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THE INFLUENCE OF THE HALOTHANE TEST ON HEART PARAMETERS, OCT-ACTIVITY, ACID-BASE BALANCE AND BLOOD ELECTROLYTES IN HALOTHANE-SENSITIVE PIGS AND IN PIGS PREMEDICATED WITH A β-BLOCKER (PROPRANOLOL)*

By

A. Schulman

SCHULMAN, A.: *The influence of the halothane test on heart parameters, OCT-activity, acid-base balance and blood electrolytes in halothane-sensitive pigs and pigs premedicated with a β-blocker (propranolol).* Acta vet. scand. 1982, *23*, 153—160. — The heart and liver functions, blood electrolytes and acid-base balance were studies in halothane-sensitive and nonsensitive pigs. An inhibition of the hyperthermia reaction was attempted by an i.v. injection of propranolol. The pulse rate of sensitive pigs was shown to be elevated already at the beginning of halothane narcosis. No other differences between sensitive and nonsensitive pigs were observed from the electrocardiogram. Ectopic beats and arythmia appeared only in 1 halothane-sensitive pig which died soon after the test. The serum OCT-activity showed no abnormalities. Hyperkalemia and acidosis occurred but the Ca^{++} was not elevated in halothane-sensitive animals. The slight elevation in Na^{+} was thought to be caused by hemoconcentration. A propranolol injection only delayed but did not inhibit the halothane reaction.

halothane test; heart function; EKG; OCT-activity; acid-base balance; blood electrolytes; β-blocker; pig.

Narcosis with 4—5 % halothane in oxygen flowing at a rate of 2—4 l/min and lasting 3—5 min triggers the malignant hyperthermia syndrome in stress-susceptible pigs when tested at more than 6 weeks of age (*Eikelenboom et al.* 1976, *Schulman* 1980,

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Webb 1981). The hyperthermia-sensitive pigs usually show an elevation of body temperature due to the extreme temperature rise in the muscles. Pigs display a metabolic and respiratory acidosis as well as a pronounced muscle rigidity when large amounts of lactic acid accumulate in their muscles (*Brenner et al.* 1978, *Jørgensen* 1981).

The exact halothane pathway is not known, but it seems that the effect is primarily induced in the striated muscles (*Britt & Kalow* 1970, *Lister* 1979, *Jørgensen* 1981). Many different theories on the halothane pathway have been proposed, but because different investigators have obtained conflicting results no single unambiguous theory has been arrived at.

In an attempt to shed more light on the way halothane acts on stress-susceptible pigs, heart and liver functions, the serum electrolyte content and blood gases were analyzed in some halothane-sensitive and nonsensitive pigs. The blockage of β-receptors was also attempted.

MATERIAL AND METHODS

The material was composed of pigs of the Finnish Landrace breed. The pigs were halothane tested at the age of 6—10 weeks. Both boars and sows were included in the test.

An electrocardiogram was performed during the halothane test on 11 sensitive and 46 nonsensitive pigs. Determination of the heart rate and the lead II complex was carried out. The first electrocardiogram measurement was made as soon as the pigs were asleep. The second measurement on the halothane-sensitive pigs was performed as soon as the halothane reaction had set in and on the nonsensitive pigs at the end of the test.

The liver function was determined by measuring the Ornithine carbamyltransferase (OCT; EC 2.1.3.3) activity in the serum from 21 halothane-sensitive and 38 nonsensitive pigs. Blood samples were collected from the vena cava cranialis as soon as the halothane test was completed and while the pigs were still asleep. The analytical method of *Ohshita et al.* (1976) was used. The K^+ and Na^+ levels in venous blood were determined by flame photometry and Ca^{++} levels by atomic spectrophotometry in samples collected immediately after the halothane test from 13 sensitive and 34 nonsensitive pigs. These analyses were conducted at the Department of Biochemistry, College of Vete-

rinary Medicine, Helsinki. Differences between means were tested for significance using the t-test.

The blood gases were determined in blood samples obtained from 8 sensitive and 4 nonsensitive pigs, collected from the vena cava cranialis immediately after the halothane test. The venous blood was drawn in a plastic syringe and the cones of the syringes sealed thermally. The syringes were then placed on ice cubes in a thermos container and analyzed within 3 h of sampling. These gas analyses were performed using an automatic analyser ABL 1, Radiometer, Copenhagen, at the Department of Veterinary Medicine, University of Helsinki.

In an attempt to block the function of the muscles by blocking the β-receptors, 5 halothane-sensitive pige were given propranolol i.v. 0.1 mg/kg body weight and 2 pigs 0.2 mg/kg body weight 10 min prior to the halothane test. All of these pigs had earlier been tested and been shown to be halothane sensitive.

