anesthetics, administered at normally used anesthetic concentrations, did not block conduction in mammalian autonomic axons. We have been unable to find reports dealing with the effect in vivo of fluorinated anesthetics on the peripheral nervous system.

The anesthetic concentration in nerve tissue was not measured, but nerve is probably only a moderately well-perfused tissue. Thus, especially with the more soluble agents (methoxyflurane and ether) the drug concentration in nerve initially will be less than the inspired anesthetic concentration, slowly approaching the latter with time. Since the C-wave amplitude increased somewhat (though not significantly) as time progressed, it is unlikely that axonal conduction would be significantly depressed upon reaching equilibrium.

Other factors that could have affected our results were the use of pentobarbital for anesthesia, and the inevitable hypotension associated with deeper levels of inhalation anesthesia. We feel reasonably certain that the light pentobarbital anesthesia used here had no influence, since the evidence indicates that—at anesthetic concentrations—pentobarbital has no demonstrable effect on impulse con-
duction. Moreover, the intravenous injection of large (up to 120 mg.) doses of pentobarbital had, in our experiments, no effect on either impulse conduction or receptor activity.

Since alpha and delta potentials, as well as receptor discharges, were unchanged even when arterial blood pressure had decreased to 50 mm. Hg, we believe that hypotension played at most a minor role. Nerve perfusion remained adequate during hypotension, since the intraarterial injection of alcohol caused a rapid fall-out of nerve potentials.

Whereas a distinct receptor response to noxious stimulation of the skin could not be obtained, we have shown that cutaneous receptors responding to touch and movement of hair are not affected by inhalation anesthetics. Whether these findings apply equally to nociceptors we do not know. In view of the minimal changes in fine non-myelinated fibers and in cutaneous touch receptors, we presume that these anesthetics have little effect on free cutaneous nerve endings.

We conclude that—when used in their usual anesthetic concentrations—ether, methoxyflurane, halothane and nitrous oxide have little or no effect on axonal conduction and cutaneous receptor responses.

Summary and Conclusion

In studies on the effects of ether, methoxyflurane, halothane and nitrous oxide on the peripheral nervous system in 16 cats, the compound action potential of the intact saphenous nerve was elicited by electrically stimulating the femoral nerve. Alpha and delta potentials remained at approximately constant amplitude during anesthesia. Amplitude of the C-potentials showed greater individual variation during anesthesia. Nevertheless, the only significant change was a 5 per cent increase during ether administration. Amplitude and frequency of firing of cutaneous receptors responding to touch and stroking of hairs was little altered by anesthetic administration.

We conclude that general anesthetics have no physiologically significant effects on impulse generation or impulse conduction.

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References