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Intravenous Dantrolene Does Not Exhibit Calcium Channel Blocking Effects on the Cardiac Conduction System in Humans

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In malignant hyperthermia, dantrolene, a drug assumed to possess calcium channel blocking properties, effectively suppresses supraventricular and ventricular arrhythmias. To investigate antiarrhythmic properties of dantrolene, six patients (three women and three men, age 42 ± 18 yr) with symptomatic atrioventricular (AV)-nodal reentry tachycardia were studied. Electrocardiographic measurements included sinus cycle length, PQ-interval, width of the QRS-complex, and QT- and rate-corrected QT-interval. During the electrophysiologic study, effective refractory periods of the right atrium, AV node, right ventricle, and AV-nodal conduction intervals were determined, and AV-nodal reentry tachycardia was induced in all patients. Dantrolene was administered intravenously over a period of 15 min at doses of 1.0, 1.5, or 3.0 mg/kg in two patients each. The dosage was not further increased because of side effects at the dose of 3.0 mg/kg. After the infusion of dantrolene, the electrocardiographic measurements and electrophysiologic study were repeated. The plasma concentrations of dantrolene ranged from 1.69 to 6.61 μg/ml at the time of the electrophysiologic study. After dantrolene administration, the sinus cycle length shortened from 686 ± 80 to 622 ± 55 ms ($P < 0.05$). No significant changes of any other parameter could be demonstrated after intravenous dantrolene. AV-nodal reentry tachycardia remained inducible in all patients without change of the tachycardia cycle length and without change in coupling intervals of tachycardia-inducing extrastimuli. Antiarrhythmic properties of dantrolene could not be demonstrated in patients with AV-nodal reentry tachycardia at therapeutic doses. These results do not give evidence for a direct verapamil-like antiarrhythmic effect of dantrolene in patients with malignant hyperthermia. Suppression of arrhythmias during treatment of MH may be due to other effects of the drug. (Key words: Neuromuscular relaxants: dantrolene. Heart, arrhythmias: electrophysiology. Hyperthermia, malignant. Ions, calcium: channel blocking effects.)

MALIGNANT HYPERTHERMIA (MH) is a potentially lethal pharmacogenetic disorder in humans and pigs, characterized by a fulminant hypermetabolic response to volatile anesthetics and depolarizing muscle relaxants.[1–3] Characteristic symptoms are skeletal muscle rigidity, increased heat production and fever, and respiratory and metabolic acidosis. MH is associated with supraventricular or ventricular arrhythmias that usually precede the onset of fever or muscle rigidity.[4,5]

The hydantoin analogue dantrolene, which exhibits calcium channel blocking properties,[6,7] has been used successfully in the prevention and treatment of MH.[1,5] Cardiovascular symptoms of MH are eliminated by dantrolene administration. It is not known, however, whether the suppression of arrhythmias by dantrolene is due to the relief of the MH crisis in general or to specific antiarrhythmic properties of the drug itself. Electrophysiologic studies *in vitro*[6–11] and *in vivo*[12],§,¶ suggest direct antiarrhythmic properties of dantrolene. To evaluate primary antiarrhythmic properties in humans, the effect of intravenous dantrolene was studied in patients with sustained atrioventricular (AV)-nodal reentry tachycardias.

Materials and Methods

To establish a dose-response curve, six groups of two patients each were to receive 1.0, 1.5, 3.0, 5.0, 7.5, and 10 mg/kg dantrolene *via* intravenous infusion over a 15-min period. Because severe side effects occurred at a dose of 3.0 mg/kg, the study had to be discontinued. Consequently, only six patients (three women and three men, age 42 ± 18 yr) with symptomatic AV-nodal reentry tachycardia were included in the study. Clinical findings and data from noninvasive investigations did not give evidence of any underlying heart disease. The study was approved by the local ethics committee. After written informed consent was obtained, patients underwent a standard electrophysiologic study in the unsedated postabsorptive state at least five half-lives after discontinuation of any antiarrhythmic drug treatment. Electrode catheters were positioned *via* the femoral venous approach in the high right atrium, coronary sinus, and right ventricular apex, and over the tricuspid valve ring at the bundle of His. Details of the study protocol have been published previously.[13] Simultaneous electrocardiographic recordings were obtained from these endocardial sites together with recording of six surface ECG leads.

