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Porcine Malignant Hyperthermia Induced by Halothane and Succinylcholine:

Failure of Treatment with Procaine or Procainamide

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Metabolic, hemodynamic and neuroendocrine responses to the combined use of halothane and succinylcholine (SCh) were measured in five normal swine and five swine susceptible to malignant hyperthermia (MH). Constant-volume ventilation was used, and no therapy was instituted. The overall response in susceptible swine was fulminant, in that it involved the rapid onset of SCh-induced MH combined with the more severe metabolic, endocrine, and cardiovascular effects of halothane-induced MH. Maximal changes in $\dot{V}_{O_2}$ were equivalent with either drug or both combined, while changes in lactate, potassium (K^+), *p*H, and catecholamines were perhaps synergistic. Utilizing similar measurements, procaine or procainamide was used in 20 susceptible swine in attempts to prevent MH initiated by halothane, SCh, or both. Recommended therapeutic doses of either drug did not prevent characteristic MH changes in oxygen consumption, cardiac output, lactate, K^+, *p*H, catecholamines, or temperature. (Key words: Hyperthermia, malignant pyrexia; Anesthetics, volatile, halothane; Neuromuscular relaxants, succinylcholine; Anesthetics, local, procaine.)

WHILE HALOTHANE[1] and succinylcholine (SCh)[2] are equally effective in increasing aerobic metabolism and temperature during malignant hyperthermia (MH), halothane is more effective than SCh in changing lactate, potassium (K^+), catecholamines, and *p*H. The present studies quantitate combined metabolic, hemodynamic and neuroendocrine effects of both agents in swine susceptible to MH (MHS swine) in order to compare these effects with those of each drug separately.

Inasmuch as there has been continuing controversy about the value of procaine in treatment of MH,[3–13] the present studies also attempt to resolve this question.

Materials and Methods

Twenty-five MHS swine were so identified by a screening test involving inhalation of halothane.[1] They and five normal Poland China swine, all weighing 30–60 kg, were prepared as previously[4] for measurements yielding values for oxygen consumption of whole body ($\dot{V}O_{2B}$) and hind limb ($\dot{V}O_{2L}$), cardiac output ($\dot{Q}$), *p*H, blood gases, lactate, K^+, catecholamines, and temperature. Anesthesia included thiopental, N_2O, and controlled ventilation to Pa_{CO_2} 40 ± 2 torr. Control data were obtained in triplicate over a 15-minute period. During each of the following protocols, ventilation remained unchanged, and subsequent measurements were made every 10 minutes.

Five MHS and the five normal swine were given continuous 1 per cent halothane and, after 15 minutes, SCh (3 mg/kg) was administered intravenously; there was no therapeutic intervention.

In attempts to prevent MH, the remaining 20 MHS swine each received an intravenous infusion of procaine or procainamide 10 minutes before the halothane and/or SCh was administered. Fifteen swine received procaine, 30 mg/kg/4 min, plus 1 mg/kg/min, continuously; five of these were then given 1 per cent halothane; five, SCh (3 mg/kg); five, both halothane and SCh, as described above. The five remaining swine received procainamide, 4 mg/kg/2 min, plus 1 mg/kg/min for

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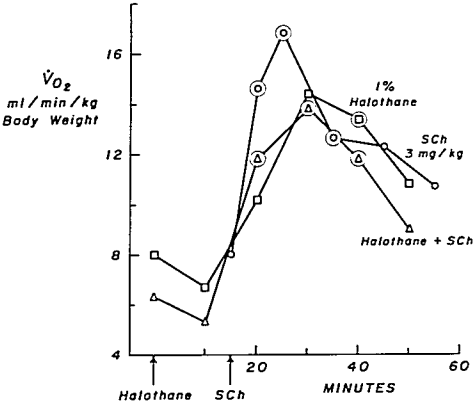

FIG. 1. Whole-body $\dot{V}_{O_2}$ of MHS swine in response to halothane, SCh, or both. SCh graph begins at 15 minutes. Mean values; ○ significantly different from control values. Data for halothane and SCh alone from prior studies.[1,2]

10 minutes followed by 0.25 mg/kg/min continuously. These animals were given both halothane and SCh as described above. No other therapy for MH was used.

