UDC 616.12-007.2:616.61-002.1]-053.32-085:615.276 https://doi.org/10.26641/2307-0404.2021.1.227960

T.P. Borysova,
O.Yu. Obolonska

INFLUENCE OF IBUPROFEN IN CLOSURE OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS ON THE DEVELOPMENT OF ACUTE KIDNEY INJURY IN PRETERM INFANTS

SE «Dnipropetrovsk medical academy of Health Ministry of Ukraine»
Department of Pediatrics 2,
V. Vernadsky str., 9, Dnipro, 49044, Ukraine
ДЗ «Дніпропетровська медична академія МОЗ України»
кафедра педіатрії 2
(зав. – д. мед. н., проф. Т.П. Борисова)
вул. В. Вернадського, 9, Дніпро, 49044, Україна
e-mail: toma.inform@gmail.com

Цитування: Медичні перспективи. 2021. Т. 26, № 1. С. 156-162
Cited: Medicni perspektivi. 2021;26(1):156-162

Key words: *preterm infants, patent ductus arteriosus, ibuprofen, acute kidney injury*
Ключові слова: *недоношені діти, відкрита артеріальна протока, ібупрофен, гостре пошкодження нирок*
Ключевые слова: *недоношенные дети, открытый артериальный проток, ибупрофен, острое повреждение почек*

Absrtact. Effect of ibuprofen for hemodynamically significant patent ductus arteriosus closure on the development of acute kidney injury in preterm infants. Borysova T.P., Obolonska O.Yu. *Premature infants with hemodynamically significant patent ductus arteriosus (HSPDA) have a high risk of developing acute kidney injury (AKI) due to renal hypoperfusion and use of ibuprofen for duct closure. The aim of the study was to evaluate the effect of ibuprofen for the closure of HSPDA on the development of AKI in preterm infants depending on high dose of the drug on the first day of life. 40 preterm infants with HSPDA who were admitted for observation on the first day of life were examined. To close the ductus arteriosus, infants received restrictive therapy. In addition, 32 (80,0%) preterm infants on the first day of life were prescribed ibuprofen: 19 infants – in high dose (20 mg/kg), 13 infants – in standard dose (10 mg/kg). Clinical examination and treatment of preterm infants was carried out according to the generally accepted methods. Echocardiography with Doppler was performed at 5-11 hours of life and then daily to determine the size and hemodynamic significance of patent ductus arteriosus. Diagnosis and stratification of the severity of AKI were performed according to the criteria of neonatal modification of KDIGO, for which the concentration of serum creatinine and diuresis were studied. According to the results of the study, it was established that the frequency of AKI on the third and fifth days of life in preterm infants with HSPDA, who received ibuprofen in a high dose (20 mg/kg) on the first day, was 73.7% and 84.2%, respectively, which is 2.2 (OR=5.6; CI: 1,43-21,95; p<0.02) and 2.5 (OR=10.67; CI: 2.31-49.31; p<0.002) times, more often than in infants without such therapy. High dose of ibuprofen on the first day of life in preterm infants with HSPDA are most often associated with the development of stage I AKI on the third or fifth day of life, which was temporary in one third of patients. The use of a high-dose ibuprofen for HSPDA closure on the first day of life in preterm infants was significantly more often associated with foci of infection in the mother, large duct size and furosemide use.*

Реферат. Вплив ібупрофену для закриття гемодинамічно значущої відкритої артеріальної протоки на розвиток гострого пошкодження нирок у недоношених дітей. Борисова Т.П., Оболонська О.Ю. *Недоношені дети з гемодинамічно значущою відкритою артеріальною протокою (ГЗВАП) мають високий ризик розвитку гострого пошкодження нирок (ГПН) у зв'язку із ренальною гіпоперфузією та використанням для закриття протоки ібупрофену. Мета роботи – оцінка впливу ібупрофену для закриття ГЗВАП на розвиток ГПН у недоношених дітей залежно від високої дози препарату в перший день життя. Обстежено 40 недоношених дітей з ГЗВАП, які надійшли під спостереження в першу добу життя. Для закриття артеріальної протоки діти отримували рестриктивну терапію. Крім того, 32 (80,0%) недоношеним у першу добу життя призначали ібупрофен: 19 дітям у високій дозі (20 мг/кг), 13 дітям у стандартній (10 мг/кг). Клінічне обстеження та лікування недоношених новонароджених здійснювалось за загальноприйнятою методикою. Ехокардіографія з доплерометрією виконувалася на 5-11 години життя і далі щодня для визначення ГЗВАП. Діагностика та стратифікація ступеня тяжкості ГПН проводились за критеріями неонатальної модифікації KDIGO, для чого вивчались концентрація сироваткового креатиніну та рівень діурезу. За*

