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HALOTHANE AND ISOFLURANE IN INTRALIPID AS INTRAVENOUS ANAESTHETICS TO DOGS

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ABSTRACT

Halothane 5% (0.6 ml/kg) and isoflurane 10% (0.4 ml/kg) in intralipid injected intravenously over one minute were the minimum doses that consistently abolished movement in response to tail clamping in dogs. The depth of anaesthesia was controlled by adjusting the infusion rate. Blood pressure decreased during induction and regained progressively during maintenance with low doses especially with isoflurane. The heart and respiratory rates were increased during maintenance with low doses while a decrease was observed by increasing the depth of anaesthesia that was more prominent with halothane. Recovery achieved after infusion of halothane 5% or isoflurane 10% for 30 minutes, was fast and survivors behaved normally. Lung tissues were macro and microscopically normal. It was concluded that, intravenous administration of halothane 5% or isoflurane 10% induced ultra short general anaesthetic effect and had a safe hemodynamic and respiratory responses especially with isoflurane.

INTRODUCTION

Severe pulmonary oedema and right heart failure were reported in a 16-year-old girl accidentally given 2.5 ml halothane intravenously[1]. Also, in an experimental study on the pulmonary damage associated with intravenous injection of halothane in dogs, a generalized pulmonary oedema and patchy alveolar haemorrhages were reported [2].

It seems somewhat paradoxical that halothane, which produces virtually no pulmonary irritation when inhaled, should cause predominent and severe pulmonary pathology when given intravenously.

The intravenous injection of halothane 5% in intralipid did not produce generalized pulmonary oedema or patchy alveolar haemorrhage, in cats [3], in dogs [4] and in rats[5]. They related the pulmonary lesions to the poor mixing in blood exposing the pulmonary capillary system to large damaging drug levels.

Karpa et al [6] concluded that isoflurane 10% was easily administered, had a reliable hemodynamic response and devoid of pulmonary oedema or haemorrhage. They added also that the intravenous administration of this preparation may prove to be a significant modality of anaesthesia delivery in the future.

In the present study, the general anaesthetic properties, the hemodynamic effects and the respiratory response of intravenous injection of halothane 5% or isoflurane 10% in dogs were evaluated. The histopathological examination of the lungs was also performed.

MATERIAL AND METHODS:

a- Drugs:

1- Fat emulsion for intravenous use (Intralipid)®, each 1000 ml contain purified soybean oil 200g, glycerol USP 22.5 g, water for injection to 1000 ml. Kabi Pharmacia AB, Sweden.

2- Isoflurane (Forane)® Abbot Laboratories, Ltd, Kent England.

3- Halothane (Fluothane)® Kahira Pharm and Chem. Ind. CO., Egypt.

b- Experimental design :

Mongrel dogs (10 - 15) kg body weight were anaesthetized using an induction dose of propofol (4 mg/kg I.V.) followed by a continuous propofol infusion of 0.5 mg/kg/ min. Dogs were spontaniously ventilated, cannulation of the femoral artery and vein was performed, heparine 100 I.U./kg was injected through the cunnula as an anticoagulant [7]. The arterial cannula was connected to PT 400 blood pressure transducer. ECG pins were inserted under the skin for electrodes fixation, the propofol infusion was discontinued. One hour later, different doses of 5% halothane or 10% isolfurane in intralipid were administered intravenously to determine the doses necessary for induction and maintenance for 30 minutes. Induction was judged satisfactory when the responses to tail clamping, corneal and vocal reflexes were abolished. The characteristics of recovery were also studied by determining the time necessary for the previous reflexes to regain their normal responses. The time elapsed from discontinuation of anaesthesia till the appearance of the standing position and the normal gait were also recorded. Blood pressure, respiratory rate and ECG pattern were recorded during the experiments.

Histopathological studies were performed at the end of the experiment. Dogs were grouped into 3 groups, each of two. The first group received intralipid alone (0.4 ml/kg / min), the second received isoflurane 10% (0.3 ml/ kg / min) and the last one received halothane 5% (0.4 ml / kg / min) intravenausly for 30 minutes for three successive days, then they were killed and the

lungs were macroscopically and microscopically examined [8]. Data were statistically analysed using student's "t" test [9].

RESULTS

Different doses of halothane 5% or isoflurane 10% were injected intravenously to determine the suitable dose which produce loss of righting to tail clamping, corneal and vocal reflexes within one minute and also the suitable infusion rate which maintain loss of the previous reflexes for 30 minutes.

