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Analisis Potensi Interaksi Obat pada Resep Spesialis Saraf di RSUD X Kabupaten Majalengka

Analysis of Potential Drug Interactions in Neurology Specialist Prescriptions at RSUD X Majalengka Regency

Siti Pandanwangi TW*, Dosi Ahmad Yani, Ahmad Azrul Zuniarto, Roni Imron Muwahid
Department of Pharmacy, YPIB Majalengka University, Cirebon, West Java, Indonesia

A R T I K E L I N F O

Kata Kunci:
Interaksi obat, penyakit saraf, rawat inap

A B S T R A K

Pengobatan penyakit *neurological disease* menggunakan banyak obat sehingga beresiko terjadinya interaksi obat. Penelitian ini bertujuan untuk mengetahui potensial interaksi obat-obat pada peresepan pasien penyakit saraf, tingkat keparahan minor, moderate dan major, hubungan karakteristik pasien terhadap interaksi obat, serta manajemen penanganan interaksi obat. Metode penelitian yang digunakan kuantitatif deskriptif berupa jenis penelitian observasional, pengambilan data secara prospektif dengan teknik quota sampling yang dilakukan bulan Maret-Mei 2024 di RSUD X Kabupaten Majalengka. Hasil penelitian dari total 60 pasien sebanyak 49 pasien (81,7%) mengalami interaksi obat, dan 11 pasien (18,3%) tidak ada interaksi. Tingkat keparahan interaksi tertinggi yaitu moderat (71,7%), minor (24,1%) dan major (4,2%). Hasil *uji chi square* interaksi obat dengan jenis kelamin diperoleh nilai signifikansi 0,181 dan nilai OR dengan CI 95% sebesar 0,429 yang artinya perempuan beresiko 0,429 kali terjadi interaksi obat daripada pasien laki-laki. Interaksi obat dengan usia diperoleh nilai signifikansi 0,017 dan nilai OR dengan CI 95% sebesar 8,762 yang artinya bahwa usia ≥ 45 tahun 8,762 kali beresiko akan terjadi interaksi obat jika dibandingkan usia < 45 tahun. Interaksi obat dengan jumlah obat diperoleh nilai signifikansi 0,000 dan nilai OR dengan CI 95% sebesar 105,750 yang artinya bahwa jumlah obat yang dikonsumsi pasien ≥ 5 macam obat 105,750 beresiko terjadinya interaksi obat dibandingkan pasien yang mengkonsumsi < dari 5 macam obat. Potensi terjadinya interaksi obat-obat di tingkat keparahan *moderate* yaitu fenofibrate – novorapid (insulin aspart), captopril-dexketoprofen, fenitoin – diazepam. Tingkat keparahan *major* diantaranya adalah cilostazol – lansoprazole. Interaksi obat dengan mekanisme farmakodinamik yaitu methylprednisolon-insulin aspart. Interaksi obat secara farmakokinetik dalam penelitian ini yaitu fenitoin – deksamethason.

Keywords:
Drug interactions, neurological diseases, inpatient care

A B S T R A C T

Neurological diseases are a significant public health issue that requires specific policies for their management, necessitating comprehensive data on their causes, progression, and symptoms. Treatment of these diseases often involves multiple medications, increasing the risk of drug interactions. Drug interactions occur when the presence of another drug alters the effect of one drug. This study aims to identify the drug interactions in the prescription of patients with neurological disorders, the frequency of potential drug interaction occurrences, the severity levels (minor, moderate, and major), the relationship between patient characteristics and drug interactions, and the management of drug interactions. The research method employed is a descriptive quantitative approach, utilising observational research, with data collection conducted prospectively through quota sampling, carried out from March to May 2024 at RSUD X, Majalengka Regency.
Results: Out of a total of 60 patients, 49 patients (81.7%) experienced drug interactions, while 11 patients (18.3%) had no interactions. The highest severity level of interactions was moderate (71.7%), followed by minor (24.1%) and major (4.2%). The chi-square test for drug interactions with gender yielded a significance value of 0.181 and an odds ratio (OR) with a 95% confidence interval (CI) of 0.429, indicating that females are 0.429 times less likely to experience drug interactions compared to males. The chi-square test for drug interactions with age yielded a significance value of 0.017 and an OR with a 95% CI of 8.762, suggesting that individuals aged ≥ 45 years are 8.762 times more likely to experience drug interactions compared to those aged < 45 years. The chi-square test for drug interactions with the number of medications yielded a significance value of 0.000 and an OR with a 95% CI of 105.750, meaning that patients taking ≥ 5 different medications are 105.750 times more likely to experience drug interactions compared to those taking < 5 medications. Potential drug interactions at the moderate severity level include fenofibrate–novorapid (insulin aspart), captopril–dexketoprofen, and phenytoin – diazepam. Major severity interactions include cilostazol–lansoprazole. Drug interactions with a pharmacodynamic mechanism include methylprednisolone–insulin aspart. Pharmacokinetic drug interactions identified in this study include phenytoin – dexamethasone.

