Published in final edited form as:

Neurocrit Care. 2009 ; 10(1): 116–121. doi:10.1007/s12028-008-9132-5.

Dantrolene mediates vasorelaxation in cerebral vasoconstriction - A Case Series

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Abstract

INTRODUCTION—Cerebral vasoconstriction syndromes such as vasospasm after subarachnoid hemorrhage (SAH) and trauma, or Call-Fleming-Syndrome are difficult to treat, and can lead to substantial disability and death. Dantrolene, a ryanodine receptor antagonist, inhibits intracellular calcium release from the sarco-endoplasmic reticulum. We examined the effect of dantrolene on middle cerebral artery (MCA) blood flow velocities as measured by transcranial Doppler (TCD).

METHODS—Three consecutive patients with elevated MCA TCD velocities receiving dantrolene (2.5mg/kg IV q6h) were retrospectively reviewed. Average MCA peak systolic, mean flow velocities, and the pulsatility index (PI) before and after the dantrolene infusion were compared within patients. Systemic physiological parameters (blood pressure, heart rate, central venous pressure, intracranial pressure, body temperature and cooling water temperature) were recorded during 6 hours before and after the dantrolene infusion.

RESULTS—MCA peak systolic velocities (mean $\pm$ SE) for the three patients were 297 ± 3 cm/s, 248 ± 8 cm/s, and 268 ± 19 cm/s before dantrolene and 159 ± 9 cm/s, 169 ± 8 cm/s and 216 ± 12 cm/s after dantrolene. Average mean flow velocities showed the same trend. Interestingly, the PI increased slightly from 0.6, 0.52 and 0.67 before dantrolene, to 1.17, 0.71 and 0.77 after dantrolene. Systemic physiological parameters remained stable in all three patients.

CONCLUSION—Dantrolene attenuated cerebral vasoconstriction as measured by TCD without altering systemic physiological parameters. This suggests that intracellular calcium release from ryanodine channels in smooth muscle might play a role in vasospasm. A prospective study is underway to test this hypothesis.

Keywords

Subarachnoid hemorrhage; vasospasm; cerebral vasoconstriction; dantrolene; transcranial Doppler; delayed ischemic neurologic deficit

BACKGROUND

Cerebral vasoconstriction syndromes are frequently observed in the neuroscience intensive care unit (neuroICU) and can cause ischemia. They include Call-Fleming syndrome (1) and

cerebral vasospasm after subarachnoid hemorrhage (SAH) or trauma. Cerebral vasospasm is the leading cause of disability and death after SAH with delayed ischemic deficits occurring in approximately one third of all aneurysmal SAH patients (2). Vasospasm occurs in up to 45% of traumatic SAH (3). There are no FDA approved medications for treating vasospasm or vasoconstriction. The only available therapies have potentially serious side effects. Triple H therapy (hypertensive, hypervolemic, hemodilutional therapy) does not improve outcome and can lead to pulmonary edema and myocardial infarction (4,5), while cerebral angiography with intra-arterial drug infusions or angioplasty, is an invasive, labor-intensive procedure with a potential risk for stroke, vessel injury, hemorrhage or renal failure (6).

Dantrolene, a ryanodine receptor antagonist, inhibits intracellular calcium release from the sarco-endoplasmic reticulum. The drug is FDA approved for the treatment of malignant hyperthermia. Dantrolene inhibits serotonin induced basilar vasoconstriction in an animal model and has synergistic inhibition when nimodipine is added (7). Furthermore, dantrolene has neuroprotective effects when delivered early or before insult (8-10). Thus, the use of dantrolene in patients at risk of, or suffering from cerebral vasospasm, might have a dual pharmacodynamic benefit-vasorelaxation and neuroprotection. We retrospectively reviewed three patients in our neuroscience intensive care unit (NeuroICU) with elevated transcranial Doppler (TCD) presumably due to cerebral vasoconstriction. Two patients received intravenous dantrolene for refractory shivering during induced normothermia for fever, and the third patient received treatment for a presumed reversible cerebral vasoconstriction syndrome (RCVS). All patients had TCD examinations performed before and after a dantrolene dose.

METHODS

Our institutional review board reviewed the study protocol and waived the need for informed consent given the retrospective nature of the study. For vasoconstriction syndromes in our NeuroICU, TCDs are performed daily from the day of admission. Cerebral vasospasm of the middle cerebral artery (MCA) is defined as a >50% mean velocity increase from the baseline mean TCD velocity (usually performed within 24 hours of admission), or peak systolic TCD velocities of 200 cm/s or higher in the MCA with a concurrent ipsilateral Lindegaard ratio of 3 or higher (11).

