COMPARISON OF THE HEPATOTOXIC EFFECTS OF HALOTHANE AND CHLOROFORM IN HYPOXIC DOGS

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THIS SERIES of experiments was undertaken to demonstrate the relative hepatotoxic properties of halothane and chloroform. Since these agents are both heavily halogenated hydrocarbons, and chloroform has had a reputation of being toxic to the liver, there was some concern that halothane might share this property. Chloroform has been found to be most dangerous in poorly nourished or poorly ventilated patients.

A study conducted in 1958¹ attempted to measure the hepatotoxic effects of halothane in the presence of mild hypoxia, i.e. 16 per cent oxygen in nitrous oxide. The mean percentage of concentration of halothane was 0.8 per cent. This concentration maintained anaesthesia but did not depress the blood pressure below 100 mm. of mercury. This series showed little effect on the liver as measured by examination of Vim-Silverman biopsy specimens.

METHOD

Mongrel dogs were used in this study. They were provided by the Vivarium and maintained on a standard diet for 1-2 weeks prior to the first experiment. All dogs were thought to be healthy apart from occasional infestation, early in the series, with tapeworms, which became evident during the experiment. Dogs thought to be suffering from infectious disease were excluded from the series. No premedication was used. Anaesthesia was induced with thiopental 2.5 per cent intravenously to a dose of 25 mg. per kg. This produced sufficient anaesthesia to permit intubation with a cuffed Magill endotracheal tube and taking of a needle biopsy specimen of the liver. The dogs were positioned supine, the abdomen and one groin shaved and washed with tincture of iodine, the needle biopsy taken, and the hypoxic atmosphere with the anaesthetic vapour administered through a non-rebreathing valve. The halothane or chloroform was vaporized from a Fluotec® vaporizer. The concentration of chloroform was estimated to be 0.75 of the indicated halothane percentage.² A cutdown onto a femoral artery was performed, the artery catheterized, and mean pressure registered on an anaeroid manometer. The blood pressure was not permitted to remain below 100 mm. of mercury. A decline below this figure was rectified by reducing the anaesthetic vapour concentration. A second needle biopsy was taken at the conclusion of 3 hours of anaesthesia. The dog was returned to the recovery cages and then to the animal house. A further liver biopsy was taken at 2 and 7 days postanaesthesia. Those dogs which survived the first anaesthetic had one-month convalescence and then received the other agent in a cross-over fashion.

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In a pilot series to determine the most severe degree of hypoxia not producing liver damage, it had been determined that 6 per cent oxygen did not cause an elevation of the B.S.P. test or observable changes in the biopsy specimen. Mixtures of 6 per cent oxygen in nitrogen were prepared by commercial sources and the actual oxygen percentage measured by a Scholander apparatus.

The Vim-Silverman needle biopsy specimens were fixed in formalin, and delivered to the pathologist, where they were embedded in paraffin, sectioned at 6 microns, and stained with haematoxylin and eosin. These specimens were examined by Dr. John Macgregor of the Department of Pathology, who was unaware of the agents used or the order of the specimens.

RESULTS

Because of the heavy casualty rate under chloroform and hypoxia it was not possible to complete the cross-over experiments.

In the 11 dogs to which it was possible to administer both agents, the pathologist's interpretation of the liver biopsy specimens indicated that halothane was not toxic to the liver in the presence of hypoxia, but that a succeeding chloroform anaesthetic produced evidence of liver damage at two days in four of seven dogs; this had cleared in all but one by the seventh day. Chloroform as the first anaesthetic produced evidence of liver damage in five of six dogs. Four of these dogs survived halothane a month later and two of these again showed liver damage in the two-day specimen. (See Tables I and II.)

A further five dogs received halothane; two died while receiving chloroform a month later, two died before the month had elapsed, and one died during the original experiment. Fifteen dogs received chloroform but did not complete the series because four died on halothane, three died within the month, and eight during the original experiment.

DISCUSSION

The heavy casualty rate is indicative that chloroform in the presence of hypoxia is a very serious stress to dogs. The evidence of liver damage on the biopsy specimens at two and seven days supports this. Where chloroform was administered, the dogs were reported by the Vivarium staff to have been lethargic; they ate poorly and showed little interest in life. It is possible that some of the liver damage reported was related to the loss of appetite.

ADDENDUM

Other variables, not considered prior to the series, became more apparent towards the conclusion. Following the heavy fatalities encountered during the chloroform administration, a closer examination of the "mongrel dogs" was made. In order for a series as small as this to be valid, the dogs should be genetically standardized, maintained under identical environmental conditions, used at the same age, and free of canine disease. Although this quality of animal is

TABLE I
EVIDENCE OF LIVER DAMAGE ON BIOPSY

Weight of dog, kg.	Sex	Number	Month	Halothane				Month	Chloroform			
11	M	54 A	Dec.	0	0	0	0	Feb.	0	0	0	0
9.5	M	59 A	Feb.	0	0	0	0	Mar.	0	0	0	0
11	M	60 A	Feb.	0	0	0	0	Mar.	0	0	+	0
7	F	61 A	Feb.	0	0	0	0	Apr.	0	0	+	0
6	F	77 A	Feb.	0	0	0	0	Mar.	0	0	+	0
10	F	V381	Oct.	0	0	0	0	Jan.	0	0	0	0
10.8	F	V470	Nov.	0	0	0	0	Dec.	0	0	++	+
9.8	M	67 A	May	0	0	0	0	July	Died on induction with pentobarbital (? distemper)			
8.5	F	68 A	May					July	Died at end of chloroform administration (? pregnant)			
9.5	?	55 A	Jan.	Died at 17 days								
11.0	F	62 A	Mar.	Died at 15 days								
11	F	75 A	Dec.	Died during experiment								

