Effects of Propofol and Thiopental Sodium on the Intracranial Pressure under Halothane or Isoflurane Anesthesia in the Rabbit

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The effects of halothane or isoflurane, alone and in combination with propofol or thiopental were investigated for their effects on intracranial pressure (ICP) in the rabbit, with inducing artificially-increased ICP with an intracranial balloon. The higher the end-tidal concentrations of either halothane or isoflurane, the lower the mean arterial pressures (MAP) and cerebral perfusion pressures (CPP). However, the ICP was not influenced by the depth of anesthesia for either inhalation anesthetics. The mean ICPs at 1.5 MAC of halothane and isoflurane were 14±2 and 20±2 mmHg, respectively. With the increase of intracranial volume using a 0.7 ml-saline balloon, the ICPs were increased to 193 and 205% in halothane and isoflurane anesthesia, respectively. The ICPs were returned to the levels prior to balloon inflation by the injection of thiopental or propofol. The authors conclude that propofol could be used to reduce ICP under halothane or isoflurane anesthesia if it is ascertained to have the characteristics of a balanced coupling between cerebral metabolism and blood flow like barbiturates do and that either halothane or isoflurane with increased concentrations may decrease MAP without significant change of ICP.

Most inhalational anesthetics may increase ICP due to anesthetic-induced changes in cerebral blood flow (CBF). The effects of commonly used anesthetics on CBF are well-known as a result of numerous animal studies that permit reliable comparisons between anesthetics (Theye and Michenfilder, 1968 a & b; Michenfilder and Theye, 1973). In general, they influence vessel caliber, either directly or indirectly by dilating the vascular wall and increasing arterial carbon dioxide tension (Cucchiara *et al.* 1974; Mann *et al.* 1979). A change in vessel caliber causes a change in cerebral blood volume which alters the volume of the cranial contents and thus increases ICP. Additionally, halothane decrease the absorption of cerebrospinal fluid (CSF) whereas isoflurane has no effect on the rate of its production or absorption (Artru, 1983 and 1984). The changes in ICP by inhalation anesthetics are generally greater in those with an increased ICP than in normal patients (Jennet and Barker, 1969; Cordon, 1970). However, it is not clear whether ICP is determined by the end-tidal concentrations of anesthetics or by the kinds of anesthetics only. One purpose of this study was to determine the relationship between ICPs and end-tidal concentrations of the anesthetics during halothane or isoflurane anesthesia in the rabbit.

Furthermore, the hypnotics thiopental, midazolam, and etomidate are recommended to decrease ICP or increase intracranial compliance (Lassen, 1968; Reves *et al.* 1985). One

hypnotic, propofol, 2, 6-diisopropylphenol, is a new intravenous anesthetic agent chemically unrelated to barbiturates. It may cause a dose-dependent decrease in CBF and hence, cerebral blood volume. It can also significantly diminish ICP when cerebral compliance especially is reduced (Michenfilder, 1974; Rea et al. 1983; Messeter, 1983; Nornstrom and Artru, 1988). It may maintain autoregulation of cerebral circulation (Vandesteene and Trempponent, 1988; Hemelrijck et al. 1990; Koch et al. 1992). However, it is not quantitatively compared with thiopental for the effect of reducing ICP. The other purpose of this study was to evaluate the effects of propofol compared with thiopental on increased ICP during halothane or isoflurane anesthesia in the rabbit.

METHODS

Seventeen unpremedicated rabbits, of either sex and weighing 2~3.5 kg were studied. Anesthesia, either halothane (10 rabbits) or isoflurane (7 rabbits), was randomly assigned. The rabbits receiving an inhaled anesthesia were placed in a 5 L-sealed chamber with an outlet and inlet port. Either halothane or isoflurane, 2~5%, in oxygen was passed through the chamber at a flow rate of 2 L. min^{-1}. When the rabbit was anesthetized, as evidenced by depression of respiration and motor activity, it was removed from the chamber.