E-mail address: sitipandanwangitw@gmail.com

1. Introduction

Neurological diseases are a significant public health issue that requires specific policies for their management, necessitating comprehensive data on their causes, progression, and symptoms (Sari, 2022). The nervous system is a complex network within the body comprising millions of interconnected nerve cells that function to control body coordination. All bodily movements and functions heavily rely on the nervous system. Various factors can lead to neurological disorders or diseases, such as headaches, vertigo, meningitis, multiple sclerosis, stroke, accidents that injure the spinal cord or skull, and other neurological conditions. The diverse risk factors and complications associated with neurological diseases often necessitate treatment with multiple medications (polypharmacy). Polypharmacy refers to the use of five or more different medications within a single treatment period (Lukman Hakim, 2022). Polypharmacy can lead to potential drug interactions that may be harmful to patients.

Drug interactions are defined as interactions between drugs, between drugs and components of food or beverages, between drugs and herbal remedies, between drugs and dietary supplements or health supplements, and between drugs and diseases, which can alter the expected therapeutic effects. These changes in effects can result in either an increase or decrease in clinical effects (intensity or duration of the effect) and may even lead to adverse effects in patients, which can be classified as mild (minor), moderate, or severe (major) (Lukman Hakim, 2022). Drug interactions are changes in the effects of a drug due to drug use with these other ingredients including traditional medicines and compounds other chemicals. Drug interaction is an interaction that occurs when the effect one drug is changed by the presence of another drug (Mahamudu et al., 2017).

A study conducted by Ahmad Azrul et al. (2020) reported that out of 200 internal medicine polypharmacy prescriptions sampled from RSU X Cirebon during the period from January to June 2018, 75.5% experienced drug interactions. Among these interactions, 32% were classified as minor, 58% as moderate, and 29.5% as major. Additionally, 62% of the interactions were of a pharmacodynamic type, while 35% were pharmacokinetic (Zuniarto et al., 2020). Meanwhile, a study conducted by Lilik and Melinda (2023) at RSUD Kota Mataram found that out of 119 patients, 113 patients (95%) experienced drug interactions. The mechanisms of these interactions were pharmacodynamic (58.45%) and pharmacokinetic (41.55%). The severity levels of the interactions were classified as major (8.85%), moderate (80.29%), and minor (10.86%). Most studies are conducted using a retrospective method, where the samples are drawn from previous cases, and the patients are no longer under hospital care (Malinda, 2023).

Unlike previous studies, this research employs a prospective method, which involves the actual sampling process while patients are still under hospital care. This approach allows for the prevention of potential drug interactions through recommendations and management strategies for prescriptions identified with drug interactions..

2. Materials and Methods

Type of research

The research method employed is a quantitative, descriptive, analytical approach, involving observational research to assess the potential for drug interactions, their severity levels, and management recommendations. This research received ethical permission with the number 101/KEPK/EC/III/2024. The study took place in the inpatient pharmacy department at RSUD X, Majalengka Regency, between March 20, 2024 and May 1, 2024.

Population and sample

The population in this study comprises all prescription sheets from inpatient patients at RSUD X, Majalengka Regency. The sample used in this study consists of prescription sheets for patients with neurological disorders in the same hospital. The study aims to use a total of 60 samples. The researcher collects 2 to 3 prescription sheets daily from the inpatient pharmacy department for analysis until the target sample size is reached. Inclusion criteria for the samples are prescriptions from neurologists and prescriptions consisting of two or more medications. Exclusion criteria include prescriptions for patients who were discharged against medical advice and prescriptions for patients who have passed away.

Data collection

Data collection was conducted prospectively using quota sampling in the inpatient pharmacy department at RSUD X, Majalengka Regency. The research tools used include Medscape.com, Drugs Interaction Checker (Drugs.com). The results read on the tool will be reviewed by looking at other libraries such as the Drug Interaction Book or journals related to drug interactions. The research materials comprised prescriptions for patients with neurological disorders in the inpatient pharmacy department at RSUD X, Majalengka Regency.