AV-nodal reentry tachycardia was diagnosed by the three following criteria. 1) During electrophysiologic study, dual AV-nodal pathways had to be demonstrated in an antegrade direction by a sudden increase of at least

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§ Brooks RR, Carpenter JF, Jones SM, Gregory CM, Moore AF: Evaluation of dantrolene sodium in rodent models of cardiac arrhythmia (abstract). Proceedings of the International Union of Pharmacologists 9th International Congress of Pharmacology, 1984, p 455.

¶ Butterfield JL, Carpenter JF, Jones SM, Brooks RR, Ellis KO: Antiarrhythmics activity of dantrolene sodium (abstract). Pharmacologist 25:246, 1983.

40 ms in the atrial His-bundle (AH)-interval after a 10-ms–shorter coupling interval of the atrial extrastimulus. 2) AV-nodal reentry tachycardia had to be initiated after change of conduction from the fast to the slow conducting pathway with the impulse traveling in an antegrade direction over the slow pathway and in a retrograde direction over the fast pathway, resulting in simultaneous atrial and ventricular activation during reentry tachycardia. 3) Existence of an accessory AV bypass tract had to be excluded.[14]

Sinus cycle length, PQ-interval, width of the QRS-complex, and the QT-interval were determined during sinus rhythm. The rate-corrected QT-interval was computed according to Bazett's formula.[15] Programmed electrical stimulation was performed at a basic pacing cycle length of 510 ms with extrastimuli from high right atrium, coronary sinus, and right ventricular apex. The following parameters were determined: the right atrial effective refractory period, AH-interval, His-bundle ventricular (HV)-interval, antegrade effective refractory period of the fast AV-nodal pathway, antegrade effective refractory period of the slow AV-nodal pathway, right ventricular effective refractory period, cycle length of AV-nodal reentry tachycardia, and AH- and HV-interval during AV-nodal reentry tachycardia.

As in experimental settings, dantrolene exhibits its electrophysiologic effects with a slight time lag and an onset about 15 min after intravenous administration,[7] and therefore repetition of the electrophysiologic study was started 15 min after intravenous dantrolene infusion. Plasma samples were collected before drug administration, directly after termination of dantrolene infusion, and 15, 30, 45, and 60 min after drug administration. Plasma samples were frozen and analyzed, using thin-layer chromatography to determine the dantrolene and 5-hydroxy-dantrolene concentrations (Röhm Pharma, Weiterstadt, FRG). Electrophysiologic data are presented as the means ± standard error of the mean. Effects of dantrolene, including mean change and its 95% confidence interval, are given for all patients together (n = 6). Statistical analysis was performed by analysis of variance for repeated measures.[16] Results were considered significant if P values were less than 0.05.

Results

After dantrolene administration, the sinus cycle length shortened from 686 ± 80 ms to 622 ± 55 ms ($P < 0.05$) without differences between dosage groups. No other surface ECG parameter differed from control values after dantrolene (table 1).

AV-nodal reentry tachycardia was inducible in all patients with the extrastimulus technique. After dantrolene infusion, AV-nodal reentry tachycardia remained inducible in all patients without change of the tachycardia cycle length and without change in coupling intervals of tachycardia-inducing extrastimuli. No significant change of any electrophysiologic parameter was found, either during sinus rhythm or during AV-nodal reentry tachycardia (table 2). Even in the subgroup of patients with a dantrolene plasma concentrations of greater than 4.4 μg/ml, no changes of electrophysiologic parameters were noted (table 2).