RESULTS

The pulse rate was elevated, being significantly higher in the halothane-sensitive than in the halothane-nonsensitive group. This was already apparent at the onset of the halothane narcosis and was even more pronounced towards the end of the test (Table 1). No significant differences were observed in the amplitudes and durations of the electrocardiograms in the halothane-sensitive group when compared to the nonsensitive group (Table 1).

One halothane-sensitive pig nevertheless contracted arythmia and some ectopic beats and died soon after the test.

In halothane-sensitive pigs the mean OCT activity in serum was 3.58 ± 0.27 and in pigs not sensitive to halothane 3.58 ± 1.17. No difference in activity between these groups could be seen. The Na^+ and K^+ levels in serum were higher in the halothane-sensitive pigs but no differences were observed in the Ca^{++} levels between the 2 groups (Table 2).

The blood pH and partial O_2 were lower in halothane-sensitive than in halothane-nonsensitive pigs. The mean pH values were 6.9 ± 0.1 and 7.19 ± 0.2 and the pO_2 values were 51 ± 3.6 and 57.5 ± 5.5 mmHg, respectively. The pCO_2 was higher in sensitive pigs than in nonsensitive pigs, showing values of 108.7 ± 21 and 88.8 ± 26 mmHg, respectively.

Table 1. Electrocardiogram of halothane-sensitive and halothane-nonsensitive pigs measured at the beginning (1) and at the end (2) of halothane narcosis.

			Halothane-sensitive $\bar{x} \pm s$ (n = 11)	Halothane-nonsensitive $\bar{x} \pm s$ (n = 46)	Level of significance of difference between means
Pulse rate		1	215 ± 28	188 ± 32	++
		2	221 ± 38	184 ± 20	+++
Amplitude (mm)	T	1	1.3 ± 0.33	1.3 ± 0.45	n.s.
		2	1.1 ± 0.35	1.2 ± 0.53	n.s.
	P	1	1.5 ± 0.91	1.3 ± 0.55	n.s.
		2	1.7 ± 0.70	1.7 ± 0.93	n.s.
Duration (msec)	P	1	36.0 ± 9.42	37.9 ± 10.61	n.s.
		2	36.5 ± 9.42	37.9 ± 10.61	n.s.
	PQ	1	73.0 ± 13.81	80.3 ± 16.07	n.s.
		2	77.0 ± 15.52	81.6 ± 11.16	n.s.
	QRS	1	46.4 ± 13.76	40.0 ± 11.80	n.s.
		2	47.5 ± 13.76	41.0 ± 10.26	n.s.
	QT	1	168.0 ± 18.33	177.0 ± 29.0	n.s.
		2	168.8 ± 24.1	179.2 ± 17.5	++
	T	1	52.5 ± 8.92	46.1 ± 9.9	n.s.
		2	57.4 ± 14.7	50.9 ± 12.0	n.s.
	T-P	1	58.5 ± 20.5	63.9 ± 21.9	n.s.
		2	54.5 ± 20.2	59.3 ± 21.9	n.s.

The propranolol injection did not arrest the development of hyperthermia but it did delay the onset of the reaction. There were no discrepancies between the two different doses of propranolol used. All pigs developed the typical halothane sensitivity reaction but the symptoms of muscle rigidity began 2.5 min after the beginning of narcosis. In the previous test the symptoms of these pigs began to develop 30 s to 1.5 min after the initiation of the halothane narcosis.

DISCUSSION

Many investigators have shown that the heart rate will rise in halothane-sensitive pigs during the halothane test (*Lucke et al.* 1976, *Jørgensen* 1981). In this investigation it was demonstrated that already at the very beginning of halothane narcosis,

Table 2. K^+, Na^+ and Ca^{++} levels in serum from halothane-sensitive and halothane-nonsensitive pigs.

Electrolytes in serum	Halothane-sensitive $\bar{x} \pm s$ (n = 13)	Halothane-nonsensitive $\bar{x} \pm s$ (n = 34)	Level of significance of difference between means
K^+	4.2 ± 0.1 mmol/l	3.5 ± 0.3 mmol/l	+++
Na^+	146 ± 20 „	143 ± 20 „	++
Ca^{++}	2.6 ± 0.3 „	2.6 ± 0.2 „	n.s.

n.s. = not significant $P > 0.05$
++ = significant $P \leq 0.01$
+++ = highly significant $P \leq 0.001$

the heart rate of halothane-sensitive pigs was higher than the pulse of nonsensitive pigs, being more than 200 beats/min. The strain inevitably caused by catching, carrying and holding the animals had a still greater influence on the pulse rate of halothane-sensitive pigs than on halothane-nonsensitive pigs. The elevation of the heart rate in halothane-sensitive animals was most probably not a result of the specific effect of halothane but rather the sign of a greater sensitivity to all forms of stress. Arythmias and ectopic pulse rate as described by *Lucke et al.* and *Jørgensen* were observed only in 1 halothane-sensitive pig, which died soon after the test.