Weight of dog, kg.	Sex	Number	Month	Chloroform				Month	Halothane			
8.5	?	58 A	Feb.	0	0	+	0	Mar.	0	0	0	0
7	F	64 A	Apr.	0	0	+	0	May	0	0	+	0
8.3	F	65 A	Apr.	0	0	+	0	May	0	0	++	0
10	M	V293	Oct.	0	0	+	0	Nov.	0	0	0	0
7.0	M	66 A	Apr.					May	Died on halothane			
7.8	M	V294	Oct.	0	0	+	0	Nov.	Died at 20 min.			
8.5	M	V475	Nov.	0	0	0	0	Dec.	Died at 2 hours			
14	M	V84	Mar.					Apr.	Died at 1½ hours			
11	?	63 A	Mar.	Died at 14 days								
11.3	M	V508	Nov.	Died at 2 days								
12	M	V833	Feb.	Died at (?) 14 days (old dog)								
8.5	F	V371	Oct.	Died at 3 hours								
11.5	F	V693	Jan.	Died at 2 hours					(Pregnant)			
10	F	V723	Jan.	Died at 2 hours								
8.5	M	V824	Feb.	Died at 40 min.								
12	M	V796	Feb.	Died at 40 min.								
10.5	F	X56	Apr.	Died at 1½ hours					(Pregnant)			
11.5	F	No tag	Jan.	Died at 1 hour								
11.0	M	No tag	May	Died in 20 min.								

TABLE II

Survived halothane and chloroform	} actual cross-over series	7	11
Survived chloroform and halothane		4	
Survived halothane, died on chloroform		2	
Survived halothane, died within one month		2	
Died during halothane		1	
			5
Survived chloroform, died on halothane		4	
Survived chloroform, died within one month		3	
Died during chloroform		8	
			15
	Total		31

employed routinely when rabbits, guinea pigs, rats, and mice are used, it is not generally considered in dog experiments. In the early part of the series the dogs were used as made available from the regular suppliers and little attention was paid to their condition. In the latter part of the experiment the dogs were used after examination and quarantine in the Vivarium. The quality of dog improved considerably.

Other factors which should be considered in a series such as this are:

1. The age of the dog.
2. The presence of pre-existing liver disease, particularly canine hepatitis (possibly infectious canine distemper and leptospira infections).
3. The nutritional state of the dog.
4. The season of the year, which would be related to such factors as Vitamin A and B deficiency, infectious diseases of seasonal incidence, and pregnancy (more probable in the spring and fall).
5. The breed of the dog.
6. The source of the dog, i.e. whether a spayed bitch pet, or a battle-scarred veteran of street-fighting.
7. Possible effects of the vermifuge (arecolime).

CONCLUSION

In the presence of hypoxia produced by 6 per cent oxygen in nitrogen, chloroform is significantly more hepatotoxic than halothane as measured by liver biopsy sections.

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RÉSUMÉ

Nous avons exécuté cette série d'expériences pour mettre en évidence les effets hépatotoxiques relatifs de l'halothane et du chloroforme. Pour faire cette étude, nous avons employé des chiens bâtards. Durant une semaine ou deux avant l'expérience, les chiens ont reçu une alimentation ordinaire. Nous avons exclu les chiens que nous croyions porteurs de maladies infectieuses. Nous n'avons pas donné de prémédication. Nous avons fait l'induction de l'anesthésie avec du thiopental à raison de 25 mg./kg. et nous avons intubé les chiens avec des tubes à ballonnet Magill; nous avons fait une biopsie hépatique à l'aiguille. Au moyen d'un système sans réinspiration, nous avons fait respirer aux chiens une atmosphère ne contenant que 6 pour cent d'oxygène dans de l'azote. Pour vaporiser l'halothane et le chloroforme nous avons utilisé un fluotec. Nous n'avons pas laissé la tension artérielle descendre au-dessous de 100 mm. Hg. Après trois heures d'anesthésie, nous répétions la biopsie hépatique, ainsi que deux jours et sept jours après l'anesthésie. Les survivants de la première expérience profitaient d'un mois de convalescence et étaient soumis à l'autre agent.

A cause du taux élevé de mortalité après l'épreuve chloroforme-hypoxie, nous n'avons pu faire l'expérience des deux agents que chez onze chiens; en présence d'hypoxie, l'halothane ne s'est pas avéré toxique pour le foie, mais une anesthésie subséquente au chloroforme a donné des signes de dommages hépatiques le deuxième jour chez quatre des sept chiens. A la première anesthésie, le chloroforme a produit des dommages hépatiques chez cinq des six chiens. Un mois plus tard, quatre de ces chiens ont survécu à une anesthésie à l'halothane, mais deux d'entre eux ont montré des dommages hépatiques à la biopsie du deuxième jour.

Nous pouvons affirmer en conclusion que, en présence d'une atmosphère hypoxique de 6 pour cent d'oxygène et d'azote, et d'après l'examen des biopsies hépatiques, le chloroforme est plus hépatotoxique que l'halothane et, cela, de façon marquée.

REFERENCES

1. HALEY, F. C. & WYANT, G. M. Canad. Anaesth. Soc. J. 6: 271-276 (1959).
2. Fluotec® Mark 2. Manufacturer's brochure.