

RESEARCH ARTICLE

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CONFLICT OF  
INTEREST NONE  
DECLARED

## In-Patient Study of Thrombocytopenia Event Induced by Ceftriaxone, Ranitidine and Ketorolac

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### ABSTRACT

**Introduction:** Drug-induced thrombocytopenia often occurs during the patient hospitalized. Through the pharmacoepidemiology study, it can be seen thrombocytopenia induced by the use of ceftriaxone, ranitidine and ketorolac. **Objective:** To assess thrombocytopenia induced by the use of ceftriaxone, ranitidine and ketorolac.

**Methods:** The assessment was done by identifying patients medical records were obtained retrospectively and concurrent. Furthermore, analysis of the data was assessed by case control study.

**Results:** In-patients using ceftriaxone, ranitidine and ketorolac risk of decreased platelets to the potential onset of thrombocytopenia. From data taken retrospectively obtained results of the odds ratio was 1.8. While the data taken concurrently, obtained *odds ratio* greater than 2.8.

**Conclusion:** Through pharmacoepidemiology studies with odds ratio analysis approach is known that the use of a ceftriaxone, ranitidine and ketorolac increases the risk of decreased platelets potentially toward thrombocytopenia.

**Keywords:** drug induced thrombocytopenia, ceftriaxone, ranitidine, ketorolac, pharmacoepidemiology, *odds ratio*.

### Introduction

Drug therapy monitoring is an activity of clinical pharmacy should be done priority in patients with criteria, geriatric patients, pediatric patients, patients with chronic diseases, patients receiving drug therapy polypharmacy, patients with impaired function of organs such as the heart, liver, kidneys and patients receiving drugs that require special attention as a drug with a narrow therapeutic index or often cause adverse side effects<sup>(1)</sup>. The side effects can occur in hematology system such as the side effects of anemia, neutropenia and thrombocytopenia. Drug-induced thrombocytopenia (DIT), although relatively rare, is associated with serious morbidity and mortality risks. The incidence of drug-induced thrombocytopenia is low, published reports are often limited to single cases, case series, and retrospective studies. Drug-induced thrombocytopenia, which also includes thrombocytopenia induced by beverages, foods, and herbal remedies, is an important clinical problem for hematologist<sup>(2,3)</sup>. Thrombocytopenia is defined as a platelet count of less than  $150 \times 10^3$  per  $\mu\text{L}$ . It is often discovered incidentally when obtaining a complete blood count. The etiology usually is not obvious, and additional investigation is required. Patient with platelet count greater than  $50 \times 10^3$  per  $\mu\text{L}$  rarely have

symptoms. A platelet count from  $30$  to  $50 \times 10^3$  per  $\mu\text{L}$  rarely manifests as purpura. A count from  $10$  to  $30 \times 10^3$  per  $\mu\text{L}$  may cause bleeding with minimal trauma. A platelet count less than  $5 \times 10^3$  per  $\mu\text{L}$  may cause spontaneous bleeding and constitutes a hematologic<sup>(4)</sup>. Verbal report has been declared thrombocytopenia in patients who received ceftriaxone in the long time. A similar incident is estimated to frequent, but not acted upon because of reports of side effects delivered by nurses (not pharmacists) to the doctors. From the literature it is known that ceftriaxone does not cause side effects thrombocytopenia, but the thrombocytosis<sup>(5)</sup>. Other literature mentions that antibiotics cephalosporins can induce thrombocytopenia with the mechanism of 'haptent-dependent'<sup>(6,7,8,9)</sup>. Ceftriaxone being used in the surgical treatment include surgical and obstetrics. The use of ceftriaxone in patients with postoperative generally accompanied ranitidine and ketorolac injection. From the literature it is known that ranitidine could induce thrombocytopenia with unknown mechanism, while the NSAID ketorolac as yet unknown cause thrombocytopenia and unlike other NSAIDs such as ibuprofen and ketoprofen can cause thrombocytopenia less than 1%<sup>(10,11)</sup>. This study wanted to know whether each drug ceftriaxone, ranitidine and

ketorolac may cause induce thrombocytopenia in the use of single or a combination of two or three drugs.

