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CORRESPONDENCE

Milrinone therapeutic drug monitoring to reduce low cardiac output syndrome in pediatric patients

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To the Editor,

Milrinone is the first-line prophylaxis and treatment of low cardiac output syndrome (LCOS) after pediatric cardiac surgery.[1,2] Identifying therapeutic levels (100–300 ng·mL^{-1}) is challenging as pharmacokinetic models predict levels poorly,[3] supratherapeutic levels are indistinguishable from LCOS, and subtherapeutic levels are ineffective. We conducted a pilot randomized controlled trial to assess the feasibility of real-time milrinone monitoring to improve the precision of therapy.

Patients between 36 post-conceptual weeks and 18 yr, undergoing cardiopulmonary bypass (CPB), with arterial and central venous access, anticipated to receive milrinone for ≥ 24 hr and who provided informed consent were randomized to either scheduled milrinone levels in a 1:1 ratio in three age-defined strata: (< 2, 2–10, and > 10 yr). Milrinone levels were measured using our in-house assay[4] until the earlier of milrinone discontinuation or seven days in patients > 8 kg (with six-hourly levels) or five days in patients < 8 kg (with eight hourly levels). Patients < 2.0 kg or receiving extracorporeal membrane oxygenation (ECMO) were ineligible.

The primary outcome was LCOS diagnosed by clinical and biochemical values (Table) at 48 hr after enrollment.[5] Feasibility was assessed using enrollment, dropouts, measured levels, dosage adjustments, and study completion (registered at ClinicalTrials.gov: NCT01841177; registered on 23 April 2013). We used a generalized estimating equation technique that accounted for clustering within patient and clinical variables to evaluate the relationship between milrinone levels and LCOS.

Of 61 patients approached, 54 (92%) consented to participate, seven (13%) withdrew (two before, five after randomization), and five were withdrawn (three ECMO, two protocol violations). The 47 who completed the study (23 intervention, 24 usual care) had a mean age of six months. Group demographics, surgical procedures, and intensive care unit (ICU) duration were similar (data not shown). The mean (standard deviation [SD]) milrinone bolus dose was 88 (22) μg·kg^{-1} for usual care patients and 90 (18) μg·kg^{-1} for intervention patients (P = 0.84). Infusions were started immediately after the bolus dose. The mean (SD) infusion rate was 0.63 (0.13) μg·kg^{-1}·min^{-1} for the usual care group and 0.58 (0.16) μg·kg^{-1}·min^{-1} for intervention groups (P = 0.24). During milrinone treatment,

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Table Demographic and surgical characteristics

	Control $N = 24$	Intervention $N = 23$	P value
Age (months), median [IQR]	6 [5.5–21]	6 [4–26.5]	0.61
Weight at surgery (kg), median [IQR]	7.4 [5.5–9.8]	7 [5.8–12]	0.92
CPB time (min), median [IQR]	137 [97–182]	119 [93–150]	0.42
Cross clamp time (min), median [IQR]	78 [55–125]	72 [59–106]	0.62
DHCA time (min), mean (SD)	0	2 (8)	0.23
ICU stay (days), mean (SD)	5.0 (4.8)	4.7 (3.7)	0.33
Highest creatinine level ($\mu mol \cdot L^{-1}$), median [IQR]	38 [28–46]	41 [31–65]	0.28
Low urine output,* *n*/total *N* (%)	15/24 (62%)	10/23 (43%)	0.34
Surgical procedures			
TOF and TOF variants	4	4	
Complete AV canal	1	2	
BCPS	1 (+ 1 Kawashima)	3	
Fontan	2	3	
Pulmonary valve repair/ replacement	2	1	
Arterial switch operation	0	1	
TGA/VSD	1	2	
Repair of VSD	4	4	
Mitral valvuloplasty	1		
Repair of DORV	5 (includes 3 intraventricular repairs)	0	
Repair of TAPVR	1	0	
Ross-Konno	1	0	
Redo sternotomy major bleeding tear of SVC	0	1	
Aortic arch augmentation	0	1	
Repair left main coronary stricture	0	1	
Milrinone levels, *n*/total *N* (%)			
$< 100\ ng \cdot mL^{-1}$	7/24 (29%)	5/23 (22%)	0.72
$100–300\ ng \cdot mL^{-1}$	8/24 (33%)	7/23 (30%)	0.82
$> 300\ ng \cdot mL^{-1}$	9/24 (37%)	11/23 (48%)	0.38
Low cardiac output syndrome	5/24 (21%)	1/23 (4%)	0.03

*Low urine output = urine output $< 1\ mL \cdot kg \cdot hr^{-1}$ averaged over 24 hr in an infant (0–1 yr) and $< 0.5\ mL \cdot kg \cdot hr^{-1}$ averaged over 24 hr in a child (> 1 yr)

AV = atrioventricular; BCPS = bidirectional cavopulmonary shunt; CPB = cardiopulmonary bypass; DHCA = deep hypothermic cardiac arrest; DORV = double outlet right ventricle; ICU = intensive care unit; SVC = superior vena cava; TAPVR = total anomalous pulmonary venous return; TGA = transposition of great arteries; TOF, tetralogy of Fallot; VSD = ventricular septal defect

epinephrine was started in two patients and increased in six patients, one patient had norepinephrine, and one patient had vasopressin increased. Vasopressin was commenced as a new drug in the 12–18 hr interval, it was not increased. The same was the case for the norepinephrine.

Among 117 samples from the 23 patients in the intervention group, the first was taken a mean (SD) 118 (44) min after the bolus was given. Levels were available 3–17 hr after sampling. In the first 12 hr of ICU admission, there were 15 supratherapeutic ($> 300\ ng \cdot mL^{-1}$) levels and six subtherapeutic levels ($< 100\ ng \cdot mL^{-1}$). Three dosage adjustments were made and in one patient with a high level ($493\ ng \cdot mL^{-1}$), milrinone was ceased. In another, a level of $79\ ng \cdot mL^{-1}$ led to a dose increase with subsequent level of $133\ ng \cdot mL^{-1}$. The third patient had the milrinone decreased and levels taken but there was no laboratory report available. Throughout milrinone treatment, eight (35%) patients maintained therapeutic levels, one remained subtherapeutic, and three remained supratherapeutic.

At 48 hr, LCOS was present in 13% of patients. The incidence of LCOS was 0% (0/15) in patients with normal milrinone levels, 17% (2/12) in patients with levels $< 100\ ng \cdot mL^{-1}$, and 20% (4/20) in patients with levels $> 300\ ng \cdot mL^{-1}$. Low cardiac output syndrome was

present in one patient (4%) receiving levels and in five patients (21%) in the control group. After adjustment for loading dose, infusion duration, age, CPB, single ventricle physiology, milrinone plasma levels, creatinine levels, and low urine output, milrinone monitoring was associated with a significant reduction in the incidence of LCOS (coefficient, -2.06; 95% CI, -3.90 to -0.22; adjusted $P = 0.03$). Seven patients had cardiac rhythm disturbances requiring treatment (three junctional dysrhythmias, two bradycardias, one complete heart block, and one junctional ectopic tachycardia).

In conclusion, this randomized pilot trial of therapeutic drug monitoring of milrinone after pediatric cardiac surgery showed feasibility of testing, a lag time to obtain results, and modest clinical responses to drug levels by clinicians. This analysis provides further evidence of the relationship between milrinone levels and clinically important outcomes and provides preliminary data suggesting a potential clinical benefit of therapeutic drug monitoring in the small sample tested. Larger randomized studies are needed.

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