In this study, the independent variable is the number of medications used by inpatient patients with neurological disorders, and the dependent variable is drug interactions. The research process begins with obtaining research permissions, conducting preliminary studies, and then collecting secondary data, specifically patient prescription records. The obtained data are then processed and analyzed descriptively by evaluating the potential for drug interactions, their severity levels, and management recommendations for actual drug interactions based on the established criteria. This analysis is informed by literature from Medscape.com, Drugs.com, and relevant journals.

Data analysis and processing

The data obtained was then processed and analyzed descriptively by analyzing the potential for drug interactions, levels severity, and management recommendations for actual drug interactions with predetermined criteria, based on literature through application medscape.com, drugs.com application and journals appropriate to the research.

3. Results and Discussion

Characteristics of neurological patients

Table 1 shows that the number of female patients is higher compared to male patients, with 32 females (53%) and 28 males (46%). According to the Ministry of Health of the Republic of Indonesia (2017), women have a higher life expectancy compared to men. This is reflected in the higher percentage of elderly females (9.53%) compared to elderly males (8.54%) (Kemenkes RI, 2017). The majority of patients are aged ≥ 45 years, comprising 53 patients (88.3%), while 7 patients (11.7%) are aged < 45 years. Pre-elderly or geriatric patients typically suffer from degenerative, chronic, and multi-pathological conditions that are interrelated, leading to the use of multiple medications simultaneously. This increases the risk of drug interactions (Zulkarnaini & Martini, 2019).

Table 1. Distribution of gender among inpatient neurological patients at RSUD X, Majalengka Regency.

Characteristics	N	Percentage (%)
Gender		
Male	28	46,7
Female	32	53,3
Age		
< 45 years	7	11,7
≥ 45 years	53	88,3
Number of medications		
< 5 medications	10	16,7
≥ 5 medications	50	83,3

Table 1 so shows that 50 patients (83.3%) are prescribed ≥ 5 different medications, while 10 patients (16.7%) are prescribed < 5 medications. Similar results are also reported in the study by Gupta et al. (2018) Among 64 geriatric patients, 37 (57.8%) are prescribed 5-9 medications, and 25 patients (39.1%) are prescribed 4 medications. This is due to the diverse risk factors and complications associated with neurological diseases, which necessitate the use of multiple medications (polypharmacy). Polypharmacy is a major factor that increases the risk of drug interactions. As age increases, the prevalence of chronic diseases also rises, leading to an increase in medication use and consequently raising the potential for drug interactions (Satish S et al.,2021).

Table 2 shows that 49 patients (81.7%) experienced drug interactions, with a total of 141 drug potential interaction incidents. Meanwhile, 11 patients (18.3%) did not experience any drug interactions. These findings are consistent with previous research conducted by Annisa (2021) Using retrospective data, it was shown that the prevalence of drug interactions in the study was quite high, with 47 out of 51 patients (92.2%) showing potential drug interactions, and a total of 270 interaction incidents (Annisa, 2021). When comparing the number of interaction incidents, Annisa's study shows a higher rate. This is attributed to the lack of management for drug interactions, unlike in the current study, where active management of drug interactions was implemented. As a result, the incidence of interactions was minimized.

Drug interaction incidents based on severity levels

Table 3 shows that among the 49 patients identified with drug interactions, there were a total of 141 interaction incidents. Based on the severity of the interactions, major interactions had the lowest percentage at 4.2% (6 cases), followed by moderate interactions with the highest percentage at 71.7% (101 cases), and minor interactions at 24.1% (34 cases). Similar results were observed in the study conducted by Agrawal, R.K., & Nagpure (2018) The study indicated that the most common drug interactions were of moderate severity, accounting for 50.6%, followed by minor severity at 8.7%, and major severity at 7.9% (Agrawal, R.K., & Nagpure, 2018).

Drug interactions frequently observed at the minor severity level include the interaction between ranitidine and paracetamol. Ranitidine can delay the absorption of paracetamol by reducing gastric emptying, resulting in decreased paracetamol levels in the blood and thus diminishing its pharmacological effect. Another example of a minor severity interaction is between Aspilet (aspirin) and lansoprazole, which occurred in 13 instances. In this interaction, lansoprazole can reduce the bioavailability of Aspilet (aspirin). Lansoprazole may decrease the lipophilicity of aspirin, adversely affecting its absorption from the gastrointestinal tract. Management of this interaction involves modifying the timing or method of drug administration (ac, pc). (Drugs.com, 2024).