Intravenous infusion of dantrolene at a dose of 1.0 or 1.5 mg/kg was tolerated in all four patients without side effects. At a dose of 3.0 mg/kg intravenous dantrolene, one patient developed muscular tremor and one patient reported nausea, dizziness, and muscular weakness. Blood pressure remained stable in all patients.

The dantrolene dose and the resulting plasma dantrolene and 5-hydroxydantrolene concentrations are given in table 3. With increasing dantrolene dose, dantrolene plasma concentration significantly increased ($P < 0.01$).

Discussion

It has been suggested that dantrolene produces its antiarrhythmic effects during treatment of MH by interfering with the slow calcium inward current, similar to the effects of verapamil.[6] Verapamil, the classic calcium chan-

TABLE 1. Surface Electrocardiogram before and after Dantrolene Administration

	Patient												Mean ± SEM		ΔMean	95% Confidence Interval of ΔMean
	1		2		3		4		5		6					
Dantrolene dose (mg/kg)	1.0		1.0		1.5		1.5		3.0		3.0					
Recording	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		
SCL (ms)	720	700	570	540	665	600	730	640	640	600	800	650	688 ± 33	622 ± 22	−65.8	−105.7 to −26.0
PQ (ms)	170	160	130	150	130	135	140	125	140	140	130	120	140 ± 6	138 ± 6	−1.7	−12.3 to 9.0
QRS (ms)	80	80	90	90	120	115	105	105	80	80	80	80	93 ± 7	92 ± 6	−0.8	−2.5 to 0.8
QTc (ms)	436	394	423	408	423	400	421	437	425	387	447	458	429 ± 4	414 ± 11	−15.2	−35.2 to 4.8

Recording = recording during sinus rhythm (before = before drug; after = after dantrolene application); SCL = sinus cycle length; PQ = PQ interval; QRS = QRS width; QTc = QTc interval.

TABLE 2. Electrophysiologic Parameters before and after Dantrolene Administration

	Patient												Mean ± SEM		Δ Mean	95% Confidence Interval of Δ Mean
	1		2		3		4		5		6					
Dantrolene dose (mg/kg)	1.0		1.0		1.5		1.5		3.0		3.0					
Dantrolene concentration (μg/ml)	1.686		3.218		4.411		5.471		6.607		6.185					
Recording	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		
AH interval (ms)	50	50	90	85	75	80	65	60	50	50	70	50	67 ± 6	63 ± 7	−4.2	−11.3 to 2.9
HV interval (ms)	40	50	30	40	40	40	35	40	40	40	40	40	38 ± 2	42 ± 2	4.2	−0.1 to 8.2
RA ERP (ms)	260	240	210	200	170	190	230	210	200	180	210	190	213 ± 12	202 ± 9	−11.7	−24.8 to 1.5
Ant fast ERP (ms)	250	230	270	280	260	260	240	255	240	230	300	260	260 ± 9	253 ± 8	−7.5	−24.3 to 9.3
Ant slow ERP (ms)	230	220	240	250	230	230	200	230	200	190	270	240	228 ± 11	227 ± 8	−1.7	−18.5 to 15.1
RV ERP (ms)	220	220	250	240	200	210	220	220	220	200	230	230	223 ± 7	220 ± 6	−3.3	−11.8 to 5.2
CL AVNT (ms)	270	310	300	300	340	310	280	300	300	300	290	290	297 ± 10	302 ± 3	5.0	−14.3 to 24.8
AH AVNT (ms)	240	250	250	250	230	195	240	225	260	240	230	230	242 ± 5	232 ± 8	−10.0	−23.5 to 3.5
HV AVNT (ms)	50	70	30	30	45	40	35	30	40	40	40	40	40 ± 3	42 ± 6	1.7	−6.0 to 9.3
Tach. ind. low (ms)	220	210	260	270	230	240	220	180	240	270	240	—	235 ± 6	235 ± 18	0.0	−23.8 to 23.8
Tach. ind. up (ms)	240	250	310	280	280	260	260	230	270	280	280	290	273 ± 10	265 ± 9	−8.3	−25.1 to 8.5
Tach. ind. range (ms)	20	40	50	10	50	20	40	50	30	10	40	—	38 ± 5	26 ± 8	−12.0	−35.3 to 11.3