It was found that halothane 5% induced anaesthesia in a dose of 0.6 ml/kg injected over one minute. On the other hand, 0.2 ml / kg / min was sufficient to maintain anaesthesia for 30 minutes.

Isoflurane 10% in a dose of 0.4 ml/kg was sufficient to induce general anaesthesia when injected over one minute and was maintained for 30 minutes by a perfusion rate of 0.15 / ml / kg / min.

Mean Arterial Pressure (MAP).

Induction with halothane 5% injected intravenously over one minute in a dose of 0.6 and 1.2 ml/kg induced a significant decrease in MAP reaching a minimum value of 89.2±4.6 and 65.2±3 mmHg respectively versus 124.6±5.6 and 123.2±6.9 mmHg for the control (Fig. 1, A). Blood pressure was increased gradually thereafter, reaching 94.5±4.2 mmHg after maintenance with intravenous infusion of 0.2 ml/kg /minute halothane 5% for 30 minutes, while 0.4 ml/ kg/min. induced a decrease in the MAP reaching, 81.2±5.8 mmHg after 30 minutes infusion in dogs received an induction dose of 0.6 ml over one minuute (Fig. 1, B).

On the other hand, induction with isoflurane 10% injected intravenously in doses of 0.4 and 0.8 ml/kg induced a significant decrease in MAP reaching minimum values of 97.2±2.7 and 77.6±2.1 mmHg respectively versus 123.5±6.6 and 124.8±5.7 mmHg for controls (Fig. 2, A). The MAP reached 107.2±4.6 and 96.2±3.2 after maintenance for 30 minutes with intravenous infusion of isoflurane 10% in doses of 0.15 and 0.3 ml/ kg/ minute respectively (Fig. 2, B).

A slight increase in the MAP was observed during the administration of the intralipid alone in the previous doses.

Heart rate:

As shown in Table (1), the heart rate values after intravenous infusion of both levels of halothane 5% (0.2 and 0.4 ml/ kg/ min) were 145 ±2.1 and 116.8±3.0 respectively, meanwhile, the heart rate values of the controls were 142.8±1.6 and 141.6±2.1 respectively. A highly significant decrease in heart rate was recorded during the infusion of 0.4 ml/kg/min. halothane 5% only.

Isoflurane 10% infusion at a dose of 0.1 ml/ kg/ min evoked a non-significant increase in heart rate, which were 148.6±2.1 after 30 min infusion against 142.2±2.1 of control. A significant decrease in heart rate between the 0.3 ml/ kg/ min infusion for 30 minutes and the control was also recorded (Table 1).

Effect on Respiration :

Shallow and slow breathing was usually observed during the two levels of induction with either halothane 5% or isoflurane 10%.

Respiratory rate was progressively increased during the infusion of 0.2 ml/ kg/ min halothane 5% or 0.15 ml/ kg/ min isoflurane 10% reaching, 18.6±0.5 and 18.6±0.5 respectively after 30 minutes versus 15.8±0.3 and 15.6±0.6 for the controls. A highly significant decrease in respiratory rate was observed when doubling the infusion rate of halothane, while a significant decrease was seen when doubling the infusion rate of isoflurane (Table 1).

Recovery

After 30 minutes intravenous infusion of the two levels of either halothane 5% or isoflurane 10%, survivors showed faint movements during tail clamping which appeared after about 20-30 seconds for halothane and 22-30 seconds for isoflurane. The dogs turn from the side to the prone position, then they regained the upright position after about 52-66 seconds for halothane and 50-68 seconds for isoflurane. Dogs appeared fully awaked after about 96-119 and 88-116 seconds after discontinuation of the intravenous infusion of the two levels of either halothane 5% or isoflurane 10% respectively. (Table, 2).

DISCUSSION

Intravenous injection of 0.6 ml/kg halothane 5% or 0.4 ml/kg isoflurane 10% in intralipid as induction doses were based on a previously designed pilot experiment. These doses were proved to be the minimum doses that consistently abolished movement in response to tail clamping in dogs. Anaesthesia was maintained in two levels by doubling the infusion rate. Recovery was fast, probably due to quick exhalation of these volatile anaesthetics.

The observed dose-dependent decrease in arterial pressure during induction was more prominent with halothane than with isoflurane injection. Our results were in accordance with that previously reported [1, 2, 3, 10]. They reported that, intravenous injection of halothane 5% induced a dose dependent decrease in arterial blood pressure and also with those results reported for isoflurane 10% [6].

