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Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

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Patent Ductus Arteriosus (PDA) Closure: Indomethacin vs. Ibuprofen - An Overview of the Local Drug Safety Profiles

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit www.bpfk.gov.my.
2. Click on 'ADR Reporting'.
3. Click to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Mail

1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
   The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Telephone

03-7883 5400
(ext. 8460/ 8461/ 8463)

Fax

03-7956 7151

Patent Ductus Arteriosus (PDA) Closure: Indomethacin vs. Ibuprofen
An Overview of the Local Drug Safety Profiles

Patent ductus arteriosus (PDA) is a congenital heart defect in which a foetal artery known as the ductus arteriosus fails to close after birth. The PDA will often close spontaneously. However, neonates with symptomatic PDA, such as respiratory distress or impaired systemic oxygen delivery, will require pharmacologic or surgical closure of the PDA.

Traditionally, indomethacin was used for closing a PDA, however over the past decade, several studies have shown ibuprofen to be as effective as indomethacin for this indication. In terms of safety, ibuprofen appears to cause less nephrotoxicity, while indomethacin has been shown to reduce the incidence of intraventricular haemorrhage (a common and major complication in premature infants, for which PDA is a risk factor)[1]. The Paediatric Protocols For Malaysian Hospitals (3rd Edition) recommends treatment options as follow[2]:

(i) IV or oral indomethacin 0.2mg/kg/day daily dose for 3 days (oral suspension must be freshly prepared)

or

(ii) IV or oral ibuprofen 10mg/kg first dose, 5mg/kg second and third doses, at 24 hour intervals.

Local ADR Reports*

Note: As the extent of use of either drug for PDA treatment in Malaysia has not been ascertained, the ADR data presented here should not be used to directly compare the medicinal products. Please see the 'Disclaimer' below.

Since year 2000, the NPCB has received a total of **716** ADR reports (1,513 adverse events) suspected to be related to **ibuprofen** used for various indications, of which 257 reports (36%) involved paediatric patients (aged ≤18 years), with seven (7) reports specifically for use in PDA closure.

For **indomethacin**, the NPCB database currently contains a total of **171** reports (319 adverse events), 19 (11%) related to use in paediatric patients. Of these, 10 reports were for the indication 'PDA closure', while the remainder were for pain relief.

Generally, the top adverse reactions reported for both drugs were periorbital/ orbital oedema, face swelling, itching, and urticaria.

The table below provides a breakdown of the 17 ADR reports involving the drugs used for **PDA closure**:

Malaysian ADR reports for Indomethacin and Ibuprofen Use in PDA Closure*

	INDOMETHACIN	IBUPROFEN
Total ADR reports	**10 reports**	**7 reports**
Dosage form	Oral suspension unless stated otherwise	All oral suspension
Types of reactions		
Worsening renal function	6 reports Time to onset: 17 hours - 4 days (Mean: 27 hrs) Patient age: 2 – 4 weeks	3 reports Time to onset: 1 - 2 days Patient age: 9 days - 3 weeks
Gastrointestinal (GI) haemorrhage	2 reports Time to onset: 4 and 9 hours Patient age: 2 months, 9 months Dosage form: IV	3 reports Time to onset: 10 hours- 2 days Patient age: 1 week
Decreased haemoglobin level (no signs of bleeding)	-	1 report Time to onset: 24 hours Patient age: 5 days
Necrotising enterocolitis	1 report Time to onset: 3 days Patient age: 2 weeks Dosage form: IV	-
Abdominal distension	1 report Time to onset: 22 hours Patient age: 4 weeks	-
Causality assessment		
MADRAC Causality	All C3 (possibly-related to the drug) as the patients were on concomitant medication which could have contributed to the ADR.	1 case of GI bleeding= C2 (probably-related) 6 cases = C3 (possibly-related)

Advice for Healthcare Professionals

- Based on the local ADR data presented above:
  - patients who are started on indomethacin or ibuprofen for treatment of PDA should be **monitored for GI bleeding or renal function abnormalities**
  - close monitoring is required especially in the **first 48 hours**

- Indomethacin and ibuprofen are **contraindicated** if[2]:
  - the infant is proven or suspected to have an untreated infection
  - there is active bleeding (especially GI or intracranial)
  - the platelet count is less than 60 x 10^9/L
  - the patient has impaired renal function (creatinine >140 micromol/L, blood urea >14 mmol/L)

- The drug should be **withheld** if there is decreased urine output (<0.6ml/kg/hr) or GI complications[2].

References:

1. Sekar KC, Corff KE (2008). Treatment of patent ductus arteriosus: indomethacin or ibuprofen? *J Perinatol.* 28(1):S60-62.
2. MOH (2012). Paediatric Protocols For Malaysian Hospitals 3rd Edition. pp 133-134.

Disclaimer:

This article is based on analysis of a small number of reports as available in the Malaysian National ADR database. The reports submitted to the NPCB come from a variety of sources and generally describe suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood that the suspected adverse reaction is drug-related is not the same in all cases.