Recording = recording during basic pacing (before = before drug; after = after dantrolene application); RA = right atrium; ERP = effective refractory period; Ant. = antegrade; fast = fast pathway; slow = slow pathway; RV = right ventricle; CL = cycle length; AVNT = AV-nodal reentrant tachycardia; Tach. ind. low = tachycardia inducing coupling interval of extrastimuli, lower limit; Tach. ind. up = tachycardia inducing coupling interval of extrastimuli, upper limit; Tach. ind. range = tachycardia inducing coupling interval of extrastimuli, range.

nel blocking drug, prolongs AV conduction times by prolonging the AH-interval.[17] Verapamil also lengthens refractory periods of the AV node without exerting pronounced effects on atrial and ventricular refractory periods.[17]

Several experimental studies have supported the hypothesis of a specific antiarrhythmic profile of dantrolene. In isolated preparations of sinus and AV node, in Purkinje fibers as well as in atrial and ventricular muscle, dantrolene at concentrations of 10–100 μM (4–40 μg/ml) significantly diminished action potential amplitude and upstroke velocity and prolonged effective refractory periods.[6–11] Whereas the reduction in action potential amplitude and upstroke velocity in ventricular muscle and Purkinje fibers may suggest a sodium-blocking effect rather than calcium antagonism, Salata and Jalife demonstrated direct vera-

TABLE 3. Dantrolene Plasma Concentrations (μg/ml)

	Patients					
Patient	1	2	3	4	5	6
Body weight (kg)	56	60	60	84	76	71
Dantrolene dose (mg/kg)	1.0	1.0	1.5	1.5	3.0	3.0
Time after dantrolene administration (min)						
0	1.905	3.160	4.689	5.638	7.498	7.128
15	1.686	3.218	4.411	5.471	6.607	6.185
30	1.471	1.980	4.744	5.174	5.799	5.880
45	1.430	1.762	4.357	4.824	5.558	5.219
60	1.285	1.570	3.831	4.673	5.313	4.978
5-hydroxy-dantrolene plasma concentrations (μg/ml)						
Dose (mg/kg)	1.0	1.0	1.5	1.5	3.0	3.0
Time after dantrolene administration (min)						
0	0.074	0.128	0.193	0.178	0.330	0.280
15	0.288	0.336	0.298	0.332	0.882	0.508
30	0.392	0.420	0.504	0.399	0.946	0.711
45	0.461	0.558	1.801	0.611	1.012	0.928
60	0.451	0.579	1.583	0.738	1.055	1.003

pamil-like effects such as depression of calcium-dependent slow action potentials in canine Purkinje fibers.[6] In rats, intravenous dantrolene decreased the incidence of ventricular tachycardia after coronary artery ligation and raised the ventricular fibrillation threshold.§ Dantrolene suppressed ventricular arrhythmias induced by chloroform in mice, whereas controversial data were reported for dogs.[18,¶] An intracardiac electrophysiologic study, performed previously by our group in anesthetized dogs, demonstrated a significant prolongation of the effective refractory period of the atrium and the ventricle, a significant increase of the atrial functional refractory period, and an increase of the AH-interval at an intravenous dantrolene dose of 10 mg/kg.[12] In contrast to these findings Lynch *et al.* did not observe effects on AV conduction in dogs with cumulative dantrolene doses of as much as 10 mg/kg.[19]

To our knowledge, there have been no previous reports on the electrophysiologic effects of dantrolene in humans. To test the hypothesis that dantrolene exhibits antiarrhythmic activity, especially due to calcium channel blocking properties, we studied patients with AV-nodal reentry tachycardias. In patients with AV-nodal reentry tachycardias the AV node functionally consists of both a slow and a fast conducting pathway, constituting the electrophysiologic basis for the reentry circuit.[20] Because arrhythmias in these patients are based exclusively on structures of the AV node, AV-nodal reentry tachycardia appears to be the most appropriate model in which to study antiarrhythmic properties of an assumed calcium channel blocking drug.