Results are expressed as mean ± standard error (SE) with comparisons by paired t test, $P < 0.05$ considered significant. Evaluation of the responses to procaine and procainamide was by comparison of individual and mean responses to previously observed responses during MH initiated by the same stimuli in the absence of therapeutic agents.[1,2]

Results

In normal swine, the combination of halothane and SCh produced either effects peculiar to one drug or cancellation of opposing physiologic trends (table 1). SCh-related effects included small increases in lactate and

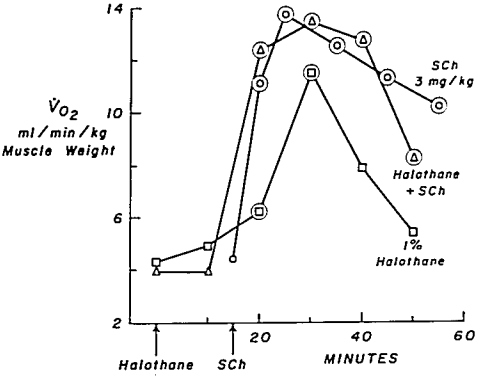

FIG. 2. Hind-limb $\dot{V}_{O_2}$ of MHS swine in response to halothane, SCh, or both. SCh graph begins at 15 minutes. Mean values; ○ significantly different from control values. Data for halothane and SCh alone from prior studies.[1,2]

TABLE 1. Effects of 1 Per Cent Halothane and Succinylcholine (3 mg/kg) in Five Normal Swine

	Control		10 Min		20 Min		30 Min		40 Min		50 Min	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Lactate (μm/ml)												
Arterial	1.6	0.3	1.7	0.2	2.1*	0.4	2.5*	0.5	2.3*	0.3	2.0	0.1
Limb vein	1.6	0.3	1.8	0.2	2.4*	0.4	2.3*	0.2	2.4*	0.2	2.4*	0.1
K^+ (mEq/l)												
Arterial	3.6	0.4	3.8	0.4	4.2*	0.5	4.2*	0.4	4.1	0.4	4.1	0.4
Limb vein	3.6	0.3	3.8	0.4	4.3*	0.5	4.4*	0.4	4.2	0.4	4.1	0.4
Limb $\dot{V}_{O_2}$ (ml/min/kg muscle weight)	4.6	0.9	4.1	1.2	5.3	1.8	4.9	1.5	5.1	1.4	5.0	1.2
Lactate/pyruvate												
Arterial	12.6	1.2	11.8	1.4	14.7	2.6	17.4	3.8	17.0	3.0	15.5	1.9
Limb vein	12.0	1.5	12.7	1.1	15.6	1.7	16.2	1.7	16.7	1.4	15.8	0.7
P_{O_2} (torr), limb vein	53	4	53	5	48	5	50	4	49	4	47	4
Temperature (C), limb vein	36.3	0.4	36.1	0.4	36.0	0.5	36.0	0.5	36.0	0.4	35.9	0.4
Heart rate (/min)	136	13	131	10	142	14	142	16	134	14	144	18
pH_a	7.50	0.03	7.52	0.02	7.48	0.03	7.48	0.03	7.49	0.02	7.47	0.02
Pa_{CO_2} (torr)	41	2	36	1	38	2	39	1	38	1	37	1
$P\bar{v}_{CO_2}$ (torr)	50	2	46	2	50	3	49	3	48	3	49	2

