Title: TOLERANCE AND CROSS TOLERANCE TO HALOTHANE, ISOFLURANE AND ENFLURANE

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Introduction. Smith et al. have shown[1] that mice exposed to nitrous oxide for prolonged periods developed a tolerance to this agent. Cross tolerance was noted with cyclopropane and isoflurane. They had previously shown[2] that the animals convulsed when withdrawn from nitrous oxide, but not from halothane, isoflurane, or enflurane. Because these volatile anesthetics are frequently used, we have attempted to assess murine tolerance to each and cross tolerance between them.

Methods. Eighteen white Swiss Webster mice and 18 brown dominant mice (Jackson) were divided into 3 groups. Every group included 6 white and 6 brown mice. One group received halothane, one isoflurane, and one enflurane, each in oxygen at a flow rate of 5 l/min. Each mouse was placed in a cage rotating 3 times/min[1], into which anesthetic was introduced. Anesthetic concentration, which was begun at 0.5% was increased by 0.25% every 15 minutes until the mouse lost its righting reflex (RR). Anesthetic concentration was confirmed by an Engström Emma Analyzer. The number of mice which lost RR at each anesthetic concentration per group was noted. During the next 2 days, each group was exposed for 30 minutes, in a nonrotating cage, to its allotted anesthetic, at a concentration 25% higher than that noted for its most tolerant mice. The following day, they were retested in the rotating cage. There were a total of 5 exposures in the rotating cage and 8 in the immobile cage. Performance of white and brown mice was compared. At the end of the experiment, cross tolerance was assessed by exposing 6 mice (3 white and 3 brown) from one anesthetic group to one of the other anesthetics. The concentration at which the mice lost RR was noted. It was then compared to the concentration at which the mice without previous exposure had lost RR in that anesthetic. Potential occurrence of convulsions was noted on withdrawl from anesthesia. Statistical significance was assessed by the Chi Square method using the Yates correction factor for small numbers. Values of $P < 0.05$ were considered significant.

Results. Enflurane mice convulsed during anesthesia. There were no withdrawl convulsions. There was no significant difference between the performance of white and brown mice. All mice exposed to halothane (table) initially lost RR at 1%, however, by day 13, 11 were still awake at this concentration ($P < 0.005$). Eleven out of 12 mice initially exposed to isoflurane lost RR at 1%, but by day 13, only 4 of them lost RR at this concentration ($P < 0.005$). All mice originally exposed to enflurane lost RR at 1.5%, however, by the 13th exposure, 8 out of 12 retained RR at that concentration ($P < 0.005$). There was no cross tolerance between mice exposed to halothane and enflurane. Mice exposed to isoflurane exhibited no cross tolerance to halothane. However, after 13 halothane exposures, mice were more tolerant to isoflurane than mice originally exposed to isoflurane. Only 2 out of 6 halothane mice lost RR in 1% isoflurane, but 11 out of 12 original isoflurane mice lost RR at 1% ($P < 0.005$). Mice exposed to isoflurane or enflurane exhibited tolerance to each other. Ten out of 12 mice originally exposed to enflurane lost RR at 1.25%, while 2 out of 6 exposed 13 times to isoflurane lost their RR when placed in 1.25% enflurane ($P < 0.01$). Conversely, 11 out of 12 mice originally exposed to isoflurane lost RR at 1%, while all mice which had been exposed 13 times to enflurane were awake when placed in 1% isoflurane ($P < 0.0005$).

Discussion. The two way cross tolerance between isoflurane and enflurane may presumably be explained because they are both ethers. The lack of cross tolerance between halothane and enflurane may be due to their different chemical composition (an alkyl halide and an ether, respectively). Although halothane has a higher lipid solubility than enflurane, the latter has convulsive properties. This may explain the lack of cross tolerance between halothane and enflurane. The cross tolerance from halothane to isoflurane (but not isoflurane to halothane) is probably due to the higher lipid solubility of halothane.

References.

1. Smith RA, Winter, PM, Smith M, Eger, EI, II: Tolerance and dependence on inhalation anesthetics. Anesthesiology 50: 505-509, 1979.

2. Smith RA, Winter, PM, Smith M, Eger, EI, II: Convulsions in mice after anesthesia. Anesthesiology 50: 501-504, 1979.

ANESTHETIC	CONC.	EXPOSURE				
		1st	4th	7th	10th	13th
HALOTHANE	1	12	10	7	1	1
	1.25	0	2	5	10	10
	1.5	0	0	0	1	1
ISOFLURANE	0.75	2	0	0	0	0
	1	9	9	7	5	4
	1.25	1	3	5	7	8
	1.5	0	0	0	0	0
ENFLURANE	1	2	0	0	0	0
	1.25	8	9	3	1	1
	1.5	2	2	6	8	3
	1.75	0	1	3	3	8

Table: Number of mice which lost their righting reflexes at each anesthetic concentration, as number of exposures increased. Conc = percent anesthetic in oxygen delivered at a rate of 5 l/min.