Three patients with elevated transcranial Doppler TCD velocities receiving dantrolene (2.5 mg/kg IV q6h) were reviewed and described in more detail below. TCDs were performed by a vascular technician or trained neurocritical care physician on a Spencer PMD 150® TCD machine (Spencer Technologies, Seattle, WA) with a hand-held 2.5mHz Doppler probe. In all three patients, the treating attending physician had requested a second confirmatory study on the same day to confirm elevated flow velocities in one particular vessel suspected to be in vasospasm. Therefore, repeat TCDs were limited to the vessel of interest. We recorded peak systolic flow velocities, mean flow velocities and pulsatility index at different depths (45cm, 50cm, 55cm, 60cm, 65cm) before and after dantrolene and averaged each parameter over the depths within each patient. In addition, we recorded and averaged the following systemic physiological parameters during 6 hours before and after the dantrolene infusion: blood pressure heart rate, central venous pressure, intracranial pressure, cerebral perfusion pressure, body temperature, cooling device water temperature when applicable, phenylephrine dose and neosynephrine dose.

REPORT OF CASES

CASE 1

A 61 year-old Caucasian woman with a Hunt & Hess grade 3, Fisher group 3 SAH with intraventricular blood from a ruptured anterior communicating aneurysm status post clipping was admitted to our NeuroICU on post-SAH day 1. An extracranial ventricular drain was placed. Daily TCDs revealed peak systolic velocities of <200 cm/s in all insonated vessels, with a stable clinical examination. On post-SAH day 5, she was placed on induced normothermia with Artic Sun® (Medivance Inc., Louisville, KY) for fever control. On the same day, TCD peak systolic velocities increased to 250 cm/s in both MCAs, with a Lindegaard ratio of 7 bilaterally, indicating cerebral vasospasm (11). HHH-therapy was started with phenylephrine infusions to elevate her systolic blood pressure to 220 mmHg, intravenous normotonic fluids at 150 ml/hr with intermittent colloid (Albumin 5% or packed red blood cells) infusions for a goal CVP of 8-10 mmHg and a goal hemoglobin of 10 g/dl. Repeat TCDs remained high on post-SAH day 7. Shiver control was difficult and not achieved despite continuous propofol (300 mg/hr), fentanyl (200 mcg/hr), meperidine (50 mg/hr) or dexmedetomidine (0.7 mcg/kg/h) infusions. Therefore, dantrolene was added (2.5 mg/kg IV every 6 hours). TCDs were performed right before, and 90 minutes after a dantrolene dose (Table 1). A CT-angiogram confirmed diffuse vasospasm.

CASE 2

A 36-year-old Latino man was admitted to the NeuroICU with a traumatic brain injury. He was intubated for a Glasgow coma scale of 3. The head CT revealed a right basal skull fracture, a left acute subdural hematoma with mass effect, and traumatic SAH along the left sylvian fissure without an aneurysm or dissection on the CT-angiogram (CTA). He underwent a left hemicraniectomy, subdural hematoma evacuation, and placement of an intraparenchymal pressure monitor. On hospital day 2, his intracranial pressure ranged between 24 and 30 mmHg. A right hemicraniectomy was performed after the repeat head CT revealed a new right parietal epidural hematoma, and bilateral temporal contusions. Daily TCDs were ordered with suspicion for vasospasm due to traumatic SAH because the patient remained comatose. On hospital day 3, the patient was started on induced normothermia for fever control. Shiver control was initially achieved on Propofol (300mg/hr) and fentanyl (150 mcg/hr). On hospital day 5, his TCDs revealed right MCA TCD peak systolic velocities of 230 cm/s. A Lindegaard ratio could not be obtained because of a cervical collar that was not removed. He was thought to be in vasospasm by the treating NeuroICU physician team. A CTA or conventional angiogram could not be obtained because the patient was felt to be too unstable to travel out of the ICU. HHH-therapy as described in patient 1 was initiated. On hospital day 7, shivering was no longer controlled, despite continuous propofol (300 mg/hr), fentanyl (200 mcg/hr), meperidine (50 mg/hr) or dexmedetomidine (0.7 mcg/kg/h) infusions. Dantrolene was started (2.5 mg/kg every 6 hours). On hospital day 8, TCDs were performed before, and 45 minutes after a dantrolene dose (Table 1).

