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Tolerance to and Dependence on Inhalational Anesthetics

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Mice continuously exposed to nitrous oxide, 50 per cent, for two to three weeks become tolerant to anesthesia, as evidenced by an increase in the concentration of nitrous oxide necessary to abolish the righting reflex from 1.49 ± 0.045 atm to 1.67 ± 0.053 atm after three weeks (auto-tolerance). Also, there was an increase in the concentration of a second anesthetic (cyclopropane or isoflurane) necessary to abolish the righting reflex (cross-tolerance). Cyclopropane ED_{50} increased from 0.130 ± 0.0068 atm to 0.148 ± 0.0044 atm after two weeks of exposure to nitrous oxide, 50 per cent. Isoflurane ED_{50} increased from 0.00570 ± 0.000163 atm to 0.00622 ± 0.000200 atm after three weeks of exposure to nitrous oxide, 50 per cent. Mice continuously exposed to isoflurane, 0.15 or 0.3 per cent, manifested neither auto- nor cross-tolerance. After three weeks of exposure, 69 per cent of mice removed from nitrous oxide, 50 per cent, convulsed when gently suspended by the tail (*i.e.*, manifested a stimulus-elicited withdrawal syndrome indicating dependence on nitrous oxide). After three weeks of exposure, 43 per cent of mice convulsed when removed from isoflurane, 0.15 per cent. However, only 4 per cent of mice convulsed after six or nine weeks of exposure to this concentration of isoflurane. (Key words: Anesthetics, gases: isoflurane; nitrous oxide. Potency: dependence; ED_{50}; tolerance.)

THE DEVELOPMENT of tolerance to any drug is usually followed by the appearance of withdrawal symptoms (*i.e.*, dependence) upon its discontinuation.[1] Concomitant development of tolerance and dependence occurs with ethanol,[2] barbiturates,[3,4] meprobamate[5,6] and phenaglycodol.[5,7] Of interest to the anesthesiologist is the possibility that cross-tolerance between or among various depressant drugs and anesthetics might occur.[8–12] Cross-tolerance implies that a higher-than-usual concentration of the anesthetic would be necessary to produce anesthesia. Not all depressant drugs show cross-tolerance with anesthetics. Lee *et al.* were unable to show consistent cross-tolerance between ethanol, morphine, or methohexital and diethyl ether, methoxyflurane, or Innovar®.[13] Recently, however, Johnstone *et al.* demonstrated that mice given ethanol for 20 days developed cross-tolerance to isoflurane that persisted for 55 days after discontinuation of ethanol administration.[14]

No study examining the development of tolerance or dependence with inhaled anesthetics themselves has been reported. A finding of tolerance or dependence would be of interest because the pharmacokinetic (dispositional) aspect of tolerance can easily be dissociated from functional (central nervous system) tolerance with these agents, *i.e.*, the inhaled concentration can be held constant so that lowering of brain levels by, for example, increasing hepatic metabolism (dispositional tolerance) can be obviated. Since alcohol, barbiturates, tranquilizers, and general anesthetics have many similar effects on model membrane systems,[15] studies of tolerance and dependence with inhaled anesthetics might yield new insight into the mechanism of anesthetic action and also provide information useful to understanding the tolerance and dependence found with other central nervous system depressants.

We report herein the effects of chronic exposure to subanesthetic concentrations of inhaled anesthetics on subsequent anesthetic requirements and on the development of dependence similar to that seen following alcohol or barbiturate withdrawal in mice.

Methods

We exposed adult ICR mice (Simonsen Laboratories) weighing 23–27 g to either nitrous oxide or isoflurane. Control animals were exposed to air in otherwise similar environments. After exposure, we measured the amount of the same or a different agent needed to abolish the righting reflex in 50 per cent of the animals compared with controls.

Two 225-l environmental chambers were used. Louvred shelves were installed in the chambers to ensure adequate gas movement inside. Chamber gases were circulated through carbon dioxide absorbent, then through thermoelectric cooling devices to remove water vapor and to maintain the desired temperature. The temperatures of the two chambers were maintained within 1 degree C of each other. Fresh gas flowed into each chamber through a separate orifice remote from the circulating system. Filtered room air was compressed with a blower and oxygen and nitrous oxide were provided from tanks. Isoflurane was added from a temperature–flow-compensated vaporizer. An extractor fan was attached to the chamber via a large-diameter stop valve so that the chamber contents could be vented without exposing laboratory personnel to

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anesthetics when the chambers were opened. Two sampling ports were provided; one to obtain the inflowing gas composition and another to determine chamber gas composition. Gas samples were drawn through the sampling ports into a carbon dioxide or halothane analyzer (Beckman LB2). The halothane analyzer is sensitive in both nitrous oxide and isoflurane. The output of the latter was coupled to a Grass chart recorder so that the concentration of anesthetic in the chamber could be monitored continuously.

