Table III—Observed Differences between GLC and HPLC Assay of Drug Blood Profiles

Drug	Percent Difference: Maximum Observed	Percent Difference: Average[a]	AUC[b], % Difference
Chlorpropamide[c,d]	8.60	4.25	1.13
Tolbutamide[d,e]	14.10	7.41	1.90

[a] Mean of absolute differences. [b] Area under the plasma concentration–time curve (chlorpropamide, 0–168 hr; and tolbutamide, 0–28 hr). [c] Chlorpropamide was extracted by Method 2 for both HPLC and GLC. [d] Conditions for HPLC as in Table I. [e] Tolbutamide was extracted by Method 2 for GLC and by Method 3 for HPLC.

fast, sensitive, and specific for the determination of chlorpropamide and tolbutamide. Application of the method to plasma profiles in human volunteers showed that it can be used in single- and multiple-dose pharmacokinetic studies.

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[x] To whom inquiries should be directed.

Effects of Intravenous Dantrolene Sodium on Respiratory and Cardiovascular Functions

K. O. ELLIS [x], F. L. WESSELS, and J. F. CARPENTER

Abstract □ Dantrolene sodium, a peripherally acting skeletal muscle relaxant, at doses up to 30 mg/kg iv had no effect on respiratory volume, respiratory rate, blood pressure, or heart rate in anesthetized dogs. The ED_{50} for inhibition of skeletal muscle contractions was 4.5 mg/kg in anesthetized dogs. In anesthetized sheep, the ED_{50} for skeletal muscle relaxation was 3.2 mg/kg under methoxyflurane anesthesia and 1.7 mg/kg under pentobarbital anesthesia. Unanesthetized sheep administered doses up to 30 mg/kg iv evidenced no dose-related cardiovascular effects. Respiratory volume decreased and respiratory rate increased, with the net result that the respiratory minute volume was not affected by dantrolene sodium. The results indicate that dantrolene sodium has no effect on the cardiovascular or respiratory systems that would preclude its use intravenously in acute conditions where direct relaxation of skeletal muscle is required, as in the management of malignant hyperthermia.

Keyphrases □ Dantrolene sodium—effects on respiratory and cardiovascular functions, dogs and sheep □ Respiratory functions—effects of dantrolene sodium, dogs and sheep □ Cardiovascular functions—effects of dantrolene sodium, dogs and sheep □ Relaxants, skeletal muscle—dantrolene sodium, effects on respiratory and cardiovascular functions, dogs and sheep

Dantrolene sodium[1], a new skeletal muscle relaxant, has therapeutic utility in chronic spasticity (1–4). The primary site of action of dantrolene sodium is outside the central nervous system (CNS) (5–8). It does not alter neuromuscular transmission or affect the electrical excitability of the muscle membrane (9, 10) but acts by uncoupling excitation–contraction mechanisms (11, 12). The hypothesized mechanism of dantrolene sodium's action is a decrease in release of Ca^{+2} from the sarcoplasmic reticulum (9, 13, 14).

The unique pharmacological action of dantrolene sodium suggests that it might be useful in the treatment of a condition characterized by muscle rigidity and elevated myoplasmic calcium (*i.e.*, malignant hyperthermia) (15). Recently, in the established syndrome of malignant hyperthermia in susceptible (MHS) swine, dantrolene sodium caused a rapid loss of muscle rigor commencing within 5 min, an immediate cessation of the increase in deep muscle temperature followed by a

[1] Dantrium, Eaton Laboratories, a subsidiary of Norwich Pharmacal Co., Division of Morton-Norwich Products, Norwich, N.Y.