результатами дослідження встановлено, що частота ГПН на третю та п'яту добу життя в недоношених з ГЗВАП, які на першу добу отримали ібупрофен у високій дозі (20 мг/кг), становила 73,7% та 84,2%, відповідно, що в 2,2 (OR=5,6; CI: 1,43-21,95; p<0,02) та 2,5 рази (OR=10,67; CI: 2,31-49,31; p<0,002) частіше, ніж у дітей без такої терапії. Висока доза ібупрофену на першу добу життя в недоношених з ГЗВАП найчастіше асоціюється з розвитком на третю-п'яту добу I стадії ГПН, яка була тимчасовою у третини пацієнтів. Використання ібупрофену у високій дозі для закриття ГЗВАП у першу добу життя в недоношених дітей значуще частіше асоціювалося з вогнищами інфекції в матері, великим розміром артеріальної протоки та застосуванням фуросеміду.

The incidence of patent ductus arteriosus (PDA) in preterm infants depends on gestational age and is 60-70% at <28 weeks and 20% at >32 weeks, as well as body weight at birth – 40-55% at <1000 g and 30% at <1500 g. Hemodynamically significant patent ductus arteriosus (HSPDA) is associated with mortality and the development of complications such as bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, acute kidney injury (AKI) [7, 10]. Drug closure of HSPDA is based on the suppression of the synthesis of prostaglandins – one of the main factors keeping the duct open. For this purpose, nonsteroidal anti-inflammatory drugs – cyclooxygenase inhibitors: ibuprofen or indomethacin – are used. A comparison of these two drugs revealed the benefits of ibuprofen associated with a reduced risk of necrotizing enterocolitis, intraventricular hemorrhage and AKI [10]. Ibuprofen, by decreasing the circulating prostaglandin levels, leads to a narrowing of the glomerular afferent arterioles, causing a decrease in glomerular filtration [2]. At the same time, the development of the "stealing" phenomenon in the greater circulation in HSPDA leads to hypoperfusion of the kidneys [7]. Thus, preterm infants with HSPDA treated with ibuprofen have at least two factors for the development of hemodynamically mediated AKI.

The incidence of AKI in preterm infants who received intravenous, oral, or rectal ibuprofen for PDA closure ranges from 6.5% to 57% [3, 6, 10, 14]. This difference in the incidence of AKI can be explained by the heterogeneity of the study groups in terms of gestational age, as well as by the different periods of time when drug treatment for PDA was undertaken (in the first three days, after the seventh day of life), ibuprofen dosages (standard dose 10-5-5 mg/kg and high dose 20-10-10 mg/kg). The effectiveness of PDA closure increases with the use of high dose of ibuprofen [10], however, according to some authors, renal side effects become more frequent [1].

Aim – to evaluate the effect of ibuprofen for HSPDA closure on the development of AKI in preterm infants, depending on the high dose of the drug on the first day of life.

MATERIALS AND METHODS OF RESEARCH

The cohort, prospective study was conducted in 2018-2019 on the basis of the Department of Anesthesiology and Intensive Care of Newborns CI "Dnipropetrovsk Regional Children's Clinical Hospital" and was approved by the commission on medical ethics of the hospital.

Inclusion criteria: preterm infants at 29-36 weeks of gestation with HSPDA, signed informed parental consent to participate in the study. Exclusion criteria: congenital malformations, intracerebral and intraventricular hemorrhages of III-IV degree, neonatal sepsis, severe asphyxia at birth, skin diseases, intrauterine growth retardation.