A high flow rate of nitrous oxide, 75 per cent, and oxygen, 25 per cent, increased the partial pressure of nitrous oxide to the desired level in 10–15 min. As soon as the chamber reached the desired concentration, the rate of the gas flow, composed of nitrous oxide, oxygen, and the balance nitrogen to maintain the nitrous oxide concentration at the deisred level, was decreased to 1.8 l/min^{-1}. Oxygen was maintained at 25 per cent and carbon dioxide at less than 0.5 per cent. The partial pressure of isoflurane was increased rapidly to the desired level by injecting a calculated amount of liquid agent into the circle absorber system. The inflowing oxygen and air were adjusted in both chambers to maintain oxygen, 25 per cent, with the balance anesthetic or nitrogen.

Mice were housed in the environmental chambers in clear plastic cages with a non-resinous bedding material (Absor-Dri® or corn cob). Food and water were provided *ad libitum*. During the twice-weekly cage changes, the mice spent a maximum of 45 min in air before returning to the chambers.

At the end of the chronic-exposure period the dose–response relationship for loss of the righting reflex was determined by placing the mice in a 20-l stainless-steel pressure chamber. Eight unrestrained mice were placed in individual wire mesh cages in a rotator that could be turned in either direction at 4 rpm, to observe the righting reflexes. Chamber temperature was adjusted to maintain rectal temperatures of two additional restrained mice at 36.5–38 C. The times taken to remove mice from the subanesthetic exposure in the environmental chamber, transport them to the pressure chamber, load them in, and begin the first dose in the pressure chamber averaged 35–40 min, so we standardized the times to 45 min in all studies. The brain concentration of nitrous oxide would be essentially zero after this period of time.

For nitrous oxide ED_{50} determinations, the chamber was flushed with oxygen and then nitrous oxide was introduced. An initial equilibration period of 30 min was allowed after the first exposure, and 15 min were allowed after subsequent stepwise additions of nitrous oxide. ED_{50} values for cyclopropane were determined by adding cyclopropane in a stepwise manner to a mixture of oxygen, 33 per cent, and helium, 67 per cent, in the pressure chamber (*i.e.*, the oxygen partial pressure was 0.33 atm). Helium rather than nitrogen was used to decrease the risk of fire. Equilibration times were the same as for nitrous oxide. ED_{50} values for isoflurane were determined by continuously passing anesthetic vapor in oxygen through the pressure chamber at ambient pressure. To increase the concentration in the chamber rapidly to each new dose level, the inflowing gas was held at a higher concentration for a few seconds. An equilibration period of 60 min was allowed for the initial exposure, and 30 min were allowed for subsequent additions. Four to six concentrations of each agent were used in the assessment of ED_{50}. With all agents used, chamber gas samples were drawn before each measurement of the righting reflex and analyzed by gas chromatography. With cyclopropane the oxygen partial pressure always remained between 0.2 and 0.33 atm.

Animals that fell over two or more times during a sequence of five cage revolutions failed the righting-reflex test. Logit analysis was used to determine the ED_{50} and standard error from the quantal responses.[16]

A test of withdrawal (dependence) was made 15 min after the mice came out of the environmental chamber following their chronic exposure and again 15 min after removal from the acute anesthetic exposure in the pressure chamber. Our test was based on that described by Goldstein and Pal.[17] The mouse was lifted gently by the tip of its tail. A positive withdrawal syndrome was characterized by grimacing, forward-pointing ears, crossed forepaws, and violent jerking and twirling.[17] We did not attempt to ascertain more than this quantal response, although it was obvious that the response varied in degree: some animals experienced continuing clonic–tonic seizures when returned to their cage.