CASE 3

A 52-year-old Caucasian woman presented with sudden onset of fluctuating levels of consciousness, dysarthria and diplopia from acute bilateral median thalamic infarcts. A CTA revealed narrowing of the basilar artery just proximal to the basilar tip, bilaterally irregular P1 segments, as well as a narrowed and irregular left M1, but normal left M2 segment and right MCA. Based on the appearance of the intracerebral vessels on CTA, a diffuse RCVS was considered to have caused the stroke (12). On hospital day 2, she was less arousable, with less movement in her left upper extremity. She underwent a repeat CTA with CT perfusion, which was unchanged and showed no territorial perfusion abnormalities. TCDs were performed on the left MCA, showing elevated velocities with peak systolic velocities of 305 cm/s. Based on

previous experience and because of dantrolene's pharmacological mechanism of action, the treating attending ordered dantrolene as off-label / compassionate use for the vasoconstriction syndrome. The patient had TCDs performed right before and one hour after a dantrolene dose (Table 1). On the repeat TCD (performed by a neurocritical care physician), a focal stenosis with significant turbulent flow was seen in the left MCA, suggesting an irregular stenosis from an atheroma, rather than from vasoconstriction. With these TCD findings, and no perfusion deficit on CTA, the possibility of RCVS was dismissed. An artery of Percheron infarct from an intracranial atheroma was the presumed cause of the stroke.

RESULTS

Systolic peak flow velocities and mean flow velocities decreased in all three patients after dantrolene (Figure). Pulsatility index increased to a small degree in all three patients (Figure). Systemic physiological parameters remained stable over the course of 6 hours after dantrolene when compared to 6 hours prior to dantrolene (Table 2).

DISCUSSION

The underlying molecular mechanism of cerebral vasospasm is closely related to endothelin-1 and serotonin action. Endothelin-1 has been shown to cause potent and long-lasting vasoconstriction after SAH (13-15). In humans, elevated endothelin-1 levels in the CSF are related to clinically relevant vasospasm (16). Serotonin augments contraction of cerebral arteries after experimental SAH (17-19). Abrogation of serotonin, but not ET-1, mediated cerebral vasoconstriction by dantrolene has been demonstrated in a rat basilar artery model (7). Here, we describe three patients, all with different brain injuries, in which MCA TCDs before and after dantrolene administration showed vasorelaxation. Interestingly, the largest degree of vasorelaxation was observed in those patients (patient 1 and 2), who had cerebral vasospasm mediated by aneurysmal SAH, and traumatic SAH, respectively. No Lindegaard ratio was obtained in patient 2, so that we cannot entirely rule out hyperemia as a reason for elevated TCD velocities.

The dantrolene infusion did not change any of the recorded physiological parameters, indicating that the change in TCD velocities was not mediated by systemic vasorelaxation, and that the dantrolene-mediated vasorelaxation did not alter the ICP or CPP. All three patients were normothermic at the time of the TCDs. Hence, hyperemia was unlikely to have been the etiology of the elevated TCD velocities. The less pronounced vasorelaxation achieved in patient 3 suggests that underlying atherosclerosis might prevent adequate relaxation of the vessel, and that the increase in peak systolic velocity prior to dantrolene was due to a “fixed” lesion.

The pulsatility index (PI), calculated as $PI = \frac{SFV - DFV}{MFV}$, where SFV=systolic flow velocity, DFV=diastolic flow velocity and MFV=mean flow velocity, interestingly increased slightly in all three patients. This indicates that after dantrolene the DFV decreased to a greater degree than SFV. This finding suggests that the resting tone of the vessel decreased to a greater degree than the cardiac output, which has greater representation in the systolic flow velocity. Evidence in animals suggests that the ryanodine channel is responsible for the maintenance of the arterial diameter (20) and in mutant mice with the ryanodine receptor knocked out in smooth muscle cells the resting tone is decreased (21).

There are important limitations to our observations. In addition to a retrospective data analysis, there was no standardized TCD protocol in place with the intent to study the effects of dantrolene on vasorelaxation. A Lindegaard ratio was only obtained in one patient, so that other causes of elevated TCD velocities cannot be entirely excluded in the other patients with

suspected vasospasm. Also, the TCD exam was limited to the vessel suspected to be in vasospasm, so that we do not know the effect of dantrolene on the other cerebral vessels.

In summary, dantrolene mediated vasorelaxation appeared to be safe, and was most prominent in patients with underlying vasospasm, suggesting that intracellular calcium release from ryanodine channels in smooth muscle might play a significant role in cerebral vasoconstriction syndromes. This finding will have to be validated in a prospective experiment with a standardized TCD protocol. Due to these encouraging results, we are currently enrolling patients in a prospective pilot study.