Table I—Effect of Dantrolene Sodium on Cardiovascular and Respiratory Functions in Anesthetized Dogs[a]

Experiment	Treatment	Arterial Blood Pressure[b], mm Hg	Mean Arterial Blood Pressure[c], mm Hg	Heart Rate, beats/min	Gastrocnemius Muscle Twitch Tension, g	Rectal Body Temperature	Respiratory Rate per Minute[d]	Respiratory Volume[e]	Minute Volume[f]
1	Control (prior to drug administration)	150/100	117	170	920	36.0°	11	142	1562
2		175/125	142	160	1280	37.0°	11	170	1870
3		155/110	125	140	1020	36.2°	14	185	2590
4		155/120	132	170	1440	37.0°	11	143	1573
5		170/115	133	150	1220	36.9°	15	99	1485
$\bar{X}$		161/114	129.8	158	1176	36.6°	12.4	147.8	1816
±*SE*		4.8/4.3	4.2	5.8	92.8	0.2°	0.9	14.7	204
1	Dantrolene sodium, 0.1 mg/kg iv	150/100	117	150	880	—	11	150	1650
2		175/125	142	150	1240	—	11	160	1760
3		160/110	127	140	990	—	14	170	2380
4		160/120	133	170	1390	37.0°	10	163	1630
5		175/115	135	150	1180	36.9°	13	118	1534
$\bar{X}$		164/114	130.8	152	1136	37.0	11.8	152.2	1790
±*SE*		4.8/4.3	4.2	4.9	90.6	0.1°	0.7	9.1	151
Percent change		+1.8/0	+0.8	−3.8	−3.4	+0.8°	−4.8	+3.0	−1.4
1	Dantrolene sodium, 0.4 mg/kg iv	150/100	117	150	720	—	11	125	1375
2		180/130	147	150	1060	37.0°	11	163	1793
3		160/110	127	130	840	36.2°	13	175	2275
4		160/120	133	170	1200	37.0°	11	160	1760
5		175/115	135	150	1020	36.8°	15	118	1770
$\bar{X}$		165/115	131.8	150	968	36.8°	12.2	148.2	1795
±*SE*		5.5/5.0	4.9	6.3	84.5	0.2°	0.8	11.2	143
Percent change		+2.5/+0.9	+1.5	−5.1	−17.7	+0.5°	−1.6	+0.3	−1.2
1	Dantrolene sodium, 1.4 mg/kg iv	150/95	113	150	510	35.5°	12	150	1800
2		185/135	152	150	840	—	11	171	1881
3		170/110	130	130	650	36.1°	11	160	1760
4		165/120	135	170	980	36.9°	11	143	1573
5		175/115	135	140	840	36.2°	16	112	1792
$\bar{X}$		169/115	133.0	148	764	36.2°	12.2	147.2	1761
±*SE*		5.8/6.5	6.2	6.6	82.4	0.3°	1.0	10.0	51
Percent change		+4.9/+0.9	+2.5	−6.3	−35.0	−1.1°	−1.6	−0.4	−3.0
1	Dantrolene sodium, 4.4 mg/kg iv	145/90	107	140	320	35.0°	14	119	1666
2		180/130	147	140	620	36.3°	12	141	1692
3		170/110	130	140	440	36.0°	14	181	2534
4		170/120	137	160	770	36.8°	12	125	1500
5		175/115	135	140	620	36.0°	16	118	1888
$\bar{X}$		168/113	131.2	144	554	36.0°	13.6	136.8	1856
±*SE*		6.0/6.6	6.7	4.0	78.5	0.3°	0.8	11.8	180
Percent change		+4.3/−0.9	+1.1	−8.9	−52.9	−1.6°	+9.7	−7.4	+2.2
1	Dantrolene sodium, 14.4 mg/kg iv	150/80	103	120	235	34.5°	12	125	1500
2		185/130	148	130	470	36.0°	12	144	1728
3		175/115	135	180	390	36.0°	16	170	2720
4		170/120	137	150	600	36.2°	10	153	1530
5		175/110	132	130	580	35.1°	13	112	1456
$\bar{X}$		171/111	131.0	142	455	35.6°	12.6	140.8	1787
±*SE*		5.8/8.4	7.5	10.7	66.9	0.3°	1.0	10.2	238
Percent change		+6.2/−2.6	+0.9	−10.1	−61.3	−2.7°	+1.6	−4.7	−1.6
1	Dantrolene sodium, 30.4 mg/kg iv	155/95	118	110	300	33.8°	10	135	1350
2		175/125	142	130	620	35.8°	11	175	1925
3		160/110	127	170	400	37.0°	15	170	2550
4		175/125	142	150	640	36.2°	8	194	1552
5		160/100	120	110	620	34.2°	10	180	1800
$\bar{X}$		165/111	129.8	134	516	35.4°	10.8	170.8	1835
±*SE*		4.2/6.2	5.2	11.7	69.7	0.6°	1.2	9.8	204
Percent change		+2.5/−2.6	0	−15.2	−56.1	−3.3°	−12.9	+15.6	+0.5
6	Control (prior to solvent administration)	115/85	95	140	1400	37.0°	13	138	1794
7		155/120	132	180	1800	36.8°	5	365	1825
$\bar{X}$		135/103	113.5	160	1600	36.9°	9	251.5	1810
±*SE*		20/18	18.5	20	200	0.1°	4	113.5	16
6	Control solvent, 0.1 mg/kg[g]	115/85	95	140	1380	37.0°	12	135	1620
7		155/120	132	180	1800	36.8°	4	390	1560
$\bar{X}$		135/103	113.5	160	1590	36.9°	8	262.5	1590
±*SE*		20/18	18.5	20	210	0.1°	4	127.5	30
Percent change		0/0	0	0	−0.6	0	−11.1	+4.4	−12.1
6	Control solvent, 0.4 mg/kg[g]	115/85	95	140	1380	36.9°	11	138	1518
7		155/120	132	170	1800	36.8°	4	343	1372
$\bar{X}$		135/103	113.5	155	1590	36.9°	7.5	240.5	1445
±*SE*		20/18	18.5	15	210	0.1°	3.5	102.5	73

