Archives of The Medicine and Case Reports
Journal Homepage: https://hmpublisher.com/index.php/AMCR/index
eISSN: 2747-2051

The Rationality of Using Diclofenac in Outpatient Cases of Osteoarthritis of Mohammad Hoesin General Hospital Palembang Period January-March 2018

Dara Prameswari[1*], M. Totong Kamaluddin[2], Nita Parisa[2]

[1]Doctor Education Study Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Rationality of Drug
Diclofenac
Osteoarthritis

Corresponding author:
Dara Prameswari

E-mail address:
daraaa15@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/AMCR.v2i1.12

ABSTRACT

Osteoarthritis (OA) is the most common disease in joints that affects people in their middle until late years. In Indonesia the prevalence of OA is relatively high and disturbs their daily activity. Diclofenac is one of the drug of choice in treating OA. To avoid multiple side effects from Diclofenac use, the usage must be in accordance to rationality indicators which are correct dose, correct frequency, and correct length of use. This study is aimed to know the rationality of Diclofenac use in Osteoarthritis outpatient cases at RSUP Mohammad Hoesin Palembang. This study is a descriptive observational with a cross-sectional approach to know the rationality of Diclofenac use in outpatient cases of osteoarthritis at RSUP Mohammad Hoesin Palembang. Samples were medical records of OA patients in outpatient setting from January to March 2018 which fulfilled the inclusion and exclusion criteria. Sampling technique used was total sampling. The amount of samples fulfilling the inclusion criteria were 201 patients, with the most were aged 46-65 years (60.2%), female (55.7%), and has a history of comorbidity which includes low back pain (22.8%). The result of this study shows pattern of Diclofenac use with dosage of 2 x 25mg (73.6%), length of use about <7 days (57.2%). In combination with other drugs there were no interaction to be found (84.4%), or synergistic interaction (8.5%) and antagonistic interaction (7.1%). The use of diclofenac in osteoarthritis cases at outpatient setting in RSUP Dr Mohammad Hoesin Palembang is rational and needs to be maintained.

1. Introduction

Osteoarthritis is a chronic disease that involves the thinning of the cartilage in the joints resulting in the bones rubbing against each other, causing stiffness, pain, and limitation of movement.[1] From an epidemiological point of view, due to the high percentage of people suffering from this disease and the high life expectancy, now OA considered as one of the most significant causes of disability in the world.[2] Basic Health Research Data (Riskesdas) in 2013 showed that the average prevalence of joint disease / rheumatism based on interviews was 24.7%. The province with the highest prevalence was East Nusa Tenggara (33.1%) and the lowest was Riau (9%), while in South Sumatra the prevalence rate was around 17%. Management of osteoarthritis is broadly divided into nonpharmacology, pharmacology and surgery. Pharmacological therapy is one of the main options because surgery options are expensive and not widely available, especially in developing countries like Indonesia. The drugs commonly prescribed by doctors to OA patients are oral Non Steroidal Anti-Inflammatory Drugs (NSAIDs), topical NSAIDs, and opioids.[3]

Diclofenac is one of the NSAIDs recommended by the Indonesian Rheumatology Association in the management of OA. Diclofenac is a non-selective NSAID in which both types of COX are inhibited. With COX-1 inhibition, there is no longer anyone responsible for protecting the mucosa of the stomach, intestines, and kidneys so that there is

irritation and toxic effects on the kidneys,[4] so that long-term use of diclofenac can cause side effects such as peptic ulcer, gastrointestinal bleeding, hepatotoxicity, and kidney failure.[5]

Rational use of drugs is the administration of drugs that have the right choice, dosage, duration of use in accordance with applicable guidelines, appropriate for clinical needs, and at low cost for service providers, communities and patients, and are distributed appropriately and eaten correctly.[6] Rationality assessment Drug use can be reviewed through several aspects contained in the Drug Use Module issued by the Indonesian Ministry of Health, namely the right diagnosis, the right indication, the right drug, the right dose, the right frequency of drug administration and the right patient.[7]

Although diclofenac is an option that is often prescribed, especially in Dr. Mohammad Hoesin Palembang.[8] In this case, the researcher wants to do research on outpatient osteoarthritis cases, seen from the frequency of the number of patients who will be more because the pain intensity in osteoarthritis is not so disturbing that it is rare for patients to be willing to be hospitalized. Therefore, the researchers concluded that research is needed to ensure that the drug is used rationally so as to minimize unwanted side effects.

