The implications of Milrinone Lactate in the Postoperative Clinical Management of Surgical Interventions for Congenital Heart Malformations in Children

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The purpose of the study was to prove to efficacy of Milrinone in the management of open heart surgery in children with congenital heart malformations, the link between Milrinone efficacy and the prevention of low cardiac output syndrome and Milrinone side effects. We conducted a retrospective study on a group of 24 patients, admitted to the Tg Mures Emergency Institute for Cardiovascular Diseases and Transplant, between August 2016 and February 2017. Milrinone was administered to children that underwent open heart surgery for different congenital heart malformations, using doses between 0.25 and 0.75 mcg per kg bodyweight, in continuous intravenous drip, before de-clamping of the Aorta, the procedures being conducted in extracorporeal circulation. We recorded demographic data, biological parameters of renal function, myocardial function and hemodynamic parameters, before and after surgery. The administration of Milrinone determined a reduction of incidence of low cardiac output syndrome, registering only 4 deaths, the survival rate being 83.33%, 13 cases presenting complications. Postoperatively we registered a significant improvement of the mean heart rate. Milrinone proved efficient in the re-establishment of hemodynamic parameters in patients with this type of clinical manifestations. Using Milrinone in children that undergo open heart surgery determines a decrease in incidence of low cardiac output syndrome, its' presence in the pharma market being necessary.

Keywords: phosphodiesterase inhibitors, positive inotropes, milrinone, low cardiac output syndrome, pediatric cardiac surgery

One of the most important neonatal morbidity and moratality coordonates is represented by congenital heart malformations. In the 20th century, due to interventional cardiology procedures and open heart surgery, infantile morality has been lowered along with a rise in life expectancy for these children.

The basic principle of preoperative, operative and postoperative mangement of a child with a congenital heart malformation is to mentain the functional integrity of cells and the intercellular functional balance by reducing the metabolic needs of the heart during the ischaemic phase of open heart surgery. The protection of miocardial cells influences the operative and postoperative mortality. Ensuring an adequate level of oxygen and energetic support is the key to a normal contractile function at the end of surgery, while a depletion of these factors increases the anaerobic glycolysis, the accumulation of metabolic waste within the cells, determining a low cardiac output syndrome [1]. The prevention of low cardiac output syndrome is a strategic objective in the postoperative management of children with congenital heart malfomations, to the shortening of in-patient stay and a rise in quality of the surgical act by lowering incidence of complications and in-hospital mortality.

Phosphodiesterases are a family of enzymes that hydrolize cyclic nucelotides, having an essential role in the maintenance of intracellular levels of Adenosine MonoPhosphate (AMPc) and Guanosine Mono Phosphate(GMPc). AMPc acts by activating proteikinase A which catalyses activation by phosphorilation of numerous intracellular proteins (ionic channels, ionic pumps, metabolic enzymes). AMPc is degraded by phosphodiesterase. Numerous pharmacological agents can interfere with this system: phosphodiestarases, which lower the effects of AMPc, while others, like phosphodiestarase inhibitors, prolong the effects of AMPc by phosphodiestarase blocking [2].

PDE3 phosphodiestarase inhibitors determine the rise in intracellular AMPc concentration, which determines proteinkinase phosphorylation, activating calcium channels within the myocardial cell membrane. An elevated level of AMPc, along with other intracellular receptors, increases contractility, heart rate and conduction velocity. AMPc is broken down by an enzyme called

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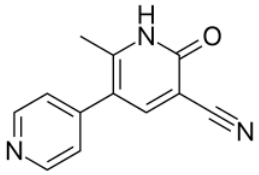
phosphodiesterase AMPc-dependant (PDE). Through the inhibition of the isoenzyme PDE3A, with affinity for myocardial cells, the distruction of AMPc is prevented, thus increasing its intracellular concentration [2-5].

Milrinone, 2-Methyl-6-oxo-1,6-dihydro-3,4'-bipyridine-5-carbonitrile (scheme 1) is a cardiotonic, positive inotrope agent with vasodilatatory properties which acts as a



Scheme 1 Chemical structure of Milrinone

selective inhibitor of PDE3A in myocardial and vessel muscles:

Milrinone causes a relaxation of the vessels'smooth muscles, leading to a reduction of both, preload and afterload. By increasing atrio-ventricular conduction velocity it improves the ventricular diastolic function.