After induction, maintenance with intravenous infusion of either halothane or isoflurane, the blood pressure was progressively increased which was more prominant with isoflurane than with halothane. The previous effect was much attenuated by increasing rates

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Fig. (1) Illustrating the mean arterial pressure of dogs during (A) induction with halothane 5% (◇ 0.6 and ○ 1.2m/ kg injected over one minute) and (B) maintenance with halothane 5% infusion (◇ 0.2 and ○ 0.4 ml/kg/min.) for 30 minutes. (mean ± S.E.)

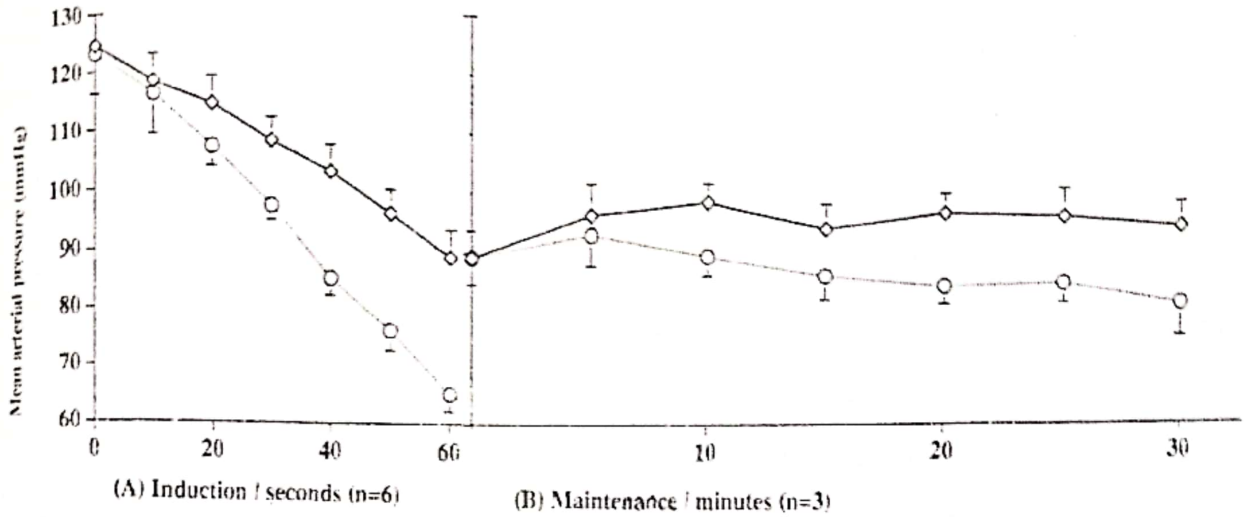

Fig. (2) Illustrating the mean arterial pressure of dogs during (A) induction with isoflurane 10% (□ 0.4 and △ 0.8 m/ kg injected over one minute) and (B) maintenance with isoflurane 10% infusion (□ 0.15 and △ 0.3 ml/kg/min.) for 30 minutes. (mean ±S.E.)