Drug interactions frequently observed at the moderate severity level include the interaction between fenofibrate and Novorapid (insulin aspart). Fenofibrate, a PPARα agonist, is commonly used to treat dyslipidemia and is also effective in improving glycemic control in hyperglycemic patients. When used in conjunction with insulin aspart, there is a risk of significantly lowering high glucose levels, potentially leading to hypoglycemia. Therefore, monitoring blood glucose levels is essential to prevent such interaction effects. This is consistent with the research conducted by Andrew T et al. (2012), which found that fenofibrate is more effective in reducing triglyceride levels and lowering cardiovascular disease risk in diabetes patients (Andrew T et al., 2012).

Drug interactions in inpatient neurological patients

Another common moderate-severity drug interaction is between captopril and dexketoprofen. This interaction between an ACE inhibitor and an NSAID represents a pharmacodynamic interaction. The antihypertensive effect of the ACE inhibitor may be reduced when administered with an NSAID, which inhibits cyclooxygenase and consequently suppresses prostaglandin synthesis.

Table 2. Percentage of drug interaction incidents in neurological patients

Drug interactions	N	Percentage (%)	Number of drug interaction incidents
Drug interactions	49	81,7	141
No drug interactions	11	18,3	0
Total	60	100	141

Table 3. Percentage of drug interaction severity levels in neurological patients

Severity of Interaction	N	Percentage (%)
Minor	34	24,1
Moderate	101	71,7
Major	6	4,2
Total	141	100

Prostaglandins act as vasodilators, and their suppression counteracts the vasodilatory effects mediated by the ACE inhibitor (Isnenia, 2020). NSAIDs can also increase sodium retention, which may further diminish the antihypertensive effects of the ACE inhibitor (Baxter, 2010). The management carried out is that if this combination is used long-term, patients are advised to monitor blood pressure regularly and monitor kidney function (Drugs.com, 2024).

Another moderate severity drug interaction is between phenytoin and diazepam, which involves a pharmacokinetic mechanism. The combination of these two drugs has the potential to reduce the efficacy of diazepam by affecting the metabolism of the enzyme CYP3A4 in the liver and intestine (Medscape, 2024). According to Miftahul (2016), the interaction between phenytoin and benzodiazepines occurs because benzodiazepines inhibit the metabolism of phenytoin, while phenytoin enhances the metabolism of benzodiazepines. This results in increased levels of phenytoin in the blood, which can lead to phenytoin toxicity (Porogoi et al., 2020). Management measures must be enforced, including performing drug side effect monitoring (MESO) for patients undergoing therapy (Drugs.com, 2024).

A major severity drug interaction commonly observed is between cilostazol and lansoprazole. This interaction should be carefully considered, as lansoprazole, can increase systemic levels of cilostazol, posing potential risks. Therefore, managing the timing of drug administration is essential. This aligns with previous research on PPIs such as omeprazole. Co-administration of cilostazol with omeprazole has been shown to increase systemic exposure to cilostazol and its active metabolite OPC-13015 by 26% and 69%, respectively. However, the systemic exposure of another active metabolite, OPC-13213, decreased by 31% due to the inhibition of cilostazol metabolism on this metabolite. These changes in systemic exposure are generally well tolerated. When co-administering cilostazol with CYP2C19 inhibitors like omeprazole, a dose of 50 mg of cilostazol twice daily should be considered (A Suri, 1999).

Table 4 shows that out of 49 patients with drug interactions and a total of 141 potential interaction incidents, the pharmacodynamic mechanism had the highest percentage, with 94 incidents (66.7%). This is consistent with the study by Sonnerstam et al. (2018), which reported that pharmacodynamic interactions were the most common, accounting for 187 incidents (46.6%) out of 401 patients. Pharmacokinetic interactions accounted for 169 incidents (42.1%). This differs from the study conducted by (Dasopang et al., 2015) In a study using 328 medical records, it was found that pharmacokinetic interactions (63.6%) were the most prevalent phase of interactions, followed by pharmacodynamic interactions (22.8%) and unknown interactions (13.6%) (Dasopang et al., 2015).

Drug interaction incidents based on interaction mechanisms

A pharmacodynamic interaction between methylprednisolone and insulin aspart is observed. Corticosteroids can reduce the effects of insulin. Corticosteroids inhibit the production and secretion of insulin, reduce peripheral glucose uptake, increase endogenous glucose production, and cause β-cell dysfunction (Suh & Park, 2017).