The curtailed duration of the QT complex and to a lesser extent all other durations in the electrocardiogram of halothane-sensitive pigs are explained by the higher pulse rate in these animals compared to pigs not sensitive to halothane. Despite many proposals to the contrary, there seems to be no firm evidence that cardiomyopathy exists in sensitive animals. Experiments with Pietrain pigs showed that cardiac output was readily stimulated often more than twofold during the reaction and only terminally was there any indication of gross impairment of the cardiac function. Clear signs of peripheral vasoconstriction was observed, however, quite early in the course of the reaction (*Lucke et al.*).

Acidosis as well as hyperkalemia developed in halothane-sensitive pigs during the halothane test. Hyperkalemia may explain the effects seen on the heart function in the terminal state of hyperthermia. According to *Brenner et al.* (1978), acidosis is both metabolic and respiratory. According to *Lister*

(1979), marked hyperkalemia is possibly due to the stimulating effect of circulating cathecolamines on hepatic glycogenolysis. The slight elevation witnessed in the Na^+ level was most likely due to the hemoconcentration which occurs in the halothane test according to *Allen et al.* (1970). An elevation in the serum Ca^{++} level was not observed in this investigation, but it has been a common finding in other studies (*Lucke et al., Van den Hende et al.* 1976, *Jørgensen*). *Jørgensen* found an increased Ca^{++} level in the serum from halothane-sensitive and nonsensitive pigs. A disturbance in the muscle Ca-metabolism is supposed to play a central role in the pathogenesis of hyperthermia, induced in stress-susceptible pigs by halothane. The results obtained for Ca metabolism are confusing, however (*Cheah & Cheah* 1976, *Lucke et al., Van den Hende et al., Jørgensen*).

According to *Berman et al.* (1970), energy metabolism in the liver will rise during the halothane test, but the liver does not seem to play an important role in the hyperthermia reaction. *Britt et al.* (1978) concluded that the liver either works normally or else abnormalities are so minor that they cannot be measured. *Hall et al.* (1980) concluded that there was no evidence of a major abnormality of the hepatic function during porcine hyperthermia. In this investigation serum OCT activity shows no abnormalities, indicating that the liver function was about normal in both halothane-sensitive and halothane-nonsensitive pigs during halothane narcosis.

If cathecolamines play a central role in the hyperthermia syndrome, then their action on the muscle glycogenolysis ought to be transmitted through the β-receptors (*Carlsson et al.* 1979). The fact that blocking these receptors with propranolol did not inhibit the hyperthermia reaction could be a result of the dosage of propranolol used or the probability that cathecolamines are not of primary importance in the development of hyperthermia in pigs. *Lister et al.* (1976) reported that they inhibit the hyperthermia reaction by blocking the α-receptors, but not the β-receptors.

CONCLUSIONS

The results of this study indicate that the effect of halothane on the muscles is most probably directed immediately toward the striated muscles and is not a consequence of disturbances of the heart or liver functions. Acidosis as well as hyperkalemia

developed. Hypercalcemia, reported by other investigators, was not observed. The cathecolamines did not seem to play a primary role in the development of the hyperthermia reaction.

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SAMMANDRAG

Halothantestens inverkan på hjärtparametrene, OCT-aktiviteten, syrebas balancen och blod elektrolyterna hos halothankänsliga och halothanresistenta grisar, samt hos grisar som prämedicinerats med en β-blokerare (propranolol).

Hjärtverksamheten, OCT serumaktiviteten, syre-basbalansen och blod elektrolyterna bestämdes på halotantestade finska lantrasgrisar. Ett försök att förhindra halotankänslighetsreaktionen med hjälp av en β-blokerare (propranolol) gjordes även.

Förutom en hos de halotankänsliga djuren redan i början av halotannarkosen konstaterad ökning av pulsfrekvensen sågs inga statistiskt signifikanta skillnader i EKG hos de känsliga och icke känsliga djuren. Hos en halotankänslig gris konstaterades dock arytmi och extra slag. Denna gris dog ca 10 min efter testen.

Mellan de känsliga och de okänsliga grisarna sågs ingen skillnad i OCT-aktiviteten.

En hyperkalemi samt lindrigt förhöjd Na^+ konstaterades hos de känsliga djuren. Ca^{++} var däremot densamma i båda grupperna.. Hos de halotankänsliga djuren utvecklades en acidos. En propranolol injection 10 min före testen fördröjde halotanreaktionen men förhindrade den icke.

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Reprints may be requested from: Axel Schulman, the National Veterinary Institute, P. O. Box 368, 00101 Helsinki 100, Finland.