## Methods

### Materials

Data were collected retrospectively from various in-patient units. Sources of data include a complete medical record (medical data and supporting data), note taking medication, medication administration records and other data that were developed when observations.

### Methods

The epidemiology studies of thrombocytopenia researched in patients using ceftriaxone, ranitidine and ketorolac in single or combination of two or more drugs. The study was conducted starting from the establishment of criteria for patients, data retrieval include thrombocytopenia and clinical data, especially the use of the medicine, data analysis and conclusion of thrombocytopenia in clinical symptoms in the use of the drug ceftriaxone, ranitidine and ketorolac.

For analysis of the data are calculated using odds ratio analysis. Principle odds ratio analysis can be described as follows:

Treatment	Result	
	Positive	Negative
X	a	b
Y	c	d

$$\text{Odds Ratio} = (axd)/(bxc)$$

## Result

### Drug Use

All the drug and its use of the patients is calculated percentage. The results indicate that the use of most drugs respectively, ranitidine injection (10.89%), ceftriaxone injection (9.28%), methylprednisolone tablet (6.5%), while ketorolac injection in the order of four (6.26%). More results can be seen in **Table 1**.

The use of drugs based classification of drugs known that ceftriaxone, ranitidine and ketorolac injection is the most widely used drugs in the cephalosporin class of antibiotics, antihistamines 2 and NSAIDs. The result of use of drugs based classification of drugs shown in **Table 2**.

### Pharmacoepidemiology Studies of Retrospective Data

In observation of retrospective data, obtained 371 patients using ceftriaxone injection, ranitidine and ketorolac. From all these patients, only 326 patients whose medical records are available. From the 326 medical records, only 129 medical records that can be assessed. Further medical records containing platelets

data before and after the therapy only 61 medical records.

Odds Ratio analysis: The results were as follows in **Table 3**.

No	Drug Name	%
1	Ranitidine Injection	10.89
2	Ceftriaxone Injection	9.28
3	Methylprednisolone Tablet	6.57
4	Ketorolac Injection	6.26
5	Metronidazole Infus	5.73
6	Paracetamol 500mg Tablet	5.29
7	Mefenamic Acid 500mg Tablet	4.47
8	Tramadol Injection	4.10
9	Tranexamic Acid Injection	3.60
10	Ibuprofen 400mg Tablet	3.44
11	Cefixime 100mg capsule	3.21
12	Omeprazole 20mg capsule	2.92
13	Phytomenadione Injection	2.76
14	Dexamethasone Injection	2.71
15	Ciprofloxacin 500mg Tablet	2.16
16	Cefotaxime Injection	1.76
17	Cefadroxil 500mg capsule	1.68
18	Amoxicillin 500mg caplet	1.58
19	Metronidazole 500mg Tablet	1.45
20	Ranitidine 150mg Tablet	1.31
21	Vit C 50mg Tablet	1.18
22	Ondansetron Injection	0.95
23	Captopril 25mg Tablet	0.92
24	Metoclopramide Injection	0.89
25	Methylprednisolone Injection	0.79
26	Calcium Lactic capsule	0.71
27	Amlodipine 5mg Tablet	0.66
28	Methyldopa 250mg Tablet	0.66
29	Captopril 12,5mg Tablet	0.63
30	Azathioprine Tablet	0.58
31	Vit B Complex Tablet	0.55
32	Gentamicin Injection	0.53

**Table 1**-The list of medication used

Class of Drug	Drug Name	Amount of Usage	Dosage Forms
Cephalosporine	Ceftriaxone	353	Injection
	Cefixime	122	Capsulee
		1	Syrup
	Cefotaxime	67	Injection
	Cefadroxil	64	Capsulee
	Ceftazidime	2	Injection
Antihistamine 2	Ranitidine	414	Injection
		50	Tablet
NSAID	Ketorolac	238	Injection
	Mefenamic Acid	170	Tablet
	Ibuprofen	131	Tablet
	Ketoprofen	9	Suppository
	Dexketoprofen+ Trometamol	8	Tablet