The mechanism of action is due to the inhibition the cardiac, cytoplasmatic PDE3A enzyme within smooth muscle fibers, which leads to an increased level of cellular AMPc.

Milrinone is synthesized by condensing thioacetamide with cu 4- (dimethylamino) -3- (4-pyridinyl) -3-buten-2-one and 4-ethoxy-3- (4-pyridinyl) -3-buten-2-one in the presence of a base, or through the reaction between 1- (4-pyridinyl) -2-propanone with ethoxymethylenmalononitrile or 4-alkoxy3- (4-pyridinyl) -3-buten-2-one with malononitrile without using an external base. The startin compound of this synthesis is 4-picoline. The alternate milrinone synthesis starts from 2-methyl-3- (4-pyridylidiene)-1,1,5-tricyano-1,4-pentadiene-5-carboxamide and 2-methyl-6-oxo-1,6-dihydro-3,4'-bipyridine -5-carboxamide (scheme 2) [6].

In pharmaceutical forms, Milrinone is found under the form of milrinone lactate, with a concentration of 1.0 mg/ml, to be diluted before intravenously administration.

Milrinone binds to proteins in 70% proportion, with a plasmatic half time of 2.3 to 2.7 h, a distribution volume of 0.33 to 0.47 L/kg and a total clearance of 0.13 to 0.14 L/kg/h. It is excreted through urine in unmodified form (85%) or milrinone glucuronide (15%). After administration, effects are noticed within 5 to 15 min, including a fast increase of cardiac output, decrease of capillary pressure, of pulmonary and peripheral vessel resistance, without a significant increase of heart rate and myocardial fiber oxygen consumption [7] respectively, of myocardial injury markers: myocardial creatinkinase (CK-MB) [8].

The adverse effects of milrinone include sinus tachycardia, arythmia [9], hypotension needing of vasopressor therapy [10,11], gastro-intestinal disorders (food intolerance, GI bleeding, vomiting, diarrhea), central nervous system disorders (agitation and convulsions) and thrombocytopenia [12].

The purpose of this study was to prove the usefullness of milrinone in the postoperative clinical management of open heart surgery in children with congenital heart malformations, particularly in preventing low cardiac output syndrome [13].

Experimental part

Materials and methods

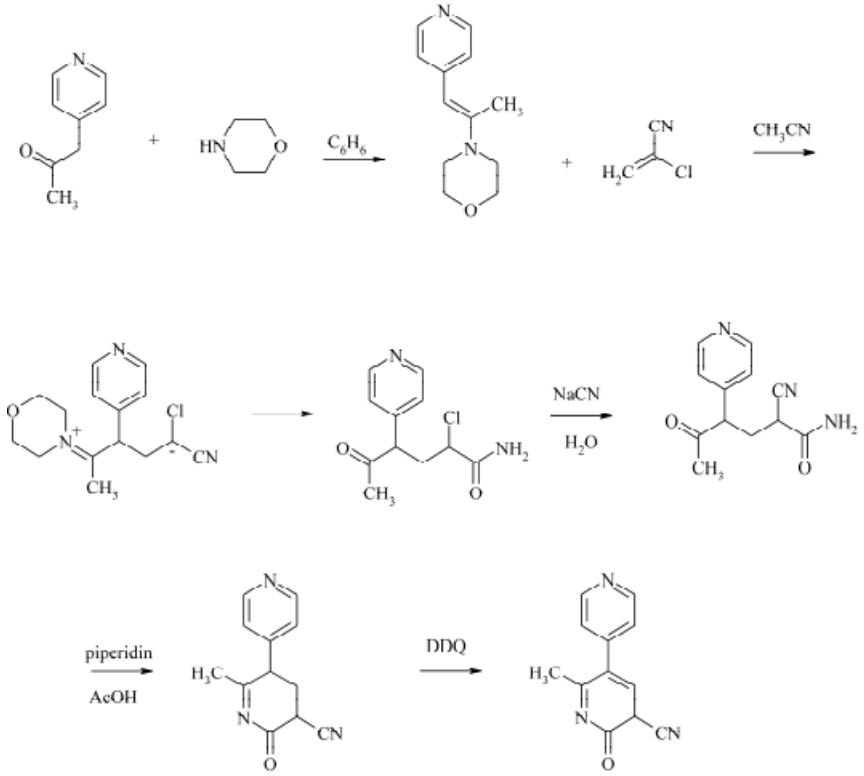
It was conducted a retrospective analysis, done on a group of 24 children admitted at the Emergency Institute for Cardiovascular Diseases and Transplant (IuBCvT), Tirgu Mures, in the period August 2016-February 2017. The infant patients underwent open heart surgery for diverse congenital heart malformations, Milrinone being administered after the surgery to prevent low cardiac output syndrome.

