Journal of Cardiothoracic and Vascular Anesthesia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Pharmacokinetics and Pharmacodynamics of Nebulized and Intratracheal Milrinone in a Swine Model of Hypercapnia Pulmonary Hypertension

Paul Gavra, PhD[*], André Y. Denault, MD, PhD[†], Yves Théoret, BPharm, PhD[‡], Louis P. Perrault, MD, PhD[§], France Varin, BPharm, PhD[*,1]

[*]*Faculty of Pharmacy, Université de Montréal, Montréal, Canada*
[†]*Department of Anesthesiology, Montreal Heart Institute, Montréal, Canada*
[‡]*Unité de Pharmacologie Clinique, CHU Ste-Justine, Montréal, Canada*
[§]*Department of Surgery, Montreal Heart Institute, Montréal, Canada*

Objectives: Milrinone pulmonary administration is used currently for the treatment of pulmonary hypertension. Several methods are available: simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization. The aim of this study was to explore the concentration-effect relationship of milrinone for each of these methods.
Design: Observational open-label pharmacokinetic/pharmacodynamics cohort study.
Setting: Single-center, hospital animal laboratory.
Participants: Twelve swine.
Interventions: After hypercapnia pulmonary hypertension, swine were administered equivalent inhaled milrinone doses of 15 or 50 μg/kg through simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization.
Measurements and Main Results: Blood and urine samples were taken up to 360 minutes postadministration. The ratio of mean systemic arterial pressure to mean pulmonary arterial pressure was monitored continuously. Right heart echographies were taken before and after hypercapnia and after drug administration. Mean elimination half-lives were similar for the 4 administrations. Mean percent changes in the ratio were of 37 (60%), 18 (31%), 17 (36%), and 20 (20%), for simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization, respectively. Mean maximum plasma concentrations for intratracheal administrations were reached at 8 and 45 min for atomization and instillation, respectively. Significant increases in right atrial diameter and right ventricular end-diastolic area were witnessed during pulmonary hypertension as well as a return to baseline values after milrinone administration.
Conclusions: The intratracheal methods, particularly intratracheal atomization, showed less hemodynamic effect than nebulizations and, in the case of intratracheal instillation, unpredictable drug exposure. Nebulization methods on the other hand, especially simple jet nebulization, suggest better efficacy and sensitivity but are less fit for emergency situations.

Key Words: milrinone; pulmonary hypertension; nebulization; intratracheal administration; pharmacokinetics; pharmacodynamics

Supported by: This work was supported by a grant from The Fonds de recherche du Québec-Santé (FRQS) in partnership with the Groupe de recherche universitaire sur le médicament (GRUM).

[1]*Address reprint requests to* F. Varin, BPharm, PhD, Faculty of Pharmacy, Université de Montréal, PO Box. 6128, Succursale Centre-Ville, Montréal, QC, Canada H3C 3J7.
E-mail address: france.varin@umontreal.ca.(F. Varin)

In an aging population, the prevalence of heart surgeries is increasing substantially and one of its most dangerous complications is difficult weaning from cardiopulmonary bypass (CPB).[1] Indeed, when difficult weaning from CPB is related to right ventricle failure, the mortality rate associated varies from 22% to 86%.[2–5] Right ventricle failure can result

https://doi.org/10.1053/j.jvca.2018.01.031
1053-0770/

from pulmonary hypertension (PH) caused by pulmonary reperfusion syndrome, which is a possible occurrence during weaning.[6] Therefore, it is critical to either treat the PH or, if possible, prevent the reperfusion syndrome.

Intravenous (IV) administration of milrinone, a phosphodiesterase III inhibitor that lowers vascular pressure through vasorelaxation, commonly is used in patients with PH and right ventricular dysfunction. However, a downside to IV milrinone is the lack of pulmonary vasorelaxation selectivity, which stems from systemic milrinone exposure.[7] Off-label pulmonary administration of milrinone was studied and showed pulmonary selectivity with no associated systemic hypotension.[8–10] This selectivity can be assessed by observing changes in the mean systemic arterial pressure (mAP) over the mean pulmonary arterial pressure (mPAP) ratio (mAP/mPAP), which increases when the severity of PH is reduced.[11–13]