2. Research Methods

This research is a descriptive observational study with a *cross-sectional* approach to determine the rationality of using diclofenac in osteoarthritis patients Dr. Mohammad Hoesin Palembang. The sample in this study was the medical records of osteoarthritis patients at the Dr. Mohammad Hoesin Palembang for the January-March 2018 period who met the inclusion and exclusion criteria. The sampling technique used in this study was total sampling. The inclusion criteria for the sample in this study were medical records of patients diagnosed with osteoarthritis with or without comorbidities at Dr. Mohammad Hoesin, who received diclofenac treatment in January-March 2018. The exclusion criteria in this study were medical records that did not have complete data such as name, age, dose, frequency, and duration of use of diclofenac drugs.

The data obtained are arranged, sorted, and grouped. Data processing is done by collecting all the data obtained to be entered into the *Microsoft Excel* program and then a descriptive analysis of each data variable that has been collected will be carried out. The research results will be explained in narrative form and will be presented in tabular form.

3. Results and Discussion

Data collection was carried out in December 2018. A total of 201 medical records of osteoarthritis patients who met the inclusion and exclusion criteria were sampled.

From Table 1, it is known that the most osteoarthritis patients are in the 46-65 years age group, namely 121 patients (60.2%), then followed by the> 65 years age group as many as 45 patients (22.4%), the 36-45 years age group as many as 24 patients (11.9%), and the least in the 26-35 years age group was 11 patients (5.5%). In this study, the oldest age of osteoarthritis patients was 82 years and the youngest was 33 years. The data in Table 2 shows that the proportion of patients with female gender (55.7%) is more than that of male patients (44.3%). As shown in Table 3, osteoarthritis patients have various history of comorbidities, the most comorbidities are *Low Back Pain* (22.8%), followed by hypertension (16.9%) and type 2 diabetes mellitus (7.9%). The distribution of patients based on the rationality of using diclofenac drugs can be seen in table 4. Subjects with a dose of 25 mg, a frequency of 2 x 25 mg, duration of use <7 days and a combination of diclofenac drugs without interactions were the most frequent in this study. From the results of table 5, it is found that the drug combination without having the most drug interactions is omeprazole, gabapentin, and paracetamol. The drug combination with the most synergistic interactions with eperisone HCl, aspirin, and clopidogrel drugs. The drug combination with the most antagonist interactions is candesartan, valsartan, and furosemide.

Table 1. Distribution of Patients by Age

Age	N	%
26-35 years	11	5.5
36-45 years	24	11.9
46-65 years	121	60.2
>65 years	45	22.4

Table 2. Distribution of Patients by Gender

Gender	N	%
Male	89	44.3
Female	112	55.7

Table 3. Distribution of Patients based on Comorbidities

Concomitant Diseases	n	%
CHF	1	0.5
CVD	11	5.4
Diabetes Mellitus Type 2	16	7.9
Dyslipidemia	1	0.5
Dyspepsia	2	0.9
Frozen Shoulder	1	0.5
Gastritis	1	0.5
Gout	1	0.5
Hamstring Strain	1	0.5
Nucleus Pulposus Hernia	3	1.5
Hypertension	34	16.9
Hyperthyroidism	1	0.5
Ischialgia	3	1.5
Low Back Pain	46	22.8
Myocardial Infarction	1	0.5
Obesity	14	6.9
Osteoporosis	1	0.5

Table 4. Distribution of Patients Based on the Rationality of Drug Use

Rationality of Drug Use	n	%
Dosage for use		
25 mg	152	75.6
50 mg	49	24.4
Frequency of Use		
2 x 25 mg	148	73.6
3 x 25 mg	4	2.0
2 x 50 mg	46	22.9
3 x 50 mg	3	1.5
Duration of Use		
<7 days	115	57.2
8-14 days	68	33.8
> 14 days	18	9.0
Drug Interactions		
There is no	307	84.4
Synergistic	31	8.5
Antagonist	26	7.1