There were examined 40 preterm infants with HSPDA who were admitted for care on the first day of life. The study period was 10 days. 6 infants discontinued participation in the study due to the development of exclusion criteria: intraventricular hemorrhage III-IV degree (4), neonatal sepsis (2).

To close the PDA all in fants received restrictive therapy [8]. In addition, 32 (80,0%) preterm infants at the end of the first day of life were prescribed ibuprofen in a three-days' course at doses of 10-5-5 mg/kg/day intravenously or 20-10-10 mg/kg/day in rectal form [8]. On the fourth day of life, the PDA was closed in all infants.

To analyze the effect of high dose of ibuprofen on the functional state of the kidneys on the first day of life, patients were divided into two groups: Group I (n=19) – infants who received ibuprofen at a dose of 20 mg/kg, Group II (n=21) – infants with standard dose of ibuprofen or only on restrictive therapy.

Clinical examination and treatment of preterm infants was carried out according to conventional methods. Echocardiography with Doppler by using a broadband microconvex sensor with a frequency of 5-8 MHz "TOSHIBA" Nemso XG model SSA-580A (Japan) was performed to determine PDA, its size and hemodynamic significance [13]on admission to the department (5-11 hours of life) and then daily.

Diagnosis and stratification of the severity of AKI was performed according to the criteria of neonatal modification of KDIGO [9], for which the concentration of serum creatinine and the level of diuresis were studied.

Conjugation tables (Pearson's consistency test or Fisher's exact test) and the Mann-Whitney test were used to test the hypothesis about presence of statistical relationship between high-dose ibuprofen on the first day of life and the development of ARF in preterm infants with HSPDA [4]. Verification of the normality of the distribution of quantitative variables was performed using the Kolmogorov-Smirnov criterion. Statistical processing of the results was performed using the software product STATISTICA 6.1 (StatSoft Inc., serial number AGAR909E415822FA).

RESULTS AND DISCUSSION

Characteristics of the examined infants with perinatal history are presented in Table 1. Average gestational age was 32.9±0.22 weeks. A gestational age was the same between the groups. At the same time in group I every third infant had a gestational age of 29-31 weeks. There was no significant difference in birth weight between the groups. Low birth weight 1501-2400 g was observed in half of the infants in both groups, very low birth weight <1500 g – in almost every sixth infant. There were no differences between the study groups by the Apgar score at the fifth minute, the frequency of partial placental abruption, rapid labor, cesarean section.

The peculiarities of the perinatal period in infants who received ibuprofen on the first day of life at a dose of 20 mg/kg were established (Table 1). Thus, 52.6% of mothers during pregnancy suffered from a urinary tract infection – 2.8 times more often than in group II (OR=4.72; CI: 1.15-19.41; p<0.05), 78.9% had anemia – 1.8 times more often compared with infants of group II (OR=5.0; CI: 1.23-20.3; p<0.03). Chronic foci of infection were found in 84.2% of mothers of group I, which led to the development of chorioamnionitis in 47.4% of cases (OR=18.0; CI: 1.99-162.62; p<0.002).

Table 1

Perinatal history in preterm infants with HSPDA depending on the ibuprofen administration, n (%)

Parameter	Ibuprofen therapy 20 mg/kg dose (first day)		
	yes, n=19 I group	no, n=21 II group	p<
History of kidney disease	7 (36.8 %)	8 (38.1 %)	ns
Threatened abortion	18 (94.7 %)	15 (71.4 %)	ns
Early gestosis	14 (73.7 %)	12 (57.1 %)	ns
Urinary tract infection during pregnancy	10 (52.6 %)	4 (19.0 %)	0.05*
Arterial hypertension of pregnancy	10 (52.6 %)	9 (42.9 %)	ns
Anemia of pregnancy	15 (78.9 %)	9 (42.9 %)	0.03*
Foci of infection in mother, including	16 (84.2 %)	12 (57.1 %)	ns
chorioamnionitis	9 (47.4 %)	1 (4.8 %)	0.002*
Gestation period 29-31 weeks	6 (31.6 %)	3 (14.3 %)	ns
Gestation period 32-34 weeks	10 (52.6 %)	14 (66.7 %)	ns
Gestation period 35-36 weeks	3 (15.8 %)	4 (19.0 %)	ns
Partial placental abruption	11 (57.9 %)	8 (38.1 %)	ns
Rapid labor	9 (47.4 %)	10 (47.6 %)	ns
Cesarean section	10 (52.6 %)	8 (38.1 %)	ns
Birth weight 1500 g and less	3 (15.8 %)	4 (19.0 %)	ns
Birth weight 1501 - 2400 g	10 (52.6 %)	13 (61.9 %)	ns
Birth weight more than 2400 g	6 (31.6 %)	4 (19.0 %)	ns
Apgar score on the fifth minute >7 points	5 (26.3 %)	7 (33.3 %)	ns