Inclusion criteria: all children between 0-18 years old that have undergone surgery for congenital heart malformations to which Milrinone was administered after import resumption of pharmaceuticals containing this selective phosphodiesterase inhibitor.

Surgery was open heart, cardio-pulmonary bypass being necessary.

Exclusion criteria: patients with kidney injury or preoperative thrombocytopenia.

Collected data: age, gender, diagnosis, length of stay in the ICU, biological parameters of kidney function (blood



Scheme 2. Milrinone synthesis

urea, blood creatinine), thrombocyte count and myocardial creatiinkinase level, before and after the surgery, 24 h after the intervention. We also monitored hemodynamic parameters (heart rate, blood pressure, central venous pressure) and arterial gases, before and after the surgery.

The statistical analysis of data was done using SPSS Programe for Windows and Microsoft Office 2010 (Microsoft Excel 2010), respectively the Wilcoxon test. A statistical significant difference was considered for p values lower than 0.05, for a confidence interval CI of 95%. The study was conducted with the approval of the Ethics Comittee of the Tg. Mures Cardiovascular disease and Transplant Institute.

Results and discussions

The study group included 24 cases, 9 female and 15 male (table 1).

Milrinone administration started before de-clamping the Aorta, with a dose of 0.25-0.75 mcg/kgbw, on a continous drip, dosage own to our center, the usual dosage in other centers being an attack dose of 50mcg/kg body weight, slow iv drip, followed by a maintanance dose of 0.375 to 0.75 mcg/kg body weight/min.

Postoperative, a significant improvement of heart rate values was recorded, 15% on average, a significant difference has been found between the medians before and after the surgery (166.00±10.07 vs. 140.00±7.50 heart beats/min), $p<0.0001$ (Wilcoxon test), values that remain constant until release from the hospital. We found minor increases in systolic blood pressure, as follows: 104.38±16.89 mmHg postoperatively vs 88.37±14.3 mmHg preoperatively (fig. 1).

Oxygen partial pressure (mmHg) following Milrinone administration, increased statistically significant (pÂ0.0001, Wilcoxon test) with about 55%, (69.83±5.26 vs. 44.97±3.04), approaching normal values (fig. 2).

In 22 cases was recorded a transient thrombocytopenia, only in 2 cases secondary throbocytopenia persisting upon release. The mean stay in the ICU was 9 days, the period being prolonged due to complications and/or comorbidities. Complications were recorded in 13 cases: 8 cases of sistolo-diastolic bi-ventricular dysfunction (cases in which inotropic treatment was long drawn and associated with dobutamine), 8 cases of arrhythmias: bradiarrhythmias and tachyarrhythmias – one case of early postoperative junctional tachycardia which required atrial pacing. There were also, symptoms of neuro-psycho-motor agitation and convulsions. Of the 24 patients included, 4 died, one in the second day after the surgery, the survival rate being of 83.33%.