Table 5. Combination of Diclofenac with Other Drugs

Use of Diclofenac with Other Drugs	n	%
No Drug Interactions		
Allopurinol	1	0.3
Amitriptyline	13	4.2
Amlodipine	19	6.2
Atorvastatin	1	0.3
Cefixime	1	0.3
Clobazam	1	0.3
Codeine	1	0.3
Diazepam	13	4.2
Phenytoin	1	0.3
Gabapentin	53	17.3
Glucosamine	18	5.9
Haloperidol	1	0.3
Colchicine	1	0.3
Lansoprazole	6	2.0
Mecobalamin	18	5.9
Metformin	9	2.9
Meviton	1	0.3
Neurodex	34	11.1
Novorapid	1	0.3
Omeprazole	57	18.6
Osteocal	1	0.3
Paracetamol	40	13.0
Ranitidine	7	2.3
Simvastatin	4	1.3
Sucralfate	3	1.0
Trihexyphenidyl	1	0.3
Vastigo	1	0.3
Synergistic Drug Interactions		
Aspirin	8	25.8
Ciprofloxacin	1	3.2
Clopidogrel	3	9.7
Digoxin	1	3.2
Eperisone HCl	13	41.9
Glimepiride	1	3.2
Methylprednisolone	1	3.2
Methotrexate	1	3.2
Spironolactone	1	3.2
Warfarin	1	3.2
Antagonist Drug Interactions		
Candesartan	14	53.8
Carbamazepine	1	3.8
Domperidone	1	3.8
Flunarizine	1	3.8
Furosemide	3	11.5
Valsartan	6	23.1

Zoetermeer Survey data shows a sequential increase in the prevalence of osteoarthritis in each age group, but the results of this study are not in accordance with these data where there is a decrease in the prevalence of osteoarthritis in the age range 65 years and over.[9] This could be due to limited sampling of OA cases. who are being treated with diclofenac, which is the choice of treatment for the elderly should be careful because elderly patients have a higher risk of gastrointestinal complications if

using NSAIDs for a long time. Morgan (2001) in his study stated that elderly patients who were treated with diclofenac sodium experienced gastrointestinal bleeding and increased serum alanine transaminase two times normal.[10] This is caused by physiological changes with increasing age, especially in kidney function.

Based on gender, the proportion of women (55.7%) was higher than that of men (44.3%). Price in his research stated that the incidence of osteoarthritis in women is higher than in men.[11] In general, the frequency of osteoarthritis between women and men under the age of 45 is relatively the same, but when they are over 50 years of age, the frequency of osteoarthritis will be more common in women. than men. This shows that hormones have an effect on the pathogenesis of osteoarthritis.[12] The role of hormone in the pathogenesis of osteoarthritis is the hormone estrogen, where one of its functions is to help synthesize bone matrix chondrocytes, so that if estrogen levels decrease, it will cause chondrocyte synthesis to decrease as well while lysosome activity increases, this is explains why osteoarthritis is more likely to occur in women.[13] In addition, menopausal women are three times more likely to be obese than premenopausal women. over time it causes damage.[14] In this study it was found that Low Back Pain is the most comorbid disease in osteoarthritis patients. A cross-sectional study conducted by Hawker (2017) states that 40% of patients with hip and knee OA complain of persistent low back pain, low back pain is also associated with a poor prognosis of pelvic OA.[15] Furthermore, the second most common comorbid disease is hypertension, which is 34 patients. (16.9%). Actually there is no direct link between hypertension and OA. However, considering that in general, the incidence of OA mostly occurs in old age, where at that age the elasticity of blood vessels decreases so that there is an increase in total peripheral resistance and will cause an increase in blood pressure.[16] For the third largest comorbid disease is diabetes mellitus, which is 7.9%. Disorders that affect glucose metabolism may support the development or development of OA. The ability of chondrocytes to regulate glucose transport capacity under extreme extracellular glucose conditions, it was found that normal chondrocytes were able to adjust to variations in the concentration of glucose extracellular Glucose Transporter Type 1 (GLUT-1) whereas chondrocytes from OA patients could not adjust GLUT-1 which resulted in accumulation. glucose and higher reactive oxygen production. This may be a pathogenic mechanism whereby DM can cause degenerative changes that facilitate the development of OA.[17]

Based on the dosage of drug use, the dose of 25 mg (75.6%) is the most widely used. Most of the onset of analgesic and antipyretic effects of diclofenac 25 mg occurred within 30 minutes. Diclofenac doses of 25 mg or 50 mg are as effective as ibuprofen 200 mg or 400 mg in relieving pain in acute low back pain, headaches, osteoarthritis, and dysmenorrhea.[18] Based on the frequency of drug use, the frequency of 2 x 25 mg was the most widely used (73.6%). Diclofenac has a dose of 100-150 mg/day, every 8-12 hours with a maximum dose of 150 mg/day.[19] Of the 201 patients, all of them stated the correct frequency of use where the dose given was appropriate and did not exceed the maximum dose per day. The use of NSAIDs in doses that exceed normal and in the long term can increase the risk of drug side effects.[20]

Meanwhile, based on the duration of drug use, the duration of less than 7 days (57.2%) was the highest. Clinical trials and epidemiological data have consistently shown an increased risk of cardiovascular disease (such as myocardial infarction or stroke) associated with diclofenac use, especially at high doses (150 mg per day) and in long-term use.[18] *The Australian Therapeutic Goods Administration* (TGA) recommend short-term use of diclofenac in the lowest effective dose.