Table I—(*Continued*)

Experiment	Treatment	Arterial Blood Pressure[b], mm Hg	Mean Arterial Blood Pressure[c], mm Hg	Heart Rate, beats/min	Gastrocnemius Muscle Twitch Tension, g	Rectal Body Temperature	Respiratory Rate per Minute[d]	Respiratory Volume[e]	Minute Volume[f]
Percent change		0/0	0	−3.1	−0.6	0	−16.7	−4.4	−20.1
6	Control solvent, 1.4 mg/kg iv[g]	120/90	100	140	1380	36.5°	13	132	1716
7		155/120	132	170	1800	36.5°	5	415	2075
$\bar{X}$		137.5/105	116	155	1590	36.5°	9	273.5	1896
±*SE*		17.5/15	16	15	210	0	4	141.5	180
Percent change		+1.9/+1.9	+2.2	−3.1	−0.6	−1.1°	0	+8.7	+4.8
6	Control solvent, 4.4 mg/kg[g]	115/85	95	130	1380	36.2°	12	132	1584
7		155/115	128	160	1800	36.1°	5	390	1950
$\bar{X}$		135/100	111.5	145	1590	36.2°	8.5	261	1767
±*SE*		20/15	16.5	15	210	0.1°	3.5	129	183
Percent change		0/−2.9	−1.8	−9.4	−0.6	−1.9°	−5.6	+3.8	−2.3
6	Control solvent, 14.4 mg/kg[g]	120/90	100	120	1380	35.6°	12	150	1800
7		155/115	128	140	1800	35.2°	4	480	1920
$\bar{X}$		137.5/102.5	114	130	1590	35.4°	8	315	1860
±*SE*		17.5/12.5	14	10	210	0.2°	4	165	60
Percent change		+1.9/−0.5	+0.4	−18.8	−0.6	−4.1°	−11.1	+25.2	+2.8
6	Control solvent, 30.4 mg/kg iv[g]	115/85	95	110	1220	34.9°	8	170	1360
7		145/100	115	100	1620	34.5°	5	488	2440
$\bar{X}$		130/92.5	105	105	1420	34.7°	6.5	329	1900
±*SE*		15/7.5	10	5	200	0.2°	1.5	159	540
Percent change		−3.7/−10	−7.5	−34.4	−11.3	−6.0°	−27.8	+30.8	+5.0