Epinephrine (μg/ml)	0.27	0.04	0.32	0.03	0.27	0.02	0.34	0.04	0.34	0.04	0.47	0.12
Norepinephrine (ng/ml)	0.52	0.11	0.55	0.14	0.63	0.11	0.61	0.13	0.57	0.10	0.64	0.13
Whole-body $\dot{V}_{O_2}$ (ml/min/kg body weight)	6.7	0.8	5.2*	0.4	5.9	0.7	5.6*	0.8	5.3*	0.6	5.2*	0.4
Temperature (C), right atrium	37.2	0.4	37.1	0.4	37.0	0.4	37.0	0.4	36.9	0.4	36.9	0.4
$\dot{Q}$ (ml/min/kg body weight)	103	8	90	4	97	8	95	6	84	7	77	5
Arterial pressure, mean (torr)	140	10	81*	7	78*	9	86*	8	86*	8	89*	8
Limb flow (ml/min/kg muscle weight)	98	9	89	10	95	10	95	7	94	9	89	8

Halothane began at zero time, SCh at 15 min.
* Significantly different from control, $P < 0.05$.

K^+.[2] Halothane-related effects included decreases in $\dot{V}O_{2s}$ and mean arterial pressure.[1] Cancellation of opposing trends was reflected in the absence of change in $\dot{V}O_{2L}$, $\dot{Q}$, and temperature.

In untreated MHS swine (table 2), halothane produced no discernible effect in the initial 10 minutes other than a decrease in mean arterial pressure. Following SCh at 15 minutes, further measurements at 20 minutes disclosed abrupt changes in most variables examined—$\dot{V}_{O_2}$, lactate, K^+, pH, Pa_{CO_2}, and P_{O_2L}. At 30 minutes, temperature, heart rate, and catecholamines had increased, while $\dot{Q}$ and limb flow were stable until the final measurements at 50 minutes. Rigidity occurred in all animals between 20 and 40 minutes. Figures 1–5 compare individual[1,2] and combined effects of halothane and SCh on $\dot{V}_{O_2}$, lactate, K^+, and catecholamines. Changes in both $\dot{V}O_{2s}$ and $\dot{V}O_{2L}$ (figs. 1 and 2) were not different in magnitude or duration. Changes in lactate, K^+, and catecholamines (figs. 3–5) after both agents combined followed the general pattern of those caused by halothane by itself, but initially appeared greater than the additive changes for the two agents individually. Additive changes were calculated as the sum of the change from the control value at a given time with halothane and the change from control at the same time with SCh. Pa_{O_2}'s remained above 120 torr in all ten animals.

Every animal given procaine or procainamide had MH that was qualitatively and quantitatively similar to mean responses in this and other[1,2] studies. Rigor was observed, as before, in swine given halothane,[1] or halothane and SCh. Neither mean nor individual values are reported, as the extensive data are not different from those previously reported. Representative values are found in table 2 and figures 1–5.

Discussion

The combined use of halothane and SCh to induce MH resulted in the abrupt onset that is associated with SCh[2] and maximal changes equal to or greater than those associated with halothane.[1] The patterns of increases in both $\dot{V}O_{2s}$ and $\dot{V}O_{2L}$ were similar to those observed following either drug alone, *e.g.*, either or both produced the same ef-

TABLE 2. Effects of 1 Per Cent Halothane and Succinylcholine (3 mg/kg) in Five MHS Swine