Table 4. Percentage of drug interaction incidents based on the mechanism of interaction

Mechanism of Interaction	N	Percentage (%)
Pharmacodynamic	94	66,7
Pharmacokinetic	46	32,6
Unknown	1	0,7
Total	141	100

Table 5. Chi-square test results for the relationship between drug interaction and gender

Drug interaction	Neurological patients		N	Sig.	OR
	Male	Female			
With interaction	21	28	49		
Without interaction	7	4	11	0,181	0,429
Total	28	32	60		

Table 6. Chi-square test results for the relationship between drug interaction and age

Drug interaction	Neurological patients		N	Sig.	OR
	< 45 years	≥ 45 years			
With interaction	3	46	49	0,017	8,762
Without interaction	4	7	11		
Total	7	53	60		

Table 7. Chi-square test results for the relationship between drug interaction and number of drugs

Drug interaction	Neurological patients		N	Sig.	OR
	< 5 drugs	≥ 5 drugs			
Interaction present	2	47	49	0,000	105,750
No interaction	9	2	11		
Total	11	49	60		

From Table 5, the significance value obtained is 0.181, and the odds ratio is 0.429, which means that females are 0.429 times less likely to experience drug interactions compared to males. However, this value is not statistically significant as the p-value is 0.181 ($p > 0.05$). This finding is consistent with the study by Maya A. (2017), which also reported that gender and the number of drugs were not significantly related to the occurrence of drug interactions, with significance values of 0.06 and 0.13, respectively ((Arfania et al., 2017).

From Table 6, it is shown that out of 53 patients aged ≥ 45 years, 46 patients were found to have drug interactions. Data analyzed using SPSS with the Chi-Square method yielded a significance value of 0.017 and an odds ratio of 8.762. This means that patients aged ≥ 45 years are 8.762 times more likely to experience drug interactions compared to those under 45 years of age. This value is significant as the significance level is 0.017 ($p < 0.05$) From this study, it can be interpreted that as patients' age increases, the likelihood of drug interactions also increases. In addition to polypharmacy, this is due to the declining function of body organs, particularly the liver and kidneys, which leads to the development of multi-pathological and chronic diseases (Martono, 2009).

Management measures need to be implemented, including monitoring blood glucose levels to prevent the effects of this interaction (Drugs.com, 2024). A pharmacokinetic drug interaction observed in this study is between phenytoin and dexamethasone. Phenytoin acts as an enzyme inducer in the liver, which can increase the metabolism and clearance of dexamethasone. This interaction has the potential to decrease the levels and pharmacological effects of dexamethasone in patients. This mechanism represents a pharmacokinetic interaction occurring at the metabolism stage (Stockley I.H., 2010). Management involves modifying the timing of drug administration.

From Table 7, it is observed that the significance value is 0.000 and the odds ratio (OR) is 105.750. This indicates that patients taking ≥ 5 types of drugs are 105.750 times more likely to experience drug interactions compared to patients taking fewer than 5 types of drugs. This result is highly significant with a p-value of 0.000 ($p < 0.05$). These findings are consistent with the study conducted by Urip Harahap in 2015, which reported a correlation between the number of drugs used and drug interactions, with a p-value of 0.000, indicating a significant relationship between drug interactions and the number of medications used (Dasopang et al., 2015).

Based on the data, it can be concluded that the more medications a patient consumes, the greater the likelihood of drug interactions occurring. The variety of risk factors and complications associated with neurological diseases often leads to the need for polypharmacy, which involves the use of five or more different medications within a single treatment period. (Lukman Hakim, 2022). Polypharmacy can lead to potential drug interactions that may be harmful to patients.

Management of drug interactions

Based on the Drugs.com (2024), drug interaction management involves several steps, including modifying the timing and method of medication administration, monitoring for side effects, recommending evaluations of blood pressure, blood glucose levels, electrolytes, and other clinical laboratory results, advising medication substitutions to the prescribing physician, and adjusting medication doses after consulting with the prescribing physician (Drugs.com, 2024).

4. Conclusion

Of the 60 inpatients with neurological conditions, 49 patients (81.7%) experienced drug interactions, while 11 patients (18.3%) did not. A total of 141 drug interaction cases were identified. The highest severity of drug interactions was moderate, with 101 cases (71.7%), followed by minor interactions with 34 cases (24.1%), and major interactions with 6 cases (4.2%). The most frequent mechanism of interaction was pharmacodynamic, with 94 cases (66.7%), followed by pharmacokinetic interactions with 46 cases (32.6%), and interactions with an unknown mechanism accounted for 1 case (0.7%).

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