**Table 2** - List of Medication Based Class of Drug

	Platelet Number Down	Platelet Number Rise	Odds Ratio
The number of patients using ceftriaxone injection, ketorolac, ranitidine	28	14	1,8
The number of patients NOT using ceftriaxone injection, ketorolac, ranitidine	10	9	

**Table 3-** Odds Ratio Analysis Of Retrospective Data

From result of odds ratio analysis, we can say that patients using ceftriaxone, ketorolac and ranitidine injection (single or combination) at risk of decreased platelets 1.8x compared to patients who did not use the injection of ceftriaxone, ketorolac and ranitidine.

#### Pharmacoepidemiology studies of Concurrent Data

A total of 175 patients were obtained on pharmacoepidemiology studies which took concurrently. Patient which included research who was patients who require injection of ranitidine or omeprazole accompanied or not accompanied by the injection of ceftriaxone, ketorolac and ranitidine.

From 175 patients, only 86 patients can be analysed, and the results are as follows in **Table 4**.

	Platelet Number Down	Platelet Number Rise	Odds Ratio
The number of patients using ceftriaxone injection, ketorolac, ranitidine	32	19	2,8
The number of patients NOT using ceftriaxone injection, ketorolac, ranitidine	14	23	

**Table 4 -** Odds Ratio Analysis Of Concurrent Data

From result of odds ratio analysis, we can say that patients using ceftriaxone, ketorolac and ranitidine injection (single or combination) at risk of decreased platelets 2.8x compared to patients who did not use the injection of ceftriaxone, ketorolac and ranitidine.

#### Discussion

Clinical case reports or case series involve the publication of one or a number of interesting clinical cases observed by a health care professional or a group of health care professionals, usually in a specific geographic region. Clinical case series are helpful to epidemiologists and clinicians alike, as the descriptions of unique cases help generate a case definition for disease as well as information on the natural history of disease, including the range of signs, symptoms, and consequences of the disease that may

manifest in an individual. In addition, cases can be analyzed to identify trends or similarities that may provide a basis for research into possible etiologic factors of the disease.

Analytic studies include cohort, case-control, nested case-control, and case-cohort. Analytic designs typically involve more thorough data collection and analyses than the descriptive studies described above; therefore, investigators using these designs can better examine possible associations between exposure and outcome and identify potential preventive measures<sup>(12)</sup>. Odds ratio results between pharmacoepidemiology studies retrospectively smaller than concurrent. This happens because the data on treated patients is still relatively complete. In the retrospective study conducted 1.8 odds ratio values fall into the category of data not strong values whereas concurrent 2.8 closer to the value strong category<sup>(13)</sup>. Decreased platelets in patients who were treated also affected by the use of other drugs that have the potential to induce the occurrence of thrombocytopenia and clinical condition of the patient. The use of combination drug ceftriaxone, ketorolac and ranitidine are often used, especially in patients with surgical treatment. It is known that side effects of hematology aspects of ceftriaxone is eosinophilia (6%), thrombocytosis (5%) and leukopenia (2%), for ketorolac, more than 1-10% could be anemia and increased bleeding time whereas ranitidine may thrombocytopenia < 1%<sup>(14)</sup>. If the risk of decreasing the patient's platelets to cause thrombocytopenia greater in these patients, it is necessary to monitor aspects of drug therapy side effects arise mainly aspects of hematology patients. Monitoring of drug therapy to also necessary to prevent the use of drugs are not suitable as long as the provision is less precise in the use of ketorolac which should not be more than five days. Monitoring drug use is also very necessary given the use of ceftriaxone, ranitidine and ketorolac are often used in combination. It has the potential to cause adverse drug interactions such as thrombocytopenia. While the mechanism of the onset of thrombocytopenia of each drug is also not yet known with certainty.

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