	Control		10 Min		20 Min		30 Min		40 Min		50 Min	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Lactate (μm/ml)												
Arterial	1.8	0.2	2.2	0.2	10.8*	1.4	15.7*	1.7	19.2*	1.9	23.1*	1.8
Limb vein	1.8	0.2	2.0	0.1	13.6*	1.7	18.0*	2.0	21.0*	1.8	23.7*	1.4
K^+ (mEq/l)												
Arterial	3.7	0.1	3.8	0.1	6.6*	0.7	7.5*	0.5	8.4*	0.5	8.9*	0.4
Limb vein	3.7	0.1	3.8	0.1	7.0*	0.6	7.9*	0.5	9.1*	0.5	10.3*	0.6
Limb $\dot{V}_{O_2}$ (ml/min/kg muscle weight)	3.9	0.4	3.9	0.4	12.3*	1.6	13.4*	1.3	12.7*	0.5	8.2*	1.6
Lactate/pyruvate												
Arterial	11.2	0.8	11.7	1.3	45.8*	6.2	72.8*	5.4	100.6*	11.3	127.1*	17.3
Limb vein	13.0	0.9	13.3	1.0	46.1*	2.6	68.9*	5.5	86.9*	5.2	105.0*	11.0
$P_{O_{2L}}$ (torr), limb vein	48	3	40	2	20*	2	18*	3	14*	1	13*	1
Temperature (C), limb vein	37.1	0.2	36.6	0.3	37.4	0.3	38.4*	0.5	39.6*	0.4	40.4*	0.0
Heart rate (/min)	137	13	121	11	178	16	211*	11	228*	11	236*	9
pH_a	7.54	0.01	7.52	0.03	7.15*	0.04	6.97*	0.05	6.89*	0.04	6.85*	0.02
$P_{a_{CO_2}}$ (torr)	37	1	37	1	69*	9	83*	9	79*	9	59*	12
$P\bar{V}_{CO_2}$ (torr)	48	2	48	2	103*	9	133*	13	141*	10	143*	8

Epinephrine (ng/ml)	0.28	0.06	0.25	0.03	2.22	1.17	6.92*	3.45	10.67*	3.66	14.96*	4.20
Norepinephrine (ng/ml)	0.42	0.12	0.37	0.09	2.66	0.88	8.43*	2.72	12.17*	2.01	11.24*	1.55
Whole-body $\dot{V}_{O_2}$ (ml/min/kg body weight)	6.3	0.6	5.3	0.4	11.8*	0.8	13.8*	1.2	11.8*	1.0	9.0	1.9
Temperature (C), right atrium	37.5	0.3	37.3	0.4	37.6	0.3	38.7*	0.4	39.8*	0.4	40.7*	0.3
$\dot{Q}$ (ml/min/kg body weight)	84	7	72	4	91	7	90	9	74	9	52*	13
Arterial pressure, mean (torr)	122	10	73*	4	69*	4	68*	8	62*	6	50*	7
Limb flow (ml/min/kg muscle weight)	66	3	49*	6	78	8	83	4	73	3	44*	8

† Halothane began at zero time, SCh at 15 min.
* Significantly different from control, $P < 0.05$.

fect without additive or synergistic effects. Once initiated, the pattern of aerobic changes was apparently related to MH *per se* and to the ensuing modifications caused by elevated temperature, stress, and circulatory failure.

As with either drug alone,[1,2] increases in muscle $\dot{V}_{O_2}$ did not entirely account for increases in whole-body $\dot{V}_{O_2}$. Control $\dot{V}O_{2_B}$ in a 40-kg pig was 252 ml/min, which increased during MH to 552 ml/min. This 300-ml increase included about 15 ml due to increased temperature, for a net increase of 285 ml. Since a well-muscled pig is about 50 per cent muscle by weight,[14] control $\dot{V}_{O_2}$ for skeletal muscle was 78 ml/min, which increased during MH to 268 ml/min. This 190-ml increase included about 6 ml due to increased temperature, for a net extrapolated increase of 184 ml. Thus, of a 285-ml increase in $\dot{V}O_{2_B}$, 184 ml may be due to increased muscle $\dot{V}_{O_2}$, leaving unaccounted for 101 ml, or 35 per cent, an amount similar to those calculated for halothane[1] and SCh[2] alone.

This discrepancy between increases in total muscle $\dot{V}_{O_2}$ and whole-body $\dot{V}_{O_2}$ may be related to errors in measurements and calculations or to active participation of other tissues in MH. Calculations based upon the Fick relationship using data obtained during an unsteady state provide only qualitative information.[15] Not all hind-limb flow could be measured, due to extensive inaccessible collateral circulation; this could result in underestimating $\dot{V}O_{2_L}$. Not all muscle throughout the body may react the same in MH. Responses were consistent, however, and appeared to reflect those changes of whole-body and muscle $\dot{V}_{O_2}$ that occur in MH resulting from the combined use of halothane and SCh.