Milrinone can be nebulized using either a simple jet nebulizer (SJ),[8] where the liquid is turned into aerosols via a gas stream vector, or nebulized through vibrating mesh nebulizer (VM)[5] via the movement of an ultrasound microgrill. In emergency circumstances, milrinone also can be administered as an intratracheal instillation (ITI) of a bolus using a simple syringe.[11] This bolus, however, is known to distribute in an uneven fashion. An alternative devoid of this downside is intratracheal atomization (ITA).[13]

Several studies have shown potential clinical benefits of nebulized milrinone on CPB weaning.[8,14,15] However, the largest multicenter, randomized clinical trial to date, although showing beneficial hemodynamic effects, did not find significant effect on CPB weaning clinical end-points.[5] Despite noncompartmental analyses indicating an adequate systemic exposure and a correlation between pharmacokinetic (PK) and pharmacodynamic (PD) partial exposures in a subset of patients (n = 19), the multicenter study determined a clinically favorable PD response in only 55% of 63 patients.[5] Denault et al.'s study administered inhaled milrinone using a VM, whereas a previous animal study, showing the benefits of milrinone for PH prevention, used a SJ. The latter demonstrated a higher endothelium-related relaxation following milrinone SJ administration when comparing it with both SJ saline and IV milrinone administrations.[8] This contrast underlines the importance of administration methods. In the present report, a non-CPB swine model was chosen to enable a titratable control of PH as opposed to what is observable after CPB. Swine have been used previously in milrinone research[8] due to the similarities between the species' cardiopulmonary system and the human one. This study aimed to explore and describe the PKs and PDs of milrinone following these 4 methods of administration in a swine model of hypercapnia PH.

Methods

Animals

Twelve 8-week-old crossbred Landrace-Yorkshire swine, obtained from Marc Lavallée farm (Montreal, QC, Canada), of either sex (ratio 1:1) and weighing 37 ± 10 kg were treated in accordance with the recommendations of the guidelines on the Care and Use of Laboratory Animals issued by the Canadian Council on Animals and approved by the institutional Animal Care and Use Committee (2012-73-01). This study adhered to the applicable ARRIVE guidelines. Swine were housed in pairs in square straw-lined pens, were given access to water and environment enrichment objects, and were not subject to restrictive diet until 1 night before the experiment when they underwent an overnight fast before experimentation.

Solutions

Injectable milrinone lactate solution (1 mg/mL) was used for all studies and obtained from Sanofi Canada (Montreal, Quebec, Canada).

Nebulizers and Breathing Pattern

The nebulizers were a VM (AeronebPro, Aerogen, Galway, Ireland) and a conventional in-line jet or SJ (Salter Labs, Arvin, CA). The endotracheal tube mucosal atomization device (MADett) was provided by Wolfe Tory Medical Inc (Salt Lake City, UT). During all experiments, animals were ventilated optimally according to their weight with a constant 66:34 oxygen:air mixture at 14 breaths per minute with a tidal volume of 6 to 8 mL/kg.

Animal Preparation

The morning of the experiment, after intramuscular ketamine hydrochloride sedation (25 mg/kg; Ayerst Veterinary Laboratories, Guelph, Ontario, Canada) and xylazine (10 mg/kg; Boehringer Ingelheim, Burlington, Ontario, Canada) in their cage, they were transported to the laboratory. Anesthesia induction was achieved using mask ventilation with 2% isoflurane (Abbott Laboratories Limited, St-Laurent, Quebec, Canada) as isoflurane is the anesthetic of choice for swine.[16] Animals were intubated subsequently and ventilated mechanically. A jugular vein and femoral artery were cannulated to obtain a central venous line and mAP, respectively. A cystostomy was performed for urine collection. Electrocardiogram was monitored continuously from 5 subcutaneous limb electrodes. All animals had a pulmonary artery catheter (Swan-Ganz, Edwards Lifesciences, Irving, CA) inserted through the jugular vein. Hemodynamic parameters, including mAP, mPAP, heart rate, oxygen saturation, and central venous pressure were measured continuously during the procedure.

Hypercapnia Pulmonary Hypertension

After 30 minutes of stabilization in normocapnic conditions, PH was induced through titration of an added carbon dioxide stream. Carbon dioxide flow varied between 0.25 and 1.2 L/min, representing up to 35% of the inhaled mixture. Carbon dioxide was titrated as to precisely double the mPAP observed during normotension, thus yielding a halved

Please cite this article as: Gavra P, et al. (2018), https://doi.org/10.1053/j.jvca.2018.01.031