[a] Pentobarbital sodium (35 mg/kg iv). [b] Systolic/diastolic. [c] Diastolic + (systolic − diastolic)/3. [d] Normal values are 15.5 ± 12.38. See Ref. 32. [e] Expired air per minute. Normal values are 198.88 ± 81.6. See Ref. 32. [f] Minute volume = $RV \times RR$. Normal values are 2923.2 ± 2585.7. See Ref. 32. [g] Control solvent at volumes necessary to deliver dantrolene sodium at these doses.

rapid decrease, and termination of the progressive acidosis characteristic of the syndrome (16). "A survival rate of 100 per cent was achieved in the last 7 of 8 experiments," with dantrolene sodium at doses ranging from 1 to 10 mg/kg iv (16).

This report presents the results of studies on the effects of intravenous administration of dantrolene sodium on cardiovascular and respiratory functions in anesthetized dogs and sheep and unanesthetized sheep.

EXPERIMENTAL

Anesthetized Dogs—Beagle dogs[2] (n = 7) of either sex, 9.3–15.3 kg, were anesthetized with 35 mg/kg iv of pentobarbital sodium. Arterial blood pressure was monitored from a catheter passed *via* the right femoral artery into the abdominal aorta. The catheter was connected to a pressure transducer[3] attached to a polygraph[4] for recording blood pressure and heart rate. The ipsilateral femoral vein was cannulated for drug administration. A tracheotomy was performed, and a trachea cannula was connected to a pneumotachograph[5] attached to a differential pressure transducer[6], which was coupled to the polygraph[4] for recording respiration.

The left gastrocnemius muscle was used to evaluate the contractility of skeletal muscle. The femur was fixed, and the dissected Achilles tendon was attached to a force displacement transducer[7] connected to the polygraph[4] for recording gastrocnemius muscle twitch tension. Resting tension of the muscle was set at 100 g. Monodirectional square-wave pulses from a stimulator[8] were conducted through an isolation unit[9] to electrodes placed in the tendon and muscle. Stimuli were supramaximal, 150 v for 5 msec at 0.1 Hz. Rectal temperature was monitored in these experiments with a telethermometer[10]. Experimentation was initiated after all recorded parameters had stabilized (about 30 min).

Anesthetized Sheep—Dorset sheep (n = 7) of either sex, 42–45 kg, were anesthetized with either 35 mg/kg iv of pentobarbital sodium or 12.5 mg/kg iv of thiamylal sodium. Sheep in which anesthesia was induced with thiamylal sodium were attached to a closed-circuit anesthesia machine[11], and anesthesia was maintained through inhalation of methoxyflurane (2%).

Experimental procedures similar to those described for dogs were conducted in the anesthetized sheep, except that the right extensor digitorum longus muscle under 50 g of resting tension and supramaximal stimuli of 90–120 v for 5 msec at 0.1 Hz were used for evaluation of skeletal muscle contractility.

Unanesthetized Sheep—Cheviot, Dorset, and Southdown rams and wethers (n = 11), 20.5–29.5 kg, were fasted overnight. Atropine sulfate, 10 mg, was administered intramuscularly, and the sheep were prepared for surgery. Anesthesia was induced with 12.5 mg/kg iv of thiamylal sodium followed by inhalation of methoxyflurane using the method already described for maintenance anesthesia.

The placement of indwelling cannulas in the femoral artery and vein was similar to that reported previously (17, 18). The exteriorized cannula ends were connected to plastic stopcocks[12] and fixed to the surface of the skin between the iliac crests with adhesive tape and branding cement[13]. The cannulas were kept filled with a 0.9% NaCl solution made up to contain approximately 500 units of heparin/ml and flushed every 1–3 days with saline to test for patency.