Notes: The $\chi 2$ test and Fisher's exact test were used; "ns" – no significant difference was observed; * – OR (odds ratio) is significant.

One of the criteria for the diagnosis of AKI is the level of blood creatinine [9]. On the third day of life, blood creatinine in preterm infants who received ibuprofen at a dose of 20 mg/kg on the first day significantly exceeded the level of creatinine in infants of group II: 125.3±53.7 (123; 99-143) μmol/l versus 83.9±82.39 (51; 41-104.5) μmol/L, p<0.006. On the tenth day of life, the level of serum creatinine in these patients also remained elevated: 125.1±74.18 (100; 55-201) μmol 1 versus 47.4±15.00 (41; 40-44) μmol/l, p<0.001.

A meta-analysis of six studies presented in the Cochrane Database Syst Rev also showed a statistically significant increase in serum creatinine on the third day after ibuprofen administration even at a standard dose for PDA closure [10]. The study of a more sensitive biomarker of renal damage, such as cystatin C, confirmed the adverse renal effect of both oral and rectal administration of ibuprofen [3].

Since the diagnosis of AKI is also based on the condition of diuresis, we evaluated this parameter in the examined groups. In the first day of life, diuresis was reduced in all infants, which is a physiological condition for preterm infants. But on the third day of life, a decrease in diuresis was observed in 84.2% of preterm infants who received ibuprofen at a dose of 20 mg/kg on the first day of life versus 23.8% of infants in group II (OR=17.07; CI: 3.48-83.71, p<0.001).

The development of oliguria in early administration of ibuprofen in a high dose in preterm infants with PDA was also shown by de Klerk JCA et al. [6], but with a lower frequency – 14%. In a meta-analysis of the safety of ibuprofen for the PDA closure in preterm infants, 4 studies were presented, which also noted the development of oliguria on the third day after ibuprofen use [10].

Analysis of the frequency of development and severity of AKI depending on the administration of a high-dose ibuprofen on the first day showed the following (Table 2). On the third day of life, AKI in infants who received ibuprofen at a dose of 20 mg/kg on the first day was diagnosed 2.2 times more often than in infants of group II (OR=5.6; CI: 1.43-21.95 p<0.02). On the fifth day of life AKI was diagnosed in two more chil infants dren of group I and the total number increased to 84.2% (OR=10.67; CI: 2.31-49.31; p<0.002). In a group of infants who received ibuprofen at a dose of 20 mg/kg, stage I of AKI was mainly diagnosed. On the seventh and tenth day of life, the number of infants with AKI who received a high dose of ibuprofen gradually decreased to 73.7% (p<0.006) and 52.6% (p<0.001), respectively. Thus, the development of AKI on 3-5 day of life in preterm infants with HSPDA was associated with a high dose of ibuprofen on the first day; significantly more often there was a first stage of AKI, which was transient in one third of patients. The reversible side effect of high-dose ibuprofen on renal function was also noted by de Klerk JCA et al. [6].

The development of AKI in preterm infants with HSPDA who received ibuprofen in the first days of life even at a standard dose was noted by Weintraub AS et al. [14], who showed a high risk of developing AKI: 15.25 (4.99-46.57). This study and our results confirm the fact that the kidneys in preterm infants in the first days of life are more vulnerable to ibuprofen [14].