The most widely used drug combination that does not have drug interactions is omeprazole (18.6%), the use of omeprazole has been shown to be effective in preventing gastric ulcers caused by long-term use of NSAIDs.[21]

The most widely used combination of drugs with synergistic drug interactions was eperisone HCl (41.9%), followed by aspirin (25.8%), and clopidogrel (9.7%).

The most widely used combination of drugs with antagonistic drug interactions were candesartan (53.8%), followed by valsartan (23.1%), and furosemide (11.5%).

Table 6. Synergistic Drug Interactions

Use of Diclofenac with Other Drugs	Information
Aspirin	Combined use of diclofenac and aspirin can increase the concentration of potassium in serum, as well as increase the incidence of gastrointestinal complications.[22]
Ciprofloxacin	The use of diclofenac and ciprofloxacin together can increase the risk of side effects on the central nervous system such as tremors, anxiety, hallucinations, and seizures.[22]
Clopidogrel	Diclofenac may increase clopidogrel side effects through synergistic pharmacodynamic interactions.[23]
Digoxin	Diclofenac can increase the serum digoxin concentration by interfering with digoxin excretion.[22]
Eperisone HCl	The combination of diclofenac with eperisone can increase the risk of hyperkalemia.[23]
Glimepiride	Diclofenac enhances the effects of glimepiride via an unknown mechanism.[22]
Methylprednisolone	Diclofenac may increase methylprednisolone toxicity through synergistic pharmacodynamic interactions.[24]
Methotrexate	Diclofenac increases the serum methotrexate concentration by inhibiting its excretion.[23]
Spironolactone	The use of diclofenac and spironolactone together can increase the concentration of potassium in the serum.[22]
Warfarin	Concomitant use of diclofenac and warfarin may increase the anticoagulation effect.[22]

Tabel 7. Interaksi Obat Antagonis

Use of Diclofenac with Other Drugs	**Information**
Candesartan	Diclofenac reduces the action of candesartan through antagonistic pharmacodynamic interactions.[22]
Carbamazepine	Carbamazepine reduces the effect and serum concentration of diclofenac by affecting the hepatic enzyme metabolism CYP2C9 / 10.[24]
Domperidone	Domperidone metabolism is reduced when combined with diclofenac. [22]
Flunarizine	Flunarizine metabolism is reduced when combined with diclofenac. [24]
Furosemide	Diclofenac reduces the action of furosemide through antagonistic pharmacodynamic interactions. [24]
Valsartan	Diclofenac reduces the action of valsartan through antagonistic pharmacodynamic interactions. [22]

4. Conclusion

The highest dose of diclofenac was given with a dose of 25 mg (75.6%), the most frequent use of diclofenac was given with a frequency of 2 x 25 mg (73.6%), the longest use of diclofenac was with a duration of less than 7 days (57.2%) . The most combination of diclofenac and other non-interacting drugs (84.4%) was omeprazole, gabapentin, and paracetamol. The combination of diclofenac with other drugs that interacted synergistically (8.5%) with eperisone HCl, aspirin, and clopidogrel. The combination of diclofenac with other drugs that interacted with antagonists (7.1%) the most with candesartan, valsartan, and furosemide.

Thus it can be concluded that the use of diclofenac both in terms of dose, frequency, duration of use, and the combination of diclofenac with other drugs is rational and needs to be maintained.

