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Analysis of Prevalence and Factors of Potential Drug-Drug Interactions in Hypertensive Patients the Coastal Area of Surabaya

Analisis dan Faktor Interaksi Obat Pada Pasien Hipertensi di Daerah Pesisir Surabaya

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Abstract

Hypertension is a severe health problem that generally requires combination therapy. Using a combination of antihypertensive therapy and long-term therapy requires monitoring the effects of potential drug-drug interactions (PDDIs) experienced by patients. This study aims to determine the drug interaction profile related to severity and mechanism. The method was descriptive and observational by recapitulating the prescription in several pharmacies in the coastal area of Surabaya. The samples are prescriptions consist of antihypertensives with other drugs. This research was conducted for three months. This study showed that 43% potential drug-drug interactions. The pharmacodynamic interactions are slightly more dominant (49%) than pharmacokinetics (45%). Meanwhile, the highest severity of drug interactions, namely minor (49%), followed by moderate (39%) and severe (12%), was in the last position. The modest drug interaction at a moderate level is amlodipine, which can decrease the pharmacological effect of metformin. Therefore, pharmacists need to monitor blood sugar levels regularly. Serious interactions are indeed the lowest incidence; otherwise, the effects can be dangerous, so pharmacists need to monitor patients who receive drugs