Thus, in patients with AV-nodal reentry tachycardias, dantrolene was administered intravenously during the electrophysiologic study. To avoid serious side effects, the dosage gradually was increased to 3.0 mg/kg, at which point side effects precluded administration of a larger dose. The occurrence of side effects may have been due in part to the rapid infusion, by which the total dantrolene dose was administered within 15 min. Others have administered 0.1 mg/kg of dantrolene intravenously every 5 min in awake volunteers.[21]

In patients successfully treated for MH, the average initial dantrolene dose given was 2.3 mg/kg.[5] In adult and healthy volunteers the intravenous dantrolene dose that produced a maximum muscle depression, measured by adductor pollicis twitch strength, was 2.4 mg/kg intravenously, resulting in a dantrolene plasma concentration of 4.2 μg/ml.[21] A dantrolene plasma concentration of 1.5 μg/ml produced 80% of the maximum muscle relaxant effect.[21] In our study the dantrolene plasma concentrations were greater than 1.5 μg/ml at the time of the electrophysiologic study in all patients. In the study by Flewellen *et al.*[21], patients receiving 1.5 or 3.0 mg/kg intravenously had dantrolene plasma concentrations greater than 4.2 μg/ml, producing a maximum muscle depression.

In the present study, the only electrophysiologic change observed after intravenous dantrolene administration was a shortening of the sinus cycle length. This cannot be explained by calcium channel blocking properties.[17] Because blood pressure remained stable, the significant increase in heart rate could be due to a direct electrophysiologic effect of dantrolene. However, unexpressed discomfort caused by unperceived muscular weakness might be a reason for the increase of heart rate. Even in the patients with a dantrolene plasma concentration greater than 4.2 μg/ml, there were no other relevant electrophysiologic effects of intravenous dantrolene. Our previous experimental data from dogs receiving a single administration of 10 mg/kg dantrolene with a subsequent dantrolene plasma concentration of 11.6 ± 3.7 μg/ml demonstrated an increase in the AH-interval.[12] Lynch *et al.*, in a study in which dogs received a cumulative administration of 10 mg/kg dantrolene over 90 min, did not report changes of AV conduction.[19] In that study, however, the maximum plasma dantrolene concentration achieved was only 7.6 ± 0.7 μg/ml.[19] The difference between the present clinical results and our previous experimental findings in dogs[12] may be explained by different plasma concentrations of the drug.

In otherwise healthy patients with AV-nodal reentry tachycardia, the electrophysiologic properties of AV-nodal pathways and atrial and ventricular myocardium were not changed by intravenous dantrolene. The present data do not give evidence that intravenous dantrolene at therapeutic doses acts as an antiarrhythmic drug in this group. Reduction of supraventricular and ventricular arrhythmias during dantrolene treatment of MH may be due to 1) relief of the MH crisis, 2) correction of electrolyte and acid/base disturbances, or 3) other than class-IV antiarrhythmic effects of dantrolene. Since the mechanisms underlying supraventricular and ventricular arrhythmias in MH are unknown, dantrolene may act as an antiarrhythmic agent in other mechanisms of arrhythmia, such as triggered activity or enhanced automaticity. Triggered activity in a number of settings is believed to result from a calcium overload in the sarcoplasmic reticulum; this overload leads to calcium release, activation of sodium exchange, and a resulting transmembranous net inward current, inducing late afterdepolarizations.[22] Dantrolene reduces calcium release from the sarcoplasmic reticulum[1] and thereby could eliminate or reduce the likelihood of late afterdepolarizations. In contrast to that of healthy humans, the myocardial tissue of patients with MH may be susceptible to these potential antiarrhythmic effects of dantrolene.

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