From the perspective of identifying an adequate positive inotrope agent: increase in contractility of the myocardial muscle cell, not arrhythmic inducing, effective in the shortest of time, available for administration concurrent

Diagnosis	Number of patients	Gender (F/ M)	Age (months at time of surgery) Mean	Weight (gr) Mean
Anomaly of origin left coronary artery from the pulmonary artery	1	0/1	3.5	5195
Atrial septal defect	1	0/1	0.5	3100
Coronary artery fistulae	1	1/0	2.1	6100
Common arterial trunk	1	0/1	4.1	4600
Complete Atrioventricular Canal	2	1/1	3.6	3635
Coarctation of the aorta	2	1/1	0.7	3425
Duble Outlet Right Ventricle	3	0/3	0.7	3350
Interrupted AorticArch	1	0/1	1.7	3100
Mitral Regurgitation	1	1/0	1.7	4900
Total anomalous pulmonary venous return	1	1/0	1.9	4100
Transposition of Great Arteries	5	1/4	1.0	3498
Tetralogy of Fallot	3	2/1	11.4	7723
Ventricular septal defect	2	1/1	9.0	5752
Total	**24**	**9/15**	**Mean±SD 3.22±1.12**	**Mean±SD 4498.31±920.63**

Table 1
DEMOGRAPHIC CHARACTERISTICS OF THE STUDIED GROUP

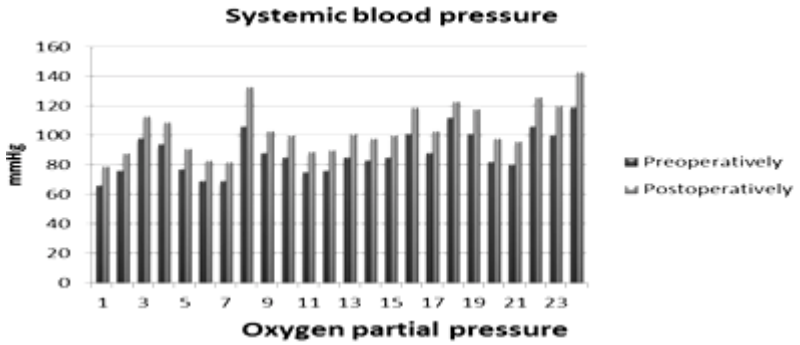


Fig. 1. Improvement of systemic blood pressure following Milrinone administration

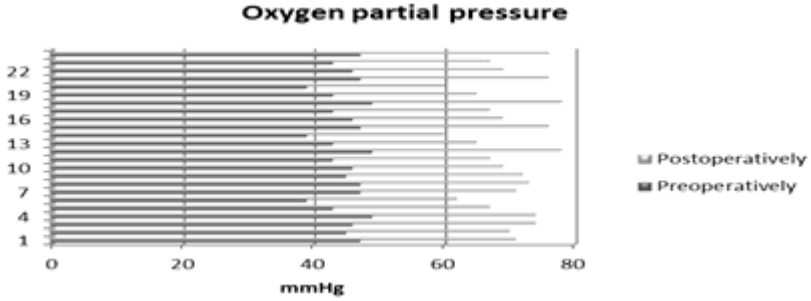


Fig.2. Improvement of oxygen partial pressure following Milrinone administration

with other vasoactive substances, there were several studies conducted.

The increase in myocardial function, the incidence of biventricular dysfunction in only a third of cases is similar to that of the study conducted by Duggal B et al, between 2001- 2003, that evaluated the effects of Milrinone on the myocardial function of children with postoperative low cardiac output syndrome [14].

Bailey et al, in 1999, studied the effects of Milrinone on 20 children, aged 3 to 22 months of age, after open heart surgery. The results of the study indicated that a dose of 50 micrograms/kg effectively increases cardiac output in children following heart surgery [15].

Conclusions

Milrinone administration, by continous iv drip, before declamping of the Aorta, while still on extracorporeal circulation, prevents the setting of low cardiac output syndrome. Milrinone proved to be effective in the re-establishment of hemodynamic parameters in patients with this type of clinical presentation.

Using milrinone in children that undergo open heart surgery, determines the decrease of low cardiac output syndrome incidence, the drug's presence being necessary within the pharma market. The benefits brought on by utilizing Milrinone are advantageous under the aspect of effectiveness-benefit analysis.

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Manuscript received: 4.04.2017