5. References

1. Ling, Shari M. dan Bathon, Joan M. 2012. Osteoarthritis: Pathophysiology. Johns Hopkins Arthritis Center. https://www.hopkinsarthritis.org/arthritis-info/osteoarthritis/oa-pathophysiology/
2. Block, Joel A., dan Scanzello, Carla. 2016. Osteoarthritis, dalam Goldman, Lee dan Schafer, Andrew I. (editor). Goldman-Cecil Medicine Edisi ke-25. Philadelphia. Elsevier.
3. World Health Organization. 2013. Osteoarthritis (http:/archives.who.int/prioritymeds/report/background/osteoarthritis.doc)
4. Tjay, T. H., dan Rahardja, K., 2015, Obat-obat Penting, Khasiat, Penggunaan dan Efek-Efek Sampingnya, Edisi ke-7, Jakarta, PT Elex Media Komputindo Kelompok Gramedia.
5. Aydin, G. I., Alparslan, G., Umen, K., Meral, N. C., Ekr, U. E., Nermin, K., dan Kalp, G. 2003. Histopathologic Changes in Liver and Renal Tissues Induced by Different Doses of Diclofenac Sodium in Rats. Turkish Journal of Veterinary and Animal Sciences, 27, hal. 1131–1140
6. Kshirsagar, Nilima A. 2016. Rational use of medicines: Cost consideration & way forward. The Indian Journal of Medical Research, 144(4), hal. 502–505. http://doi.org/10.4103/0971-5916.200901
7. Kemenkes RI. 2011. Modul Penggunaan Obat Rasional. Jakarta, hal. 1-32.
8. Dasti, Filia Nurul. 2016. Rasionalitas Penggunaan Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Pada Pasien Osteoarthritis Di RSUP Moh. Hoesin Palembang. Universitas Sriwijaya Palembang, hal. 44.
9. Zhang, W., Doherty, M., Peat, G., dkk. 2010. EULAR Evidence-Based Recommendations for the Diagnosis of Knee Osteoarthritis. Ann Rheum Dis. 69, hal. 483-489.
10. Morgan, G.J., Kaine, J., Delapp, R., dan Palmer, R. 2001. Treatment of elderly patients with nabumetone or diclofenac: gastrointestinal safety profile. Journal of Clinical Gastroenterology, 32(4). hal. 310-314. https://insights.ovid.com/pubmed?pmid=11276273.
11. Price, Sylvia A., Wilson Lorraine M. 2006. Patofisiologi, Konsep Klinis Proses-Proses Penyakit Edisi 6. Jakarta : Penerbit Buku Kedokteran EGC.
12. Soeroso J, Isbagio H, Kalim H, Broto R, Pramudiyo R. 2007. Osteoartritis, dalam Sudoyo AW, Setiyohadi B, Alwi I, Simadibrata M, Setiati S, (editor). Buku Ajar Ilmu Penyakit Dalam. Edisi ke-4. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam Fakultas Kedokteran Indonesia. hal. 1195-201.
13. Khairani, Yulidar. 2013. Hubungan Umur, Jenis Kelamin, IMT, dan Aktivitas Fisik Dengan Kejadian Osteoarthritis Lutut. Artikel Ilmiah. Jambi: Fakultas Kedokteran dan Ilmu Kesehatan Universitas Jambi.
14. Lizcano, F., dan Guzman, G. 2014. Estrogen Deficiency and the Origin of Obesity during Menopause. BioMed Research International vol. 2014. https://doi.org/10.1155/2014/757461.
15. Hawker, G. A., Stupar, M., Cote, P., dan French, M. R. 2017. The Association Between Low Back Pain and Osteoarthritis

of the Hip and Knee: A Population-Based Cohort Study. Journal of Manipulative and Physiological Therapeutics, 33(5), hal. 349–354. http://doi:10.1016/j.jmpt.2010.05.008.

16. Soeroso J, Isbagio H, Kalim H, Broto R, Pramudiyo R. 2007. Osteoartritis, dalam Sudoyo AW, Setiyohadi B, Alwi I, Simadibrata M, Setiati S, (editor). Buku Ajar Ilmu Penyakit Dalam. Edisi ke-4. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam Fakultas Kedokteran Indonesia. hal. 1195-201.
17. Nieves-Plaza, Mariely., Castro-Santana, Lesliane E., Font, Yvonne M., Mayor, Angel M., Vilá, Luis M., 2014. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. Journal Clinical Rheumatology. Vol. 19, No. 1, p. 1-16.
18. Moore, N. 2017. Diclofenac Sodium Tablets for Mild to Moderate Pain and Fever. Clinical Drug Invest 27(3), hal. 163-195.
19. Management Sciences for Health. 2012. Managing Access to Medicines and Health Technologies: Managing for Rational Medicine Use. Arlington, VA: Management Sciences for Health.
20. Todd, P.A., dan Sorkin, E.M. 2012. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 35(3), hal. 244-285. https://doi.org/10.2165/00003495-198835030-00004
21. Labenz, J., Blum, A. L., Bolten, W. W., dan Stolte, M. 2002. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in Helicobacter pylori positive patients: a randomised, double blind, placebo controlled, clinical trial. Gut.;51(3), hal. 329-335.
22. Aronson, J.K., 2015, Meyler'S Side Effect of Drugs Edisi ke-16. The International Encyclopedia of Adverse Drug Reactions and Interaction, Elsevier, Oslo, Norway.
23. Brenner, G.M. and Stevens, C.W., 2017, Pharmacology. Edisi ke-5. Elsevier, Philadelphia.
24. Waldman S.A. dan Terzic, A. 2009. Pharmacology and Therapeutics Principles to Practise. Philladelphia : Saunders Elseviers