A 22G-Angiocath needle was inserted into a vein in the left ear and 3 mg · kg^{-1} of pentobarbital was administered. An endotracheal tube (2.5~4 mm sized in I.D.) was inserted into the trachea via tracheostomy, and mechanical ventilation was commenced with the Ugobasyl® animal ventilator, initially delivering breaths of 10 ml · kg^{-1} at a rate of 50 cycles · min^{-1}. Ventilation was adjusted to maintain the PECO2 between 35~45 mmHg. The femoral vein and artery were cannulated for the infusion of fluids and drugs and to monitor the intraarterial pressure and arterial blood gases. End-tidal concentrations of the inhaled anesthetics were determined by infrared spectrometry (Lamtec® 605). To monitor ICP, the scalp and underlying muscles were

dissected and biparietal penetrations of the skulls with an electric drill were performed; a 4F-angiocatheter filled with saline was inserted to monitor ICP through one hole and a 4F-catheter with a 2 ml-balloon to induce increasing intracranial volume was inserted through the other hole (contralateral side) into the epidural space. All bone holes were made airtight with bone wax. Body temperature was monitored with a YS-I® Telethermometer and heart rates were monitored on standard lead II during all the experiments. Mean arterial pressures and ICP were recorded via transducers on a Grass® 79E Model polygraph.

After completion of calibration, half an hour to one hour was needed for stabilization under 1.5 MAC of either inhaled anesthetic. At that time, ICP was measured at 1.5 MAC halothane (1.3%) or isoflurane (2.2%). Thereafter, the anesthetic concentration was changed in random order to 1.0 and 2.0 MAC. The MAC was stabilized at each concentration and ICPs were measured.

Then, the anesthetic concentration was returned to 1.5 MAC and maintained for one hour. The intracranial balloon was inflated with 0.7 ml-saline to induce an increase in ICP. Fifteen mg · kg^{-1} of thiopental or seven mg · kg^{-1} of propofol were administered intravenously in random order with one hour intermission between change of agents to minimize the residual effect of the preceding agent.

All the values were expressed as mean± SD. Among the three different MACs, each parameter was compared by ANOVA with the Student-Newman-Keuls test. In the same anesthetic, the same parameter was compared by paired t-test. For all the statistical comparisons, differences were considered significant when there was a p value of less than 0.05.

RESULTS

As the concentration of anesthetics, either halothane or isoflurane, were increased, the MAPs and CPPs decreased, but ICP did not. The MAP at 2.0 MAC of isoflurane anesthesia was significantly lower than that at 1.0

Table 1. Changes of heart rates (HR), mean arterial pressures (MAP), intracranial pressures (ICP) and cerebral perfusion pressures (CPP) at various MAC levels during halothane or isoflurane anesthesia

MAC	Halothane (n=10)			Isoflurane (n=7)		
	1.0	1.5	2.0	1.0	1.5	2.0
Parameter						
HR (beats/min)	284±57	291±54	302±54	330±54	310±44	330±38
MAP (mmHg)	98.5±19.9	92.3±16.8	82.3±17.7	117.2±14.8	104.3±7.9	90.7**±12.7
ICP (mmHg)	14.9± 6.6	14.4± 6.6	14.0± 6.6	20.4± 4.5	20.0±4.2	19.9± 3.2
CPP (mmHg)	83.5±18.3	77.9±17.7	69.2*±16.8	96.7±18.0	84.3±7.7	70.9**±12.2

The MAC values assumed are 0.87 and 1.46 vol% in halothane and isoflurane, respectively.
CPP is calculated as the difference between MAP and ICP.
All values are expressed as mean±SD.
*$p<0.006$ MAC 2.0 vs 1.0, **$p<0.0001$ MAC 2.0 vs 1.0 & 1.5, ***$p<0.001$ MAC 2.0 vs 1.0

Table 2. Changes of mean arterial pressures (MAP) and cerebral perfusion pressures (CPP) related to artificially-increased intracranial pressures (ICP)