Four to 5 days after surgery, training of the sheep to accept the face

[2] Raised at Norwich Pharmacal Co. Animal Research Center.
[3] Statham P23DC.
[4] Grass model 7C.
[5] Fleisch 1/a 7318 No. 0.
[6] Statham PM15.
[7] Grass FT-10.
[8] Grass S88.
[9] Grass SIU-5A.
[10] Yellow Springs Instruments.
[11] Heidbrink–Ohio Medical Products.
[12] Tomac.
[13] Brand-Rite.

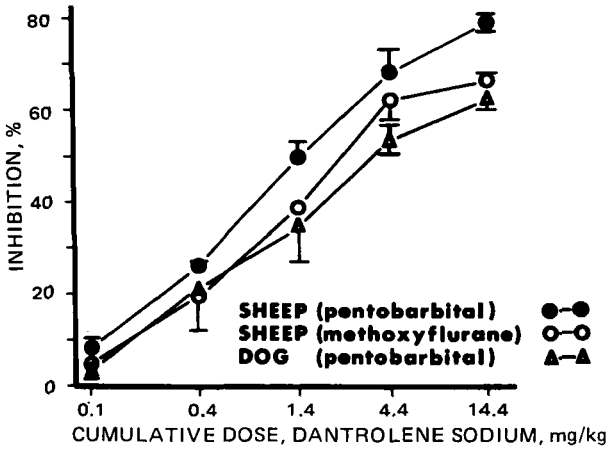

Figure 1—*Effects of intravenous dantrolene sodium on the twitch contraction of the gastrocnemius muscle in anesthetized dogs and the extensor digitorum longus muscle in anesthetized sheep. See* Experimental *for muscle stimulation parameters, techniques of anesthesia, and drug administration.*

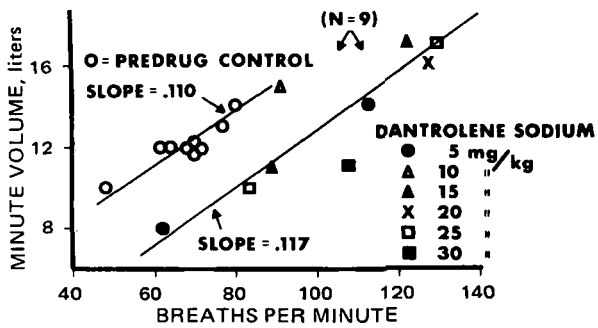

Figure 2—*Effects of dantrolene sodium, intravenously, on respiration (estimated relative respiration rate; see text for details) in unanesthetized sheep. Each symbol represents a single dose studied in one animal.*

mask (19) and to obtain baseline control values was started; this training required approximately 2 weeks before drug administration was initiated. Abdominal–aortic blood pressure and heart rate were monitored *via* a pressure transducer[3] connected to a polygraph[14].

Respiratory volumes were measured using a spirometer[15] attached to the face mask held by the investigator. The volumes of expired air were recorded for 15-sec intervals, and the rate of respiration was recorded by counting the audible closings of the air intake valve. During training and experimentation, the animals were confined in a goat milking stanchion for up to 6 hr in a warm room (22–28°).

Drugs—Dantrolene sodium was administered in a mannitol–sodium hydroxide solvent (dantrolene sodium, 0.5 mg/ml; mannitol, 44 mg/ml; sodium hydroxide, 0.08 mg/ml; and water for injection, pH ≈10.5). Dantrolene sodium, or the solvent, was administered in a cumulative dose manner through the venous cannula with an infusion pump[16] at a rate of 3.82 mg/min in sheep and 2.49 mg/min in dogs.

RESULTS

Skeletal Muscle Function under Anesthesia—In anesthetized dogs and sheep, dantrolene sodium produced dose-related inhibition of the muscle twitch responses (Fig. 1). The minimum effective dose was 0.4 mg/kg; peak effect was evident at 14.4 mg/kg in both species. Measurements of twitch tension were made after muscle contractions had stabilized following drug administration. The sodium hydroxide–mannitol solvent alone had no effect on the muscle contractions. In dogs, the ED_{50} (20) for gastrocnemius twitch tension inhibition was 4.5 mg/kg (2.0–10.3); in sheep, the ED_{50} for inhibition of the extensor digitorum longus muscle was 3.2 mg/kg (0.75–14.5) under methoxyflurane anesthesia and 1.7 mg/kg (0.72–3.9) under pentobarbital anesthesia.