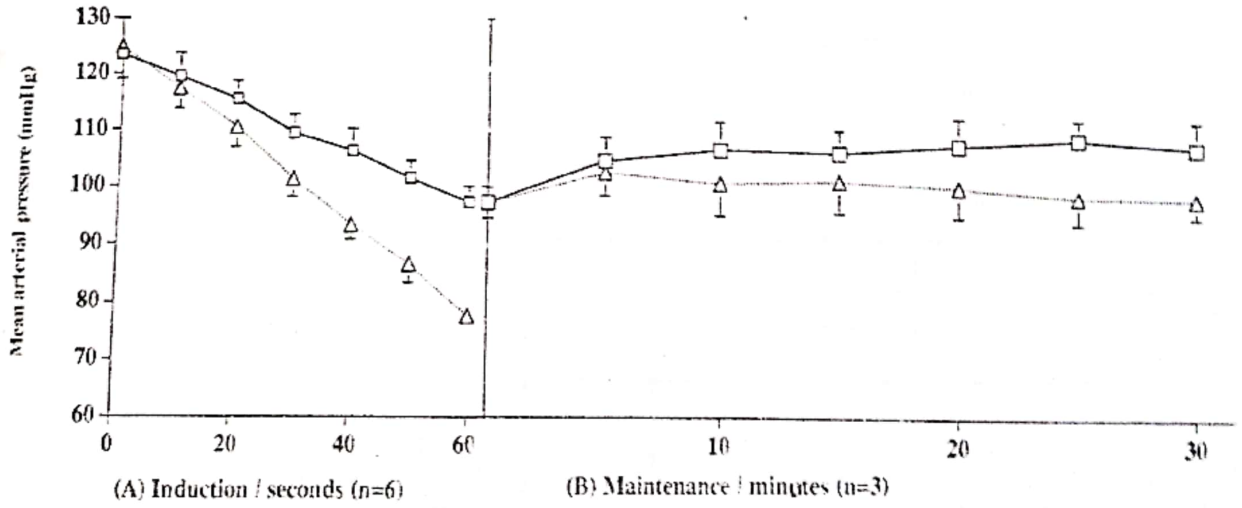

Table (1) Effect of intravenous infusion of halothane 5% (0.2 and 0.4 ml/kg / min.) or isoflurane 10% (0.15 and 0.3 ml/ kg /min.) in intralipid for 30 minutes on the heart and respiratory rate of dogs . (mean ± S.E.) n=6

	drug	dose kg / min	Time/ minutes						
			Control	5	10	15	20	25	30
Heat rate beet / minute	Halothane 5%	0.2 ml	142.8±1.6	146.8±1.6	147.4±1.8	146.4±1.6	145.6±1.6	147.8±1.7	145.4±2.1
		0.4 ml	141.6±2.1	130±2.2**	123.8±1.8**	122.4±1.8**	120.4±1.6**	118.6±1.6**	116.8±3.0**
	Isoflurane 10%	0.15 ml	142.2±2.1	147.0±1.9	146.8±1.6	147.2±2.2	147.6±1.9	148.2±1.8	148.6±2.1
		0.3 ml	141.0±2.2	138±2.1	138.4±1.9	139.8±1.9	138.8±1.9	137.2±2.1	138.8±1.9
Respiratory rate / minute	Halothane 5%	0.2 ml	15.8±0.5	16.8±0.6	18.6±0.5**	18.4±0.3**	17.6±0.5*	17.2±0.2*	18.6±0.5**
		0.4 ml	14.8±0.3	13.8±0.3	13.2±0.7	11.8±0.3**	10.6±0.4**	10.4±0.3**	9.8±6.0**
	Isoflurane 10%	0.15 ml	15.6±0.6	17.4±0.2*	17.9±0.2**	18.2±0.3**	17.8±0.3**	18.6±0.4**	18.8±0.4**
		0.3 ml	15.2±0.3	14.2±0.3*	13.8±0.3**	14.0±0.3*	13.2±0.5**	136±0.4**	14.2±0.3*

* P < 0.05 ** P < 0.01

Table (2) Time in seconds after the end of infusion of 5% halothane or 10% isoflurane in intralipid for the appearance of different signs of wakefullness. n = 6

	Halothane 5%				Isoflurane 10%			
	0.2 ml/ kg/ min		0.4 ml/ kg/ min		0.15 ml/ kg/ min		0.2 ml/ kg/ min	
	range	X ± S.E	range	X ± S.E	range	X ± S.E	rang	X ± S.E
Response to tail clamping	15-3	208±2.2	20-45	30±3.1	15-30	22.5±1.9	20-50	30±4.3
vocal reflex	20-35	25.8±2.5	25-60	34.1±5.3	20-40	28.3±2.8	30-60	39.1±4.8
Corneal reflex	30-45	34.1±2.5	30-70	10.0±6.1	30-50	35.0±3.1	35-70	45.0±5.1
Standing position	45-65	52.0±2.1	60-85	66.6±3.7	45-60	50.8±2.2	60-90	68.3±4.2
Normal gait	70-120	96.6±7.5	100-150	118+7.3	70-110	88.3±5.5	90-160	116.6±9.5

All results wre non-significant

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of intravenous infusion.

It seems likely that no difference exists between the inhalation and the injection routes of the tested volatile anaesthetics. A progressive decrease in systemic blood pressure was achieved by increasing depth of anaesthesia with isoflurane inhalation which was lesser than halothane (11-13).

Heart rate was non-significantly increased by infusing 0.2 ml/ kg/ min. halothane 5%. By doubling the rate of infusion, a non-significant decrease in heart rate was observed. On the other hand, isoflurane 10% infusion in a rate of 0.15/ ml/ kg/ minute induced a highly significant increase in heart rate, while by doubling the dose, a non significant decrease in heart rate was recorded.