	Halothane (n=10)		Isoflurane (n=7)	
	Pre-balloon	Balloon	Pre-balloon	Balloon
ICP	14± 6	27± 6*	20±5	41± 5*
MAP	92±16	96±19	104±8	118±12*
CPP	78±19	68±25*	84±8	77±34

Pre-balloon and balloon represent the time sequences, prior to balloon and immediately after balloon inflation, respectively. The end-tidal anesthetic concentration of 1.5 MAC level were maintained in all the cats.
All values are expressed as mean±SD, mmHg.
*$p<0.05$

and 1.5 MACs ($p<0.0001$). At 2.0 MAC of either agents, CPPs were significantly lower than those at 1.0 and 1.5 MACs ($p<0.006$, $p<0.001$). ICPs were higher with isoflurane ($19.9±3.2 \sim 20.4±4.5$ mmHg) than with halothane anesthesia ($14.0±6.6 \sim 14.9±6.6$ mmHg); however, ICP was not altered by a change of anesthetic concentrations during either inhalation anesthesia (Table 1).

By the inflation of the intracranial balloon with 0.7 mL-saline under 1.5 MAC of either agents, the ICPs increased immediately to 193 and 205% in halothane and isoflurane anesthesia, respectively. About five minutes later they were maintained at 143 and 120% of the initial levels. The MAPs during isoflurane anesthesia were increased immediately after the inflation of the intracranial balloon. The CPPs after the inflation of the balloon with halothane anesthesia were decreased transiently, but not with isoflurane anesthesia (Table 2).

The intravenous bolus injection of both thiopental and propofol under 1.5 MAC halothane or isoflurane anesthesia produced a decrease in the increased ICP which was induced by the inflation of the intracranial balloon of 0.7 mL-saline. There was no significant difference in the degree of the decrease between thiopental and propofol treatment. And also, there was no significant difference in this effect between halothane and isoflurane anesthesia (Fig. 1).
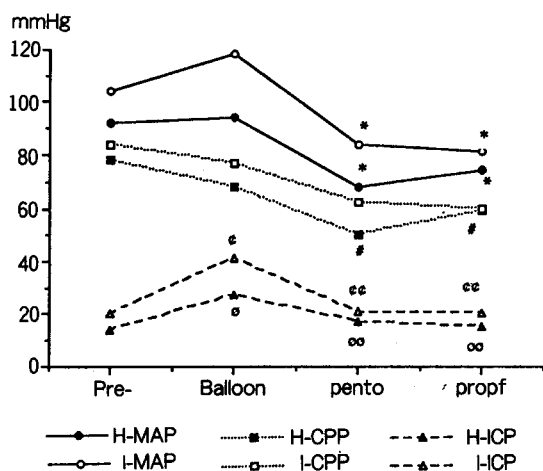
mmHg

Fig. 1. Effects of thiopental or propofol on artificially-increased intracranial pressures under 1.5 MAC of halothane or isoflurane anesthesia.

In the legends, alphabets H and I refer to halothane and isoflurane anesthesia, respectively.

Pre-, Ballon, Pento and Propf in abscissa represent the sequences prior to balloon, at the balloon, and at the injection of thiopental and propofol, respectively.

DISCUSSION

The present study aimed to elucidate the change of ICP with an alteration of end-tidal concentration in halothane or isoflurane anesthesia and to evaluate the effects of propofol compared to thiopental on the increased ICP under 1.5 MAC halothane or isoflurane anesthesia in the rabbit. We found that a change of the end-tidal anesthetic concentration did not alter ICP, although the higher the anesthetic concentration, the lower the MAP and CPP. This is in accordance with Hartung's result (1987), where the CPP showed a small decrease in both propofol and thiopental in humans. High doses of inhalation anesthetics can cause a total loss of autoregulation, that is, ICP becomes totally blood pressure dependent. According to Eger (1981), isoflurane with 1.1 MAC did not

influence CBF, but increased CBF two-fold when above 1.6 MAC. In humans, halothane, enflurane and isoflurane under 1.1 MAC increase CBF to 190, 37 and 18%, respectively, when MAP is maintained at 80 mmHg (Murphy *et al.* 1974). Furthermore, Artru *et al.* (1983 and 1984) reported that increased ICP returns to baseline in isoflurane anesthesia in contrast to halothane or enflurane anesthesia. ICP is also influenced by changes in the rate of production or absorption of CSF. Halothane decreases its absorption whereas isoflurane has no effect on the rate of production or absorption of CSF.