To date, high dose of ibuprofen has been proven to be more effective than the standard dose regimen for the PDA closure [10]. However, scientists' opinion on the frequency of side effects with high dose of ibuprofen compared to the standard ones differ. Some researchers believe that the renal effects do not increase [5], others – that they become more frequent [1].

Our study showed that AKI was 2.2 times more common in infants who received ibuprofen on the first day at a high dose of 20 mg/kg than in infants with a standard dosage of the drug or only on restrictive therapy (OR=5.6; CI: 1.43-21.95, p<0.02). The significant frequency of AKI in infants with a high dose of ibuprofen can be explained not only by the action of this drug but also by a number of other risk factors that our patients had. This is, first of all, the large size of PDA on the first day of life in infants of group I, which exceeded the same figure in group II (2.69±0.92 vs. 2.06±0.63 mm, p<0.01), leading to more significant hemodynamic disorders with decreased renal perfusion. In addition, the renal consequences of preterm birth are a disorder of nephronogenesis with a decrease in the number of nephrons and disturbance of their structure [12]. In our sample, half of the infants who received a high dose of ibuprofen on the first day of life had a complicated perinatal history, particularly chorioamnionitis. It is known that prenatal exposure to endotoxin in chorioamnionitis causes intrauterine inflammation of the kidneys in the fetus and postnatally in preterm infants, explaining the potential increased risk of kidney damage in preterm infants born to mothers with chorioamnionitis [11]. As a result, the kidneys in preterm infants in the postnatal period are more sensitive to hypoperfusion, which occurs in HSPDA and ibuprofen use.

It should also be taken into account that the management of preterm infants in the intensive care unit entails the treatment of severe perinatal pathology, which requires the introduction of a combination of potentially nephrotoxic drugs. It is established that the risk of developing AKI in

preterm infants increases with the simultaneous use of nonsteroidal anti-inflammatory drugs with other nephrotoxic agents (eg, antibiotics, diuretics) [2]. In our study, infants who received iburoprofen at a dose of 20 mg/kg and developed AKI were more often treated with furosemide 84.2% vs. 38.1%, p<0.004. In addition, an adverse effect of the combination of ibuprofen and restrictive therapy on the kidneys functional status is not excluded.

Table 2

Ibuprofen administration and AKI development in preterm infants with HSPDA, n (%)

Parameter	Ibuprofen 20 mg/kg dose (first day)		
	yes, n=19 (19) I group	no, n=21 (15) II group	p<
AKI on third day	14 (73,7 %)	7 (33,3 %)	0,02 *
I stage	7 (36,8 %)	3 (14,3 %)	ns
II stage	5 (26,3 %)	3 (14,3 %)	ns
III stage	2 (10,5 %)	1 (4,8 %)	ns
AKI on fifth day	16 (84,2 %)	7 (33,3 %)	0,002 *
I stage	8 (42,1 %)	2 (9,5 %)	0,03 *
II stage	4 (21,1 %)	4 (19 %)	ns
III stage	4 (21,1 %)	1 (4,8 %)	ns
AKI on seventh day	14 (73,7 %)	6 (28,6 %)	0,006 *
I stage	6 (31,6 %)	1 (4,8 %)	0,04
II stage	3 (15,8 %)	2 (9,5 %)	ns
III stage	5 (26,3 %)	3 (14,3 %)	ns
AKI on tenth day	10 (52,6 %)	0 (0,0 %)	0,001
I stage	2 (10,5 %)	0 (0,0 %)	ns
II stage	4 (21,1 %)	0 (0,0 %)	ns
III stage	4 (21,1 %)	0 (0,0 %)	ns
AKI totally	16 (84,2 %)	7 (33,3 %)	0,002 *

Notes. The $\chi 2$ test and Fisher's exact test were used; "ns" - no significant difference was observed; * – OR (odds ratio) is significant; the sample size on the 10th day is given in parentheses.

Thus, the use of ibuprofen for HSPDA closure in preterm infants on the first day of life in high dose is associated with an increased risk of AKI. Taken together, the effects of renal hypoperfusion in infants with HSPDA and that of ibuprofen, that led to a decrease in glomerular filtration, are mechanisms of AKI development in preterm infants, which are more vulnerable to kidney injury due to impaired nephrogenesis, complicated perinatal history and the use of several nephrotoxic drugs.