Acknowledgments

DISCLOSURES: Dr. John Sims is supported by NIH 1 K08 NS049241-01A2. None of the authors have any conflict of interest.

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FIGURE.

Values averaged over the insonated depths of each patient's MCA before and after dantrolene are shown; a) mean peak systolic flow velocities (PSV); b) average mean flow velocities (MFV); c) pulsatility index.

Peak systolic flow velocities, mean flow velocities and pulsatility index at each insonation depth for each patient is shown. Both peak systolic and mean flow velocities decrease (- change), while the pulsatility index increases slightly.

TABLE 1

Patient	Vessel	Insonation depth [mm]	Peak systolic velocities [cm/s]			Mean flow velocities [cm/s]			Pulsatility index		
			Prior dantrolene	Post dantrolene	Change	Prior dantrolene	Post dantrolene	Change	Prior dantrolene	Post dantrolene	
1	left MCA	45	300	129	-171	217	76	-140	0.58	1.03	
		50	299	166	-133	216	89	-126	0.58	1.29	
		55	303	165	-138	215	92	-123	0.61	1.2	
		60	286	177	-109	202	100	-102	0.62	1.16	
		65	n/i	n/i	n/i	n/i	n/i	n/i	n/i	n/i	
Average			297	159	-138	212	89	-123	0.6	1.17	
2	right MCA	45	n/i	n/i	n/i	n/i	n/i	n/i	n/i	n/i	
		50	241	152	-89	187	98	-89	0.48	0.92	
		55	228	188	-40	159	134	-25	0.72	0.67	
		60	229	151	-78	177	109	-68	0.48	0.64	
		65	268	161	-107	212	114	-98	0.44	0.68	
3	left MCA	70	272	192	-80	211	137	-74	0.48	0.66	
		Average			248	169	-79	189	118	0.52	0.71
		45	283	185	-98	174	125	-49	0.93	0.72	
		50	290	237	-53	194	145	-49	0.74	0.95	
		55	203	200	-3	172	137	-36	0.27	0.7	
3	left MCA	60	297	240	-57	199	163	-36	0.74	0.7	
		65	n/i	n/i	n/i	n/i	n/i	n/i	n/i	n/i	
		Average			268	216	-53	185	143	0.67	0.77

Abbreviation: n/i, not insonated

Systemic physiological parameters before and after dantrolene are shown for each patients. Values represent means $\pm$ standard error during a 6-hour-period before and after the dantrolene dose.

TABLE 2

Patient	6hr Average	HR [bpm]	SBP [mmHg]	MAP [mmHg]	ICP [cm H ₂ O]	CPP [mmHg]	CVP [mmHg]	Temp [°C]	Water Temp [°C]	phenylephrine [mcg/min]	norepinephrine [mcg/min]
1	Before	89 $\pm$ 0.9	147 $\pm$ 3.1	95 $\pm$ 2.3	6 $\pm$ 0.3	89 $\pm$ 2.2	8 $\pm$ 0.5	36.9 $\pm$ 0.02	33.5 $\pm$ 1.1	142 $\pm$ 4.9	50 $\pm$ 0
	After	87 $\pm$ 0.6	162 $\pm$ 3.9	108 $\pm$ 2.8	8 $\pm$ 0.3	100 $\pm$ 2.7	8 $\pm$ 1	36.9 $\pm$ 0.02	33.6 $\pm$ 0.6	139 $\pm$ 5.8	50 $\pm$ 0
2	Before	81 $\pm$ 2.3	143 $\pm$ 3.8	101 $\pm$ 3	9 $\pm$ 0.8	92 $\pm$ 2.6	5 $\pm$ 0.8	37 $\pm$ 0.1	29.6 $\pm$ 3	0	0
	After	83 $\pm$ 6.1	158 $\pm$ 3.3	114 $\pm$ 3.7	10 $\pm$ 1.2	105 $\pm$ 3.7	7 $\pm$ 0	37.1 $\pm$ 0.1	19.9 $\pm$ 2.8	0	0
3	Before	62 $\pm$ 2.2	158 $\pm$ 4.6	103 $\pm$ 3.4	n/a	n/a	13 $\pm$ 0	37.4 $\pm$ 0.02	n/a	0	0
	After	65 $\pm$ 2.8	148 $\pm$ 3.8	98 $\pm$ 2.2	n/a	n/a	5 $\pm$ 0.5	37 $\pm$ 0	n/a	0	0

Abbreviations: HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CVP, central venous pressure; temp, body temperature (bladder); water temp, water temperature Arctic Sun® cooling device