Five groups of mice were exposed to nitrous oxide, 50 per cent, as follows: Group 1, one day; Group 2, six days; Group 3, 14 days; Groups 4 and 5, 21 days (table 1). Groups 1, 2, and 4 were subsequently tested to determine ED_{50} value for nitrous oxide. Animals in Group 4 were returned to air for seven days and then retested with nitrous oxide (group 4B). Group 3 was tested to determine cyclopropane ED_{50} values. Group 5 was tested for isoflurane ED_{50} values. Group 6 was exposed to nitrous oxide, 40 per cent, for 21 days, and the nitrous oxide ED_{50} value then determined. Group 7 was exposed to isoflurane, 0.3 per cent, for 21 days, and the isoflurane ED_{50} value determined. Group 8 was exposed to isoflurane, 0.15 per cent, for 21 days, and the ED_{50} value determined. These animals then were returned to isoflurane, 0.15 per cent, for a further 21 days, and the ED_{50} value redetermined after a total of 42 days in isoflurane, 0.15 per cent. Following this, they again were returned to isoflurane,

TABLE 1. ED_{50} Values ± SE for Loss of Righting Reflex in Control Mice and Mice Exposed to Subanesthetic Concentrations of Anesthetic Agents

	Exposure Time (Days)	Experimental Subanesthetic Concentration (Per Cent atm)	ED_{50} Tested with	Control		Experimental		Percentage Change in ED_{50} (Δ)
				ED_{50} ± SE (atm)	n	ED_{50} ± SE (atm)	n	
Group 1	1	50 per cent N_2O	N_2O	1.52 ± 0.083	8	1.47 ± 0.124	8	Δ = −3
Group 2	6	50 per cent N_2O	N_2O	1.46 ± 0.148	7	1.51 ± 0.083	8	Δ = +3
Group 3	14	50 per cent N_2O	cC_3H_6	0.130 ± 0.0068	16	0.148 ± 0.0044	16	Δ = +14*
Group 4a	21	50 per cent N_2O	N_2O	1.49 ± 0.045	27	1.67 ± 0.053	29	Δ = +12*
Group 4b	(4a) + 7 = 28	Air	N_2O	1.46 ± 0.056	19	1.51 ± 0.049	21	Δ = +3
Group 5	21	50 per cent N_2O	Isoflurane	0.00570 ± 0.000163	32	0.00622 ± 0.000200	32	Δ = +9*
Group 6	21	40 per cent N_2O	N_2O	1.43 ± 0.064	16	1.59 ± 0.088	16	Δ = +11
Group 7	21	0.3 per cent isoflurane	Isoflurane	0.00572 ± 0.000230	32	0.00610 ± 0.000246	31	Δ = +7
Group 8a	21	0.15 per cent isoflurane	Isoflurane	0.00536 ± 0.000450	28	0.00582 ± 0.000360	28	Δ = +9
Group 8b	(8a) + 21 = 42	0.15 per cent isoflurane	Isoflurane	0.00645 ± 0.000261	28	0.00659 ± 0.000256	28	Δ = +2
Group 8c	(8b) + 21 = 63	0.15 per cent isoflurane	N_2O	1.49 ± 0.044	28	1.52 ± 0.049	26	Δ = +2

* $P < 0.05$.

0.15 per cent, for yet another 21 days (63 days total), after which the nitrous oxide ED_{50} value was determined.

Results

The results showed that in mice, chronic exposure to nitrous oxide, 50 per cent, can produce auto-tolerance to nitrous oxide or cross-tolerance to cyclopropane or isoflurane in 14 to 21 days (table 1). Mice tolerant to nitrous oxide, 50 per cent, after 21 days lost this tolerance after seven days in air. Forty per cent nitrous oxide for 21 days did not cause significant tolerance. Neither isoflurane, 0.3 per cent, for 21 days, not isoflurane, 0.15 per cent, for 21 to 63 days, produced measurable auto-tolerance or cross-tolerance to nitrous oxide.

The ED_{50} values for loss of righting reflex in the control mice in Groups 1, 2, 4a, 4b, 6, and 8c revealed a high degree of consistency. The mean ED_{50} over six determinations was 1.48 ± 0.03 atm (n = 86), *i.e.*, a standard deviation of ±2 per cent. The isoflurane ED_{50} values in the control mice in Groups 5, 7, and 8a–8b gave a mean of 0.00565 ± 0.000162 atm (n = 92), *i.e.*, standard deviation of ±3 per cent. The isoflurane ED_{50} value was the same (0.0057 ± 0.00115 atm) as that reported by Kent *et al.*[18] Although reproducibility is generally good, the importance of a control peer group is indicated by the results in Group 8b, where both experimental and control animals showed substantial increases in isoflurane ED_{50} values over Group 8a. Whatever the source of this variation, it certainly was not associated with our attempts to produce tolerance in the experimental animals.