Effects of dantrolene sodium and the solvent vehicle on respiratory and cardiovascular functions and the gastrocnemius muscle twitch tension in anesthetized dogs are shown in Table I. Dantrolene sodium had no significant effect from the control solvent on blood pressure ($p = 0.12$), heart rate ($p = 0.67$), or respiratory volume ($p = 0.09$) or rate ($p = 0.24$). The small changes in diastolic pressure and heart rate seen with the drug and vehicle appeared to be inconsistent and not related to dose or volume. No drug-related effects were noted on the body temperature, because the temperature of control animals decreased the same degree as dantrolene sodium-treated animals. This decrease in body temperature most likely was due to the barbiturate anesthetic (21).

Unanesthetized Sheep—In unanesthetized sheep, the estimated respiration rate was a count of the audible closings of the air intake valve and did not distinguish between panting and normal breathing. (Drug-treated and control animals were studied under the same conditions.) Treatment with dantrolene sodium caused a decrease in the tidal volume, but there was a concomitant increase in the rate of respiration. The slopes of the lines for the predrug control and dantrolene sodium data were not significantly different ($p > 0.3$) (Fig. 2).

Skeletal muscle relaxation was evident (by gross observation) at all doses of dantrolene sodium tested (5–30 mg/kg), and the effects on cardiovascular function noted in the unanesthetized sheep were inconsistent and not dose related (nonsignificant regression function) (Table II). Prior to drug administration, the animals were alert and bleated normally; however, bleating was weak following administration of dantrolene sodium, and the weakness appeared to be dose related. The ability for foot placement was affected; the relaxed animals dragged their hooves as they walked, a behavior not seen in control animals.

Head droop was observed, with the animals resting their heads on the stanchion during experimentation; again this behavior was not observed in the control animals. Dantrolene sodium-treated animals could be pushed down to a kneeling position with little or no resistance; however, when this force was removed, the animals regained normal posture, walked in a slow wobbly manner, and exhibited head droop. No loss of motor coordination or alertness was observed; the sheep were able to negotiate an inclined ramp and a winding route back to the housing area.

DISCUSSION

The effective intravenous dose of dantrolene sodium noted in this study with directly stimulated muscles of the dog and sheep is consistent with what other investigators have reported for other species (7, 16, 22–24). In all instances, the peak of the dose–response curve was approximately 4.4–14.4 mg/kg iv. A significant reduction in twitch tension was observed in the dose range of 1.2–5 mg/kg iv. Increasing the dose beyond 14.4 mg/kg iv did not produce any further significant increase in the twitch inhibition. Maximum inhibition of twitch appears species dependent [*e.g.*, dog, 50–54% (21); and cat, 80–98% (22)], with some variation probably attributable to differences in vehicles and rates of administration.

Dantrolene sodium's lack of significant effect on the cardiovascular measurements and its specificity for skeletal muscle are also in agreement with previously reported studies (21, 22). Harrison (16) reported that dantrolene sodium, contrary to procaine as presently used in treatment of malignant hyperthermia, had no effect on the myocardium. Nott and Bowman (10) reported that, in the absence of a neuromuscular blocker, spontaneous breathing in cats continued even after administration of dantrolene sodium sufficient to produce a 90% reduction of skeletal muscle twitch. The present results show that dantrolene sodium (up to 30 mg/kg iv) did not cause respiratory abnormality in unanesthetized sheep and anesthetized dogs. Other skeletal muscle relaxants depress respiratory function at doses that produce muscle relaxation through CNS depression or peripheral muscular paralysis. The lack of CNS depression (5–8) with dantrolene sodium would seem to allow for a compensatory increase in the rate, so that the minute volume is not changed.