Baseline ICP under 1.0 MAC halothane or isoflurane was 14-20 mmHg in our rabbits, in contrast to 7.1 mmHg in cats under 0.5%-isoflurane (Thiagarajah *et al.* 1988) and 7.9 ~ 9.8 mmHg in dogs under 1%-halothane or 2.5%-enflurane with 60%-nitrous oxide (Artru, 1983). This difference most likely was caused by the different species and anesthetic depth because our rabbits had no other additional experimental conditions apart from those in the other reports.

Another result of this step in the present study was the difference of baseline ICP between halothane (14±6) and isoflurane anesthesia (20±5 mmHg). The reason why ICP increases with isoflurane use perhaps can be explained by the same reason that Artru (1983) suggested for ICP increase in enflurane use. Unlike the case of halothane, this cause probably has to do with anesthetic-induced changes which cause increased production of CSF in enflurane and isoflurane.

The 2nd step of this study was designed to increase ICP by the inflation of the intracranial balloon into the epidural space on a parietal area. About 200% to the baseline ICP in either inhalation anesthesia could be gained by the inflation of the balloon with 0.7 ml-saline. Five minutes later, ICP was allowed to be lowered 5 mmHg or more from the baseline value before the balloon was inflated. It may be indicated that within this circumstance the intracranial compensation tool remains. At the inflation of the balloons, the MAPs were increased in isoflurane (13%) and CPPs were decreased in halothane anesthesia (13%).

The rabbits were administered an intravenous injection of 15 mg · kg^{-1} of thiopental and

7 mg · kg⁻¹ of propofol under the inflation of the intracranial balloon, in random order, with one hour or more waiting time. The ICPs were significantly lower after the administration of thiopental or propofol than immediately after the balloon inflation. However, there was no difference for the reduction of increased ICP between thiopental and propofol. At that time, the CPPs were decreased only in halothane anesthesia, although the MAPs were significantly decreased with both inhalation anesthesias. This suggests that CPP may be preserved in isoflurane anesthesia in spite of decreased MAP when thiopental or propofol is given to decrease ICP. In contrast to our result, a previous report demonstrated that the autoregulatory response to blood pressure changes was not impaired by propofol (Hemerlrijck *et al.* 1990). Its effect may be dose-dependent.

The potent cerebrovasoconstricting actions of thiopental have led to its use as an induction or treating agent for patients with the potential for developing intracranial hypertension. This agent induces a dose dependent reduction of CBF and CMR, approximately paralleling CNS depression (Michenfilder, 1974; Nornstrm and Messeter, 1983; Rea and Rockswold, 1983; Artru, 1988;). With the onset of anesthesia, CBF and CMR are reduced by about 30 percent ; and, when large doses of thiopental cause EEG suppression to the isoelectric point, CBF and CMR are reduced by about 50 percent (Siesjo, 1984). Thiopental's inhibition of phosphoproctokinase decreases production of lactate which decreases intracellular pH and therefore serves as a protection against ischemic brain (Chapman and Nordstorm, 1978). Propofol, a rapid acting intravenous anesthetic, decreases cerebral oxygen consumption and CBF in humans and animals to a similar degree as reported for thiopental (Hemelrijck *et al.* 1990; Koch *et al.* 1992), but has not been found for the effect of lactate metabolism. One of the most important factors influencing the ICP is arterial carbon dioxide tension. It was maintained in our rabbits by controlled ventilation within the range of 35 to 40 mmHg throughout the experiment.

In conclusion, using propofol would allow us to reduce ICP if it is ascertained that it has the characteristics of balanced coupling between cerebral metabolism and blood flow as do barbiturates. However, the marked cardiovascular side effects of propofol must be taken into consideration.

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