Increases in lactate, K^+, and catecholamines were consistently greater (figs. 3–5) than the sums of the individual increases previously reported for SCh[2] and halothane.[1] This possible synergism between halothane and SCh is consistent with the inhibitory effect of halothane upon the calcium pump and calcium storage areas of MH subjects.[16] After prior inhibition by halothane, the abnormal calcium-fixing mechanism is less efficient in handling the increase in free intracellular calcium produced by SCh,[2] and the immediate response is greater than that expected from their added

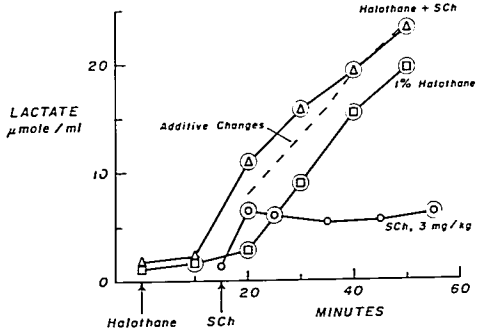

FIG. 3. Arterial plasma lactate concentrations of MHS swine in response to halothane, SCh, or both. SCh graph begins at 15 minutes. ---- is graph of additive changes from control of halothane and of SCh. O significantly different from control values. Data for halothane and SCh alone from prior studies.[12]

effects. However, $\dot{V}_{O_2}$ was, unexpectedly, not different with either or both agents. $\dot{V}_{O_2}$ may increase more than two- or threefold during exercise,[17] but this magnitude of increase is apparently the limit for the mean response of MHS swine. Halothane also has been reported to affect normal human muscle in such a manner that SCh induces a greater postoperative release of creatine phosphokinase[18] than that observed after N_2O. This, too, suggests an effect of halothane upon the muscle fiber membrane or upon intracellular mechanisms.

The use of recommended therapeutic doses[5-7] of procaine and procainamide in the treatment of MH provided no protection in porcine MH. Findings in every animal satisfied previous pathophysiologic criteria.[1,2] Human and porcine MH, although probably not identical, have many similarities. Inasmuch as the toxic limitations of procaine in pig and man *in vivo* prevent the attainment of concentrations considered effective *in vitro*,[8,13] the implication is that procaine is probably also ineffective in protecting against human MH. Reports supportive of the therapeutic role of procaine[5-8] generally arise from studies that also include the use of adjunctive therapy such as cooling, hyperventilation, and bicarbonate, and it is difficult to know which were effective in finally "turning the tide."

Harrison[7] reported that procaine limited or blocked MH induced by SCh or halothane but not MH induced by both agents. His studies included measurements of temperature, some biochemical studies, and observations of rigor. Monitoring primarily temperature and limb muscle tone is generally inadequate in estimating either the magnitude of the MH response[1,2]—aerobic and anaerobic metabolism, acidosis, hyperkalemia, hypo-

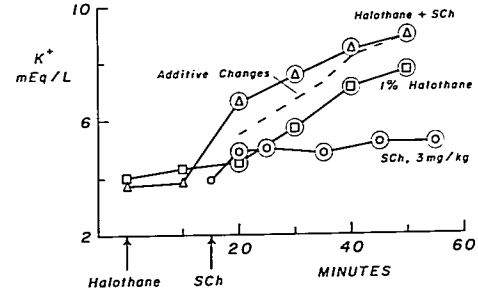

FIG. 4. Arterial plasma K^+ concentrations of MHS swine in response to halothane, SCh, or both. SCh graph begins at 15 minutes. ---- is graph of additive changes from control of halothane and of SCh. O significantly different from control values. Data for halothane and SCh alone from prior studies.[1,2]