CONCLUSIONS

1. The frequency of AKI on the third and fifth day of life in preterm infants with HSPDA, who received ibuprofen in a high dose (20 mg/kg) on the first day was 73.7% and 84.2%, respectively, that in 2.2 (OR=5.6; CI: 1.43-21.95; p<0.02) and 2.5 (OR=10.67; CI: 2.31-49.31; p<0.002) times more often than in infants without such therapy.
2. High dose of ibuprofen on the first day of life in preterm infants with HSPDA are most often associated with the development of stage I AKI on the third or fifth day of life, which was temporary in one third of patients.
3. The use of high-dose ibuprofen for HSPDA closure on the first day of life in preterm infants was significantly more often associated with foci of infection in the mother, large duct size and furosemide use.

Conflict of interests. The authors declare no conflict of interest.

REFERENCES

1. Desfrere L, Zohar S, Morville P, et al. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. J Clin Pharm Ther. 2005 Apr;30(2):121-32. doi: https://doi.org/10.1111/j.1365-2710.2005.00630.x
2. Girardi A, Raschi E, Galletti S, Poluzzi E, Faldella G, Allegaert K, De Ponti F. Drug-induced renal damage in preterm neonates: state of the art and methods for early detection. Drug Saf. 2015;38(6):535-51. doi: https://doi.org/10.1007/s40264-015-0288-6
3. Demir N, Peker E, Ece İ, Balahoroğlu R, Tuncer O. Efficacy and safety of rectal ibuprofen for patent ductus arteriosus closure in very low birth weight preterm infants. J Matern Fetal Neonatal Med. 2017 Sep;30(17):2119-25. doi: https://doi.org/10.1080/14767058.2016.1238897
4. Schildcrout JS, Schisterman EF, Mercaldo ND, Rathouz PJ, Heagerty PJ. Extending the Case-Control Design to Longitudinal Data: Stratified Sampling Based on Repeated Binary Outcomes. Epidemiology. 2018 Jan;29(1):67-75. doi: https://doi.org/10.1097/EDE.0000000000000764
5. Dani C, Vangi V, Bertini G, et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. Clin Pharmacol Ther. 2012 Apr;91(4):590-6. doi: https://doi.org/10.1038/clpt.2011.284
6. de Klerk JCA, van Paassen N, van Beynum IM, Flint RB, Reiss IKM, Simons SHP. Ibuprofen treatment after the first days of life in preterm neonates with patent ductus arteriosus. J Matern Fetal Neonatal Med. 2019 Sep 23:1-7. doi: https://doi.org/10.1080/14767058.2019.1667323
7. Majed B, Bateman DA, Uy N, Lin F. Patent ductus arteriosus is associated with acute kidney injury in the preterm infant. Pediatr Nephrol. 2019 Jun;34(6):1129-39. doi: https://doi.org/10.1007/s00467-019-4194-5
8. Obolonskyi A, Snisar V, Surkov D, Obolonska O, Kapustina O, Dereza K. Management of patent ductus arteriosus in preterm infants. Medicni perspektivi. 2019;24(2):33-40. doi: https://doi.org/10.26641/2307-0404.2019.2.170125
9. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal Acute Kidney Injury. Pediatrics. 2015 Aug;136(2):e463-73. doi: https://doi.org/10.1542/peds.2014-3819
10. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database of Systematic Reviews 2020;2:CD003481. doi: https://doi.org/10.1002/14651858.CD003481.pub8
11. Muk T, Jiang PP, Stensballe A, Skovgaard K, Sangild PT, Nguyen DN. Prenatal Endotoxin Exposure Induces Fetal and Neonatal Renal Inflammation via Innate and Th1 Immune Activation in Preterm Pigs. Front Immunol. 2020;11:565484. doi: https://doi.org/10.3389/fimmu.2020.565484
12. Stritzke A, Thomas S, Amin H, Fusch C, Lodha A. Renal consequences of preterm birth. Mol Cell Pediatr. 2017;4(1):2. doi: https://doi.org/10.1186/s40348-016-0068-0
13. Shepherd JL, Noori S. What is a hemodynamically significant PDA in preterm infants? Congenit Heart Dis. 2019 Jan;14(1):21-26. doi: https://doi.org/10.1111/chd.12727
14. Weintraub AS, Connors J, Carey A, Blanco V, Green RS. The spectrum of onset of acute kidney injury in preterm infants less than 30 weeks gestation. J Perinatol. 2016;36:474-80. doi: https://doi.org/10.1038/jp.2015.217