The mortality rates were 3 of 167 in both control and experimentally exposed groups of animals. However, Group 7 mice, in isoflurane, 0.3 per cent, ate little, lost weight, and spent much time sleeping. Body weights were maintained in all other groups.

The percentages of control or experimental animals convulsing 15 min after leaving the environmental chambers are shown in table 2 as "pre-ED_{50}." The percentages convulsing 15 min after the ED_{50} determination are shown as "post-ED_{50}." Only one control mouse convulsed before the ED_{50} determination. Experimental mice in Groups 1 through 4a, exposed to nitrous oxide, showed variable incidences of the stimulus-elicited withdrawal syndrome. Nitrous oxide, 40 per cent (Group 6), produced a lower percentage of convulsions than did nitrous oxide, 50 per cent (Group 4a). The appearance of convulsions was also variable in the isoflurane-exposed mice, although the higher dose produced more dependence than did the lower dose. Incidences of withdrawal convulsions 15 min after the ED_{50} determination with either nitrous oxide or cyclopropane were high in both control and experimental animals in Groups 1 through 4b, 6, and 8c. Conversely, after ED_{50} determination with isoflurane (Groups 7, 8a, and 8b) the incidence of convulsions were virtually unchanged in both control and experimental mice. The number of animals in Group 4b was smaller than that in Group 4a because some animals were accidentally discarded before testing.

Discussion

We found that nitrous oxide, 50 per cent, given to mice for 21 days produced significant tolerance to nitrous oxide, and for 14 days, produced cross-tolerance to the ability of both cyclopropane and isoflurane to impair the righting reflex. A high incidence of a stimulus-elicited withdrawal syndrome develops concomitantly with this tolerance. Conversely, a low incidence of stimulus-elicited withdrawal is observed

TABLE 2. Percentages of Mice Showing Stimulus-elicited Withdrawal Syndrome (Convulsions) 15 Min after Chronic Exposure to Subanesthetic Concentrations of Anesthetic Agents Compared with Controls (Pre-ED_{50}) and 15 Min after a Subsequent ED_{50} Determination Compared with Controls (Post-ED_{50})

	Exposure Time (Days)	Experimental Subanesthetic Concentration (Per Cent atm)	ED_{50} Tested with	Control Mice			Experimental Mice		
				Pre-ED_{50} (Per Cent)	Post-ED_{50} (Per Cent)	n	Pre-ED_{50} (Per Cent)	Post-ED_{50} (Per Cent)	n
Group 1	1	50 per cent N_2O	N_2O	0	88	8	25	63	8
Group 2	6	50 per cent N_2O	N_2O	0	86	7	0	25	8
Group 3	14	50 per cent N_2O	cC_3H_6	0	81	16	63	94	16
Group 4a	21	50 per cent N_2O	N_2O	0	85	27	69	97	29
Group 4b	(4a) + 7 = 28	Air	N_2O	5	58	19	5	62	21
Group 5	21	50 per cent N_2O	Isoflurane	No assay of withdrawal behavior					
Group 6	21	40 per cent N_2O	N_2O	0	88	8	13	100	8
Group 7	21	0.3 per cent isoflurane	Isoflurane	0	0	32	67	73	31
Group 8a	21	0.15 per cent isoflurane	Isoflurane	0	7	28	43	18	28
Group 8b	(8a) + 21 = 42	0.15 per cent isoflurane	Isoflurane	0	0	28	4	0	28
Group 8c	(8b) + 21 = 63	0.15 per cent isoflurane	N_2O	0	93	28	4	92	26

when there is no tolerance, as in Groups 2, 4b, 8b, and 8c. However, in several instances moderately high incidences of convulsions occurred without tolerance, as in Groups 1, 6, 7, and 8a. Thus, we cannot say unequivocally that tolerance and dependence occur concomitantly, nor can we say that they are separate occurrences. The high incidences of stimulus-elicited withdrawal in both control and experimental mice after an ED_{50} test with nitrous oxide or cyclopropane suggested that, in addition to producing chronic tolerance (*i.e.*, tolerance after repeated or very long exposures), nitrous oxide might also produce an acute tolerance (tolerance during the first few minutes of the exposure period). Tolerances that developed to a maximum during the first 10 min of exposure were found for nitrous oxide and for ethylene combined with helium.[19] Similar parallel developments of tolerance and dependence have been demonstrated for ethanol,[2] barbiturates,[3,4] meprobamate,[5,6] phenaglycodol,[5,7] and tranquilizers.[20,21]