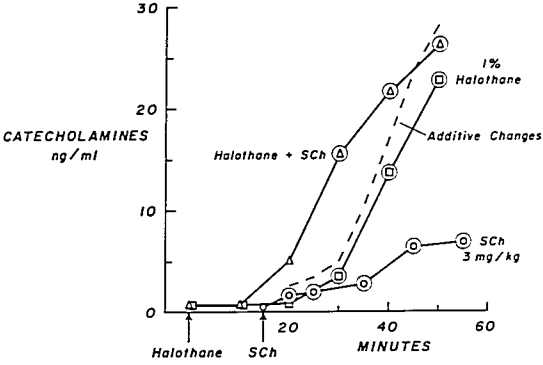

FIG. 5. Total plasma catecholamines of MHS swine in response to halothane, SCh, or both. SCh graph begins at 15 minutes. - - - - is graph of additive changes from control of halothane and of SCh. O significantly different from control values. Data for halothane and SCh alone from prior studies.[1,2]

tension, and declining cardiac output—or the progression of MH[1,2]. In the absence of therapy, if $\dot{V}_{O_2}$ and Pa_{CO_2} have returned towards normal and acidosis is primarily metabolic, then MH is nearing its end-stage.[1]

In the present study, the use of procaine was not associated with arrhythmias or hypotension, despite the warnings of Harrison.[7] We relate this absence of complications to normal blood gases, metabolism and temperatures prior to the cautious introduction of procaine, plus constant monitoring of electrocardiogram and direct arterial pressure.

The overall MH response following the use of halothane and SCh combined is fulminating, in that it involves the rapid onset of severe metabolic and endocrine responses that lead inexorably to fatal acid–base, temperature, and circulatory disorders. The present results suggest that a predictable and complete porcine model of MH requires the use of both agents as triggers. Successful treatment of established MH and prevention of its inception must also be determined in relation to the most fulminant form of MH. Procaine and procainamide were ineffective in preventing MH, and are therefore unlikely to be helpful in the treatment of established MH.

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Obstetric Anesthesia

CESAREAN SECTION UNDER LOCAL The histories of 5,010 patients whose infants were delivered by the senior author over a period of 25 years are reviewed. Of these deliveries, cesarean section was performed in 283 (5.6 per cent). In 218 of these patients, only local field block of the abdominal wall was done prior to the birth of the baby. When local anesthesia was used, 92 per cent of newborn babies cried spontaneously at once. There were 48 premature babies and seven neonatal deaths, the latter caused primarily by complications of pregnancy and secondarily by prematurity. Fetuses already at high risk are most benefited by the use of local anesthesia prior to birth. Many of the patients experiencing this method had second, third, and even fourth cesarean sections with the use of local anesthesia. *(Ranney B, Stanage WF: Advantages of Local Anesthesia for Cesarean Section. Obstet Gynecol 45: 163–167, 1975.)*

BUPIVACAINE EPIDURAL Lumbar epidural analgesia with bupivacaine was given to 37 women for uncomplicated labor. After the blockade, serial determinations of *p*H and bupivacaine concentration were made in fetal scalp blood and maternal venous blood and there was continuous monitoring of the fetal heart rate. Fetal scalp blood *p*H was within normal limits and no pathologic FHR tracings were elicited by the blockade, although a temporary decrease of the baseline fetal heart rate irregularity was seen in about a fifth of the cases. Fetal drug concentrations were low, about 1 fourth of corresponding maternal values. After reinjection of bupivacaine the extents of drug accumulation in fetal and maternal blood were fairly similar. *(Belfrage P, and others: Lumbar Epidural Analgesia with Bupivacaine in Labor. Am J Obstet Gynecol 121: 360–365, 1975.)*

Fetal Development

NEURAL TUBE DEFECTS The prenatal diagnosis of neural tube defects (such as anencephaly, myelomeningocele) is now possible in about 90 per cent of cases by assaying the amniotic fluid for alpha-fetoprotein. The accuracy of beta-trace protein assays on amniotic fluid samples from defective fetuses was compared with alpha-fetoprotein studies. Alpha-fetoprotein studies provided more reliable results than beta-trace protein. *(Milunsky A, and others: Prenatal Detection of Neural Tube Defects. Am J Obstet Gynecol 122: 313–315, 1975.)*