СПИСОК ЛІТЕРАТУРИ

1. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method / L. Desfrere et al. *J Clin Pharm Ther*. 2005. Vol. 30, No. 2. P. 121-132. DOI: https://doi.org/10.1111/j.1365-2710.2005.00630.x
2. Drug-induced renal damage in preterm neonates: state of the art and methods for early detection / A. Girardi et al. *Drug Saf*. 2015. Vol. 38, No. 6. P. 535-551. DOI: https://doi.org/10.1007/s40264-015-0288-6

3. Efficacy and safety of rectal ibuprofen for patent ductus arteriosus closure in very low birth weight preterm infants / N. Demir et al. *J Matern Fetal Neonatal Med*. 2017. Vol. 30, No. 17. P. 2119-2125.
DOI: https://doi.org/10.1080/14767058.2016.1238897

4. Extending the Case-Control Design to Longitudinal Data: Stratified Sampling Based on Repeated Binary Outcomes / J.S. Schildcrout et al. *Epidemiology*. 2018.Vol. 29, No. 1. P. 67-75.
DOI: https://doi.org/10.1097/EDE.0000000000000764

5. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study / C. Dani et al. *Clin Pharmacol Ther*. 2012. Vol. 91, No. 4. P. 590-596.
DOI: https://doi.org/10.1038/clpt.2011.284

6. Ibuprofen treatment after the first days of life in preterm neonates with patent ductus arteriosus / J. C. A. de Klerk et al. *J Matern Fetal Neonatal Med*. 2019. Vol. 23. P. 1-7.
DOI: https://doi.org/10.100/14767058.2019.1667323

7. Majed B., Bateman D. A., Uy N. Patent ductus arteriosus is associated with acute kidney injury in the preterm infant. *Ped. Nephrol*. 2019. Vol. 34, No. 6. P. 1129-1139.
DOI: https://doi.org/10.1007/s00467-019-4194-5

8. Management of patent ductus arteriosus in premature infants / A. Obolonskyi et al. *Medicni perspektivi.* 2019. Vol. 24, No. 2. P. 33-40.
DOI: https://doi.org/10.26641/2307-0404.2019.2.170125

9. Neonatal Acute Kidney Injury / D. T. Selewski et al. *Pediatrics*. 2015. Vol. 136, No. 2. P. 463-473.
DOI: https://doi.org/10.1542/peds.2014-3819

10. Ohlsson A., Walia R., Shah S. S. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database of Systematic Reviews* 2020. Issue 2. Art. No.:CD003481.
DOI: https://doi.org/10.1002/14651858.CD003481.pub8

11. Prenatal Endotoxin Exposure Induces Fetal and Neonatal Renal Inflammation via Innate and Th1 Immune Activation in Preterm Pigs / T. Muk et al. *Front Immunol*. 2020. Vol. 11. P. 565484.
doi: https://doi.org/10.3389/fimmu.2020.565484

12. Renal consequences of preterm birth / A. Stritzke et al. *Mol Cell Pediatr*. 2017. Vol. 4, No. 1. P. 2.
DOI: https://doi.org/10.1186/s40348-016-0068-0

13. Shepherd J. L., Noori S. What is a hemodynamically significant PDA in preterm infants? *Congenit Heart Dis*. 2019. Vol. 14, No. 1. P. 21-26.
DOI: https://doi.org/10.1111/chd.12727

14. The spectrum of onset of acute kidney injury in premature infants less than 30 weeks gestation / A. S. Weintraub et al. *J. Perinatol.* 2016. Vol. 36. P. 474-480.
DOI: https://doi.org/10.1038/jp.2015.217

The article was received
02020.12.07