

Overview Off-label Drug Uses in Pediatric Patients at Ulin's Hospital, Banjarmasin

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Abstract

Profile of off-label drug uses in Indonesia particularly in South Borneo is yet unknown. Study of off-label drug uses is necessary because its safety and effectiveness treatment for children are not guaranteed. The purpose of this study was to identify the percentage of pediatric patients who received off-label drug, the most commonly drug that used as an off-label drug, and the percentage of off-label drug based on the criteria, including: age, dose, route of administration, and indication. This research used a prospective study. The study population on this research was patients aged a month to 18 years who is treated at Ulin's Hospital during March to May 2013. The samples of this research were patients who received antibiotics, analgesics, and antipyretics, anti-inflammatory, antihistamine, anticonvulsant, and antiemetic drug therapy. There was 86 people (32.58%) of the 264 patients who received an off-label drug, anti-inflammatory drug was the most commonly used as an off-label drug with 38 cases (30.64 %) of the 124 cases of an off-label drug, and based on the criteria, there was 41 cases (33,06 %) off-label of age, 45 cases (36.29%) off-label of dose, no cases off-label of route of administration, and 38 cases (30,65 %) off-label of indication. Further research is needed to determine the safety and efficacy of an off-label drug.

Key words: Off-label drug, pediatrics, RSUD Ulin Banjarmasin

Gambaran Penggunaan Obat Off-label pada Pasien Pediatrik di Rumah Sakit Ulin, Banjarmasin

Abstrak

Penggunaan obat *off-label* pada anak-anak di Indonesia khususnya Kalimantan Selatan tidak diketahui. Penelitian ini diperlukan karena tidak terdapat jaminan keamanan dan efektivitas pengobatan bagi anak-anak. Tujuan dari penelitian ini adalah untuk mengidentifikasi pasien anak yang mendapatkan obat *off-label*, mengidentifikasi obat yang paling umum digunakan sebagai *off-label*, dan menentukan persentase obat *off-label* berdasarkan kriteria usia, dosis, cara pemberian, dan indikasi. Metode penelitian ini menggunakan prospektif studi. Populasi penelitian adalah pasien 1 bulan hingga 18 tahun yang dirawat di RSUD Ulin pada bulan Maret hingga Mei 2013. Sampel penelitian adalah semua pasien usia 1 bulan hingga 18 tahun yang mendapat antibiotik, analgetik, dan antipiretik, antiinflamasi, antihistamin, antikonvulsan, dan antiemetik. Total pasien yang memperoleh obat *off-label* adalah 86 (32,58%) dari 264 pasien, golongan obat yang biasa digunakan *off-label* adalah antiinflamasi 38 (30,64%) dari 124 obat *off-label*. Jumlah obat *off-label* menurut kriteria usia adalah 41 (33,06%) dari 124 obat *off-label*, kriteria dosis 45 (36,29%), pada rute pemberian obat 0 (0%), dan kriteria indikasi 38 (30,65%). Diperlukan penelitian lebih lanjut untuk menentukan keamanan dan kemanjuran obat.

Kata kunci: Obat *off-label*, pasien anak, RSUD Ulin Banjarmasin

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Introduction

Regulations state that all of the drug that revolve must have a permission to be distributed (Product License=PL) or distribution license (Marketing Authorization = MA), which is issued by the NA-DFC. Off-label refers to the use of drug which is not approved by the FDA or NA-DFC (beyond the provisions of PL or MA). It called an off-label drug if the indication, dose, or route of administration are different with what already stated in drug license.¹

All of information in the product license is designed to ensure the safety and the effectiveness of prescribing, but there is many drug that have not available yet for children. There was two incidents (a gray baby syndrome in newborns received chloramphenicol and phocomelia due to thalidomide used) which caused the United States and Britain made a drug license to ensure that the new drug have been checked and safe to be used for children.² New uses, doses, or indications will not be approved by the FDA until the substantial evidence of safety and effectiveness is submitted. It takes several years or never at all. Therefore, many practitioners still prefer to prescribe a medication for children with a limited data.