Tolerance to the analgesic effect of continuous nitrous oxide therapy for the treatment of intractable pain has been observed.[11] Whitwam *et al.* also found acute tolerance to the analgesic effect of nitrous oxide in some subjects during a short exposure.[22] Diving lore contains many subjective reports of adaptation to nitrogen narcosis, especially after long and frequent dives.[23] Langley *et al.* used somatic-evoked brain responses to make an objective assessment of such tolerance, but found only slight evidence for adaptation.[24]

The increase in the ED_{50} produced by exposure to nitrous oxide averaged 0.18 atm. Since these mice were exposed to 0.5 atm nitrous oxide, it is clear that the tolerance was incomplete (*i.e.*, the increase in the ED_{50} was less than 0.5 atm nitrous oxide). Mice exposed for longer times might show greater tolerance, although we found no significant difference between the effects of a two-week and a three-week exposure on cross-versus auto-tolerance.

Finck *et al.*[25] have shown that dose-related analgesia in the rat can be antagonized by naloxone. Thus, nitrous oxide-induced analgesia could be mediated via the release of endogenous opiate-like compounds, and the tolerance to nitrous oxide could be comparable to tolerance to opiates. However, naloxone has no effect on the ED_{50} of nitrous oxide necessary to abolish the righting reflex in mice[26] or on the ED_{50} of halothane needed to abolish the righting reflex in rats.[27] Furthermore, halothane MAC in rats was unchanged by large doses of naloxone.[28] Since we have used the ED_{50} for loss of the righting reflex to measure anesthesia, we cannot assume that the mechanism causing tolerance to nitrous oxide is similar to or related to that causing tolerance to opiates.

Several mechanisms might cause the augmentation of central nervous system activity that produces tolerance. For example, an increase in the number or size of quanta of neurotransmitters released at an excitatory synapse, a decrease in the rate of reuptake of transmitter, or a decrease in the rate of transmitter destruction each might increase neurotransmission. Alternatively, the system could respond by increasing the number of available receptor sites or the affinity for transmitter at the receptor. Since nitrous oxide may fluidize membranes, an opposing response might "stiffen" the membrane. This might be accomplished by incorporating longer-chain fatty acids, nonsaturated fatty acids, or cholesterol into the lipid matrix of the membranes. Such a response would be limited by the ability of adult mice to incorporate new lipids into neuronal membranes.

Our inability to produce tolerance to isoflurane may limit the general applicability of our findings with nitrous oxide. This inability may have been due to variability in response rather than an absence of tolerance. As shown in table 1, the average ED_{50} value for isoflurane did increase after chronic exposure, and this increase was 50 to 60 per cent of the maximum tolerance developed with chronic exposure to nitrous oxide. However, the variance associated with this increase was large enough to preclude significance.

The failure to find tolerance was not the result of the use of a lower dose of isoflurane. We used half the ED_{50} of isoflurane, compared with a third the ED_{50} of nitrous oxide. Similarly a 42-day exposure at a fourth the ED_{50} of isoflurane was insufficient to produce auto-tolerance. Even after 63 days' exposure cross-tolerance was not observed. Despite this inability to find tolerance, our withdrawal studies indicated that some dependence developed, especially in mice exposed to the higher concentration. However, at the lower concentration dependence seemed to disappear as exposure time increased, whereas the reverse would be expected. Thus, we place little weight on the incidence of withdrawal convulsions in the mice exposed to isoflurane, 0.3 per cent, because, as mentioned above, they were underweight and almost certainly dehydrated. We therefore feel that tolerance and dependence to isoflurane do not develop, or at least, that only slight dependence develops, without tolerance.

Our study has demonstrated, for the first time, a small but significant auto- and cross-tolerance to a gaseous anesthetic that is similar to the tolerance seen with sedative–hypnotic compounds. Moreover, this tolerance is accompanied by a withdrawal syndrome, although a withdrawal syndrome was also seen in some animals that had not become tolerance. These effects may not be applicable to other inhalational anesthetics, although more experiments must be performed before this can be considered well established. The differences between the two agents we have studied may give important clues to the mechanisms of anesthetic tolerance and dependence.

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