Early studies showed a direct depressant effect on myocardial contractility by isoflurane on the papillary muscle in cats (14) and isoflurane and halothane on the atria of guinea pigs and rats (15,16). These invitro studies however, do not completely correlate with those in-vivo. Isoflurane inhalation produced an increase in heart rate (17,19). They added that myocardial depression occurred only by increasing the depth of anaesthesia.

Our results correlate with those previously recorded by **kissin et al** (2). They reported that the cardiovascular margin of safety is greater with isoflurane than with halothane. This was assesed on the basis of the ratio of anaesthetic concentrations necessary to produce cardiovascular collapse.

A highly significant increase in respiratory rate was observed during intravenous infusion of halothane in a rate of 0.2 ml/ kg/ minute or isoflurane 0.15 ml/ kg/ minute. Doubling the rate of infusion induced a decrease in respiratory rate which is highly significant with halothane and significant with isoflurane.

Recovery was fast, survivors behave normally. The lung tissues were macro and microscopically normal.

These findings are contradicted with the previous experience of accidental injection of undiluted halothane in man (1) and intentional injection in dogs (2). However, it was in correlation with that obtained after intravenous injection of halothane 5% in rats (5), in dogs (4), in rabbit (1) and for intravenous injection of isoflurane 10% in dogs (6).

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الحقن الوريدى للهالوثين و الايزوفلورين فى مستحلب دهنى كمخدر للكلاب

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تم تحضير الهالوثين ٥٪ والايزوفلورين ١٠٪ فى مستحلب دهنى خاص للحقن فى الوريد وقد تم اعطاء جرعات مختلفة من كل مستحضر عن طريق الوريد لتعيين الجرعات المؤثرة فى خلال دقيقه ومعدل التسريب الوريدى اللازم لاستمرار الكلاب مخدره لمدة ٣٠ دقيقة مع دراسة التأثير على ضغط الدم ومعدل ضربات القلب والتنفس أثناء هذه المدة وكذا دراسة خواص الافاقه بعد توقف التسريب الوريدى لكل من المستحضرين .

وقد وجد أن ٦ر٠ ملليتر/ كجم هالوثين ٥٪ و٤ر٠ ملليتر/كجم أيزوفلورين ١٠٪ هى تقريباً أقل جرعة تسبب تخدير كلى للكلاب وأن التسريب الوريدى بمعدل ٢ر٠ ملليتر/كجم فى الدقيقة هالوثين ٥٪ و ١٥ر٠ ملليتر/كجم فى الدقيقة أيزوفلورين ١٠٪ هى تقريباً أقل معدل تسريب يمكن به استمرار التخدير لمدة ٣٠ دقيقة كما وجد أيضاً أن عمق التخدير يمكن التحكم فيه بضبط معدل التسريب الوريدى .

كما تبين من هذه الدراسة حدوث انخفاض شديد فى ضغط الدم اثناء حقن الجرعة المؤثرة لكل من الهالوثين والايزوفلورين وإن هذا الانخفاض يتراجع تدريجياً اثناء التسريب الوريدى ويكون التراجع اكثر وضوحاً مع الايزوفلورين عنه مع الهالوثين ومع الجرعات الصغيرة عنه فى الجرعات الكبيرة وقد احدثت الجرعات الصغيرة زيادة فى معدل ضربات القلب والتنفس بينما احدثت الجرعات الكبيرة نقصاً فى معدل ضربات القلب والتنفس خاصة عند التسريب الوريدى بالهالوثين . وقد اتضح ان فترة الافاقه قصيرة جداً وكان سلوك الكلاب طبيعياً بعد الافاقه بالنسبة لكل من المستحضرين ، واتضح ان الرئه طبيعية بعد الفحص التشريحى والمجهرى لكل من الكلاب التى خدرت لمدة نصف ساعة يومياً وذلك لمدة ثلاث أيام متتالية بالهالوثين أو الايزوفلورين عن طريق الوريد .

ويستخلص من هذه الدراسة ان حقن الهالوثين ٥٪ أو الايزوفلورين ١٠٪ فى مستحلب دهنى بالوريد يحدث تخديراً كليا لفترة وجيزة جداً فى الكلاب وكان الاستخدام آمن من حيث ضغط الدم والتنفس وخاصة مع الايزوفلورين وانه يمكن التحكم فى عمق التخدير بضبط معدل التسريب الوريدى .