Swedish study reported 70% of drug is given to babies in the hospital was off-label.³ One-third of pediatric patients who is hospitalized received an off-label drugs.⁴ The most commonly drugs prescribed for children were antibiotics and analgesics.⁵ The most widely drugs used were analgesics (42%), anesthetics (39%) and antiemetics (33.8%).⁶ Even though the practitioner has a responsibility for their decision, the problem can not be left because children should be protected from unsafe and ineffective drug and it may establish a variety of legal action.¹

Study of an off-label drug uses in Indonesia, particularly in South Kalimantan

is yet unknown. Based on the potential negative impact of an off-label drug use, the researcher is suppose to know about the description of the off-label drug in Ulin's hospitals. We prefer to focus on antibiotics, analgesics and antipyretics, anti-inflammatory, antihistamine, anticonvulsant and antiemetic drug therapy.

Methods

Research Instrument

Data collection form was designed to obtain data prospectively from all patients aged a month to 18 years admitted Ulin's Hospital from March to May 2013 then received antibiotics, analgesics and antipyretics, anti-inflammatory, antihistamine, anticonvulsant and antiemetic drug therapy. The off-label drug uses is identified when the age, dose, route of administration, and indications are not covered by the product license on the British National Formulary (BNF) for Children from 2011 to 2012, Data on Drug in Indonesia (DOI) 11st edition, and the Indonesian National Medicine Information (IONI).⁷⁻⁹

Operational Definition

1. Off-label drug refer to drug usage beyond the product license in terms of age, dose, route of administration and indications based on British National Formulary for Children (BNFC), List of Drug in Indonesia and Indonesian National Medicine Information (IONI).
2. Pediatric patients aged a month–18 years.
3. Off-label of age is a drug usage beyond the range of age that has been approved by the operational definition of off-label.
4. Off-label of dose is an inappropriate dose usage based on the dose that has been approved by the operational definition of off-label.
5. Off-label of route of administration is an

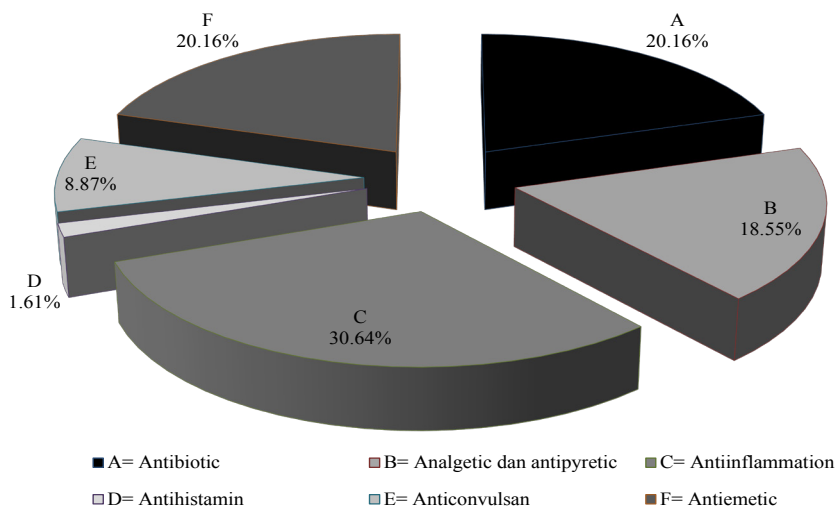


Figure 1 Distribution of Off-label Drug Use

1. Inappropriate technique of drug delivery based on the operational definition of off-label.
2. Off-label of indications is a drug usage beyond of the efficacy of drug that have been approved by the operational definition of off-label.

Establishment of Amount Samples

Amount of pediatric patients in Sedap Malam room during March to May were 361 patients. There was 264 patients belong to the criteria of inclusions.

Result

Based on the criteria of inclusion, the number of patients who received off-label drug from March to May 2013 can be seen in Table 1.

Table 1 Number of Patient

Month (2013)	Number of Patient	% off-label drug (n = 264)
March	41	15.56
April	20	7.58
May	25	9.47
Total	86	32.58