Anesthetic-induced malignant hyperthermia, a phenomenon that has a reported fatality rate of over 70% (25), appears to result from some intrinsic abnormality of muscle (26); some evidence indicates

[14] Beckman-Type RS dynograph.
[15] Collins-Vitalometer.
[16] Harvard Apparatus.

Table II—Effect of Dantrolene Sodium on Cardiovascular Functions in Unanesthetized Sheep

Experiment[a]	Treatment	Arterial Blood Pressure[b], mm Hg	Mean Arterial Blood Pressure[c], mm Hg	Heart Rate, beats/min
1	Control	78/56	63	144
	Dantrolene sodium, 5 mg/kg iv	88/66	73	124
	Percent change	+13/+18	+16	−14
2	Control	82/56	65	156
	Dantrolene sodium, 5 mg/kg iv	82/60	67	118
	Percent change	0/+7	+3	−24
3	Control	80/62	68	126
	Dantrolene sodium, 10 mg/kg iv	75/59	64	128
	Percent change	−6/−5	−6	+2
4	Control	100/90	93	108
	Dantrolene sodium, 15 mg/kg iv	97/76	89	114
	Percent change	−3/−16	−4	+6
5	Control	112/106	108	96
	Dantrolene sodium, 15 mg/kg iv	80/70	73	102
	Percent change	−29/−34	−32	+6
6	Control	93/70	78	132
	Dantrolene sodium, 20 mg/kg iv	89/81	86	117
	Percent change	−4/+16	+10	−12
7	Control	118/60	79	114
	Dantrolene sodium, 25 mg/kg iv	106/70	82	97
	Percent change	−10/+17	+4	−15
8	Control	110/86	94	99
	Dantrolene sodium, 30 mg/kg iv	109/92	98	97
	Percent change	−1/+7	+4	−2
9	Control	80/64	69	114
	Solvent control, 10 mg/kg[d]	81/69	73	126
	Percent change	+1/+8	+6	+11
10	Control	106/70	82	96
	Solvent control, 25 mg/kg[d]	103/72	82	108
	Percent change	−3/+3	0	+13

[a] Each experiment consisted of one animal at each dose. [b] Systolic/diastolic. [c] Diastolic + (systolic − diastolic)/3. [d] Control solvent at volumes necessary to deliver dantrolene sodium at these doses.

that this defect is in the sarcoplasmic reticulum (27). Schwartz and Gracia (28) reported that among the clinical signs of malignant hyperthermia, that may develop during the initial general anesthetic procedure or not until the patient has been given a general anesthetic, are temperature elevation (as high as 45°), rigidity of skeletal muscle, ventricular arrhythmias, tachycardia, tachypnea, and mottled cyanosis. Among the drugs suggested as a treatment for this condition is procainamide (29). Procaine and procainamide lower myoplasmic calcium by transporting calcium out of the myoplasm into the sarcoplasmic reticulum. Their value in the treatment of malignant hyperthermia has been demonstrated in laboratory and clinical use (15). However, intravenous procainamide depresses cardiac contractility and causes a fall in blood pressure (30). Neuromuscular blocking agents can cause respiratory paralysis (30), and centrally acting drugs (*e.g.*, diazepam) can produce CNS depression and cardiorespiratory arrest (31).

The results of these animal studies with intravenous dantrolene sodium demonstrated its lack of cardiovascular and respiratory complications as well as a significant reduction in muscle contractile responses with doses of 2–5 mg/kg. Those results, in conjunction with the reported unique mechanism of action (5) and Harrison's reported (16) success in MHS swine, suggest that dantrolene sodium may be useful in the treatment of conditions where prompt relaxation of skeletal muscle is required (*e.g.*, in management of malignant hyperthermia).

CONCLUSIONS

The results of this study indicate that dantrolene sodium has no effect on the cardiovascular or respiratory systems that would preclude its use intravenously in acute conditions where direct relaxation of skeletal muscle is required, as in the management of malignant hyperthermia.

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[x] To whom inquiries should be directed.

Spectrophotometric Study of Complex Formation between Oxovanadium(IV) and Antiamebic Drugs

R. ABU-EITTAH [x] and M. S. EL-NASR

Abstract □ Complex formation between oxovanadium(IV) and the antiamebic drugs 5,7-dibromo-8-quinolinol and 5,7-dichloro-8-quinolinol was studied in the pH 1.5–2.0 range, using ethanol, dioxane–water, and dimethylformamide as solvents. The composition of the formed complexes was determined by more than one procedure. In ethanol and dioxane–water, the 1:1 and 1:2 complexes were formed; in dimethylformamide, the 1:1, 1:2, and 1:3 complexes were formed. The stability constants were computed using two procedures: the molar ratio method and the extrapolation method. The reproducibility of results is satisfactory.

Keyphrases □ Complex formation—oxovanadium(IV) and substituted 8-quinolinols, spectrophotometric study in various solvents □ Oxovanadium(IV)—complex formation with substituted 8-quinolinols, spectrophotometric study in various solvents □ 8-Quinolinols, substituted—complex formation with oxovanadium(IV), spectrophotometric study in various solvents □ Spectrophotometry—determination of composition of complexes of oxovanadium(IV) and substituted 8-quinolinols in various solvents □ Antiamebic drugs—5,7-dibromo- and 5,7-dichloro-8-quinolinols, complex formation with oxovanadium(IV)

Quinoline derivatives, especially the iodinated ones, are active in amebiasis. Early work on these drugs was reviewed previously (1). Drugs such as 5,7-dibromo-8-quinolinol, 5,7-dichloro-8-quinolinol, and other 8-quinolinol derivatives were effective only in intestinal amebiasis (2). The chelating properties, ionization potential, and oil–water partition are predominant structure–activity factors (3).

The antibacterial action of the 8-quinolinol drugs, but not their efficiency as amebicides, is dependent on their chelating properties (4). The metal chelates of the studied drugs have tuberculostatic and fungitoxic activities (5, 6).

The chemistry of vanadium(IV) is almost entirely that of oxovanadium or vanadyl compounds. Selbin (7, 8) showed that VO^{+2} is probably the most stable diatomic ion known. The mixed ligand complexes of VO^{+2} with 8-quinolinol and thiocyanate were studied (9). The formation constant and free energy of formation of $[VOL(NCS)_2]HL$, where HL is 8-quinolinol and L is its anion, have been computed.

The chemistry of some 8-quinolinol complexes of vanadium, iron, and nickel was studied (10, 11). The use of 5,7-dibromo-8-quinolinol in the detection of vanadium was recommended (12, 13). Vanadium complexes of 8-quinolinol and its derivatives were used as sensitive indicators for the colorimetric determination of phenols and alcohols (14).

In this work, the complex formation between VO^{+2} and some 8-quinolinols was investigated in several organic solvents. The composition and formation constants of the formed complexes were found to be solvent dependent. Vanadyl quinolinolates may have tuberculostatic and fungitoxic activities similar to those of the copper derivatives (5).

EXPERIMENTAL

Materials—5,7-Dibromo-8-quinolinol (I) and 6,7-dichloro-8-quinolinol (II) were prepared by direct halogenation of 8-quinolinol[1] in acetic acid (15, 16). Vanadyl sulfate[2] solution was standardized potentiometrically (17). Ethanol (96%), dioxane, and dimethylformamide were purified by conventional methods (18).

Apparatus and Method—Electronic absorption spectra were determined[3] using 1.0-cm fused silica cells. To determine the composition and stability constant of the complexes, solutions of the metal ion and ligands were mixed just before scanning the spectra.

The solution pH was measured on a precision pH meter[4] by using the millivolt scale, and the corresponding pH values were calculated.

[1] British Drug Houses grade reagent.
[2] Prolabograde reagent.
[3] Unicam SP 8000 spectrophotometer.
[4] Radelkis type OP-205.