Title: ISOFLURANE vs HALOTHANE: SAFETY MARGINS

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Introduction. As anesthesiologists take a more active role in controlling the circulation through pharmacologic means, they become progressively less fearful of the cardiovascular depression inherent in anesthesia.[1] Nevertheless, the relative margins of safety, the whole depth of which can be measured only in animal experiments, remain an important factor in comparing anesthetic agents. The aim of the present study was to compare the cardiovascular safety margins for isoflurane and halothane.

Methods. In 305 Sprague-Dawley rats (300-350 g), dose-response curves for three different end-points of anesthesia, severe hypotension and lethal effect (due to cardiovascular failure) were determined with isoflurane and halothane. The following end-points of anesthesia were used: loss of righting reflex (RR); prevention of purposeful movement response to a noxious stimulus (PM); prevention of the rise in heart rate in response to a noxious stimulus (HR).[2] End-point for severe hypotension was 50 mmHg in femoral artery (AP), and for lethal effect - 7 mmHg (static pressure) with artificial ventilation (LD). The rats were anesthetized in a special chamber. The anesthetics were vaporized in a Draeger vaporizer (O_2 carrier) and their level in the chamber was monitored with an Engstrom Emma gas analyzer (for the high concentrations of isoflurane, a copper kettle was used). Each rat was exposed to only one predetermined concentration of the anesthetic for 30 min (at rectal t° 37°C), then presence or absence of the end-point was determined, the rat was killed, the whole brain homogenized and anesthetic concentration in it measured.[3] For severe hypotension and lethal end-points, rats were tracheotomized and ventilated through an endotracheal device inserted into a tracheostomy.

With each of the agents, five series of experiments were performed according to the number of end-points. In each series of experiments, five - six groups of animals (5-7 rats in a group) exposed to various concentrations of the agent were used. Determination of the dose-response curves for the chosen end-points was based on brain anesthetic concentration (logit analysis) and on their inspired concentration (probit analysis).

Results. Inspired concentration-response curves corresponded to the brain concentration-response curves. Median points of the obtained dose-response curves (for inspired concentrations) are presented in the Table. The degree of separation between doses producing the loss of RR, prevention of PM response or HR response were similar for isoflurane and halothane. HR ED50/RR ED50 was 3.6 for isoflurane and 3.3 for halothane. At the same time, the margin between the highest of anesthetic doses - the loss of HR response - and the lethal dose was greater for isoflurane than for halothane (LD 50/HR ED50 was 4.3 vs. 2.2, $p < 0.01$). The margin between the dose causing severe hypotension and lethal dose was also greater for isoflurane than for halothane (LD 50/AP ED50 was 1.7 vs. 1.1, $p < 0.02$). Since safety margins best reflect safety when a dose producing anesthetic effect in almost all exposed animals is compared with a dose that may cause death in a minimal number of animals, we used standard safety margin (SSM = (LD5-ED95)/ED95 x 100). The SSM for the loss of HR response was greater with isoflurane than with halothane (142 vs 43, $p<0.05$). This data confirms previous observation that isoflurane is safer than halothane.[3]

Conclusion. Isoflurane provides the degree of separation between dose-response curves for different end-points of anesthesia comparable to halothane. At the same time, it has greater margins of anesthetic safety.

Table

ED50 of isoflurane and halothane for different end-points of anesthesia, severe hypotension and lethal effect in rats

End-point	ED50 (Inspired concentrations, %)	
	Isoflurane	Halothane
RR	0.81 (0.76-0.86)*	0.64 (0.58-0.72)
PM	1.74 (1.66-1.84)	1.14 (1.03-1.27)
HR	2.89 (2.57-3.21)	2.14 (1.96-2.32)
AP	7.44 (6.67-8.06)	4.36 (3.86-4.50)
LD	12.52 (11.06-14.58)	4.73 (4.63-4.93)

* 95 percent fiducial limits

RR loss of righting reflex

PM prevention of purposeful movement in response to a noxious stimulus

HR prevention of increase in heart rate in response to a noxious stimulus

AP reduction of arterial pressure to a level of 50 mmHg (effect was evaluated as a quantal response)

LD lethal effect (due to cardiovascular depression)

References.

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3. Wolfson B, Hetrick WD, Lake CL, Siker ES: Anesthetic indices - further data. Anesthesiology 48:187-190, 1978