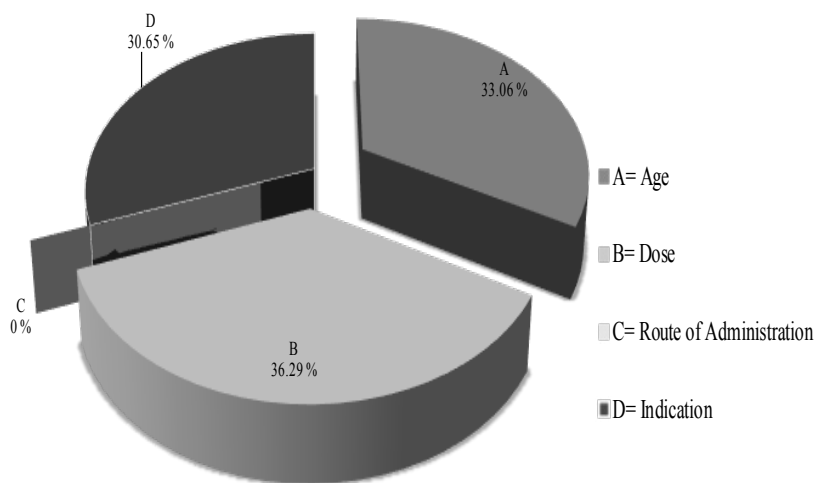


Figure 2 Distribution of Off-label Drug Use

Based on the criteria of inclusion, several drugs that used as an off-label drug were 714 drugs. The classification of drug which is the most commonly used as an off-label drug can be seen in Figure 1. The most commonly drug which used as an off-label drug was Anti-inflammatory drug that found in 15 cases of dexamethasone. Analysis of off-label drug uses in this study based on the criteria, including: age, dose, route of administration and indications can be seen in Table 2. The drug which most commonly used as an off-label of age was metamizole injection (20 cases) as an analgesic, off-label of dose was dexamethasone as anti-inflammatory, there was no cases of off-label of route of administration, and off-label of indication was prednisone as anti-inflammatory.

Discussion

There was 32,58% patients who prescribed an off-label drug at least one time. Analysis of off-label drug uses only for antibiotics, analgesic and antipyretic, anti-inflammatory, antihistamine, anticonvulsant & antiemetic. Based on interview with medical personnel in Ulin's hospitals, those drug were the most widely used in pediatric patients at Sedap Malam room. The drug which most commonly used as an off-label drug was anti-inflammatory drug therapy. This result was different from the off-label drug in Europe and America, the most often used as an off-label drug are analgesics (26.9%; 70.2%).^{13,14}

Anti-inflammatory drugs which used as an off-label were dexamethasone, prednisone and methylprednisolone. Dexamethasone Injection was an off-label drug, the product contains of 1 ml per ampoules and each ml contains 5 mg of dexamethasone. Thus we hard to calculate the right dose for children. Seventeen cases of Prednisone belonged to off-label of indication. Clinical practice guidelines of pediatrics¹⁵ in the Medical

School Pediatrics Lambung Mangkurat University stated that immunosuppressant such as corticosteroid is used to treat aplastic anemia. Corticosteroid such as prednisone, is also able to treat meningitis with dose 1–2 mg/kilogram/day. Simply based on Summaries of Product Characteristics (SPCs) and PL or MA provisions, the usage of Prednisone on those cases were beyond of indication.

Based on the criteria, the highest percentage was off-label of dose with 36.29%. There was not quietly different from the consequences of other research on the off-label drug usage. The highest percentage of an off-label drug in Uppsala, Marburg and Bergamo was off-label of dose, with the percentage was 50%.^{11,16} The only reason why it can be happened is because the lack of information and clinical studies of drug uses in children, therefore the use of drug in children are based on the use for adults.

1. Off-label of Age: The most commonly used was Metamizole injection as an analgesic (20 cases). Metamizole is an Indonesian medicine product that has not been licensed by FDA and it isn't listed on pediatric clinical guide practice, but it is given to pediatric patients.
2. Off-label of Dose: The most commonly used was dexamethasone as anti-inflammatory (15 cases). The dose for children aged a month–18 years is 10–100 mcg/kg daily in divided doses every 6–12 hours, but in this case Dexamethasone was used more than it suppose to.
3. Off-label of Route of Administration: There's none of this criteria because rarely to found in children with discrepancy of regimens of therapy.
4. Off-label of Indication: The most commonly used was Prednisone as anti-inflammatory (17 cases). In RSUD Ulin Banjarmasin, Prednisone is used to treat aplastic anemia and meningitis. However based on Summaries of Product

Characteristics (SPCs) and the provisions of their PL or MA, the usage of Prednisone on this cases were beyond of indication.

Conclusion

There was 32.58% of pediatric patients got off-label drug. The most commonly used as an off-label drug was anti-inflammatory drug and the highest off-label used based on the criteria was off-label of dose. This study showed that the potency of off-label prescriptions for children is relatively high so it requires special surveillance to use, thus the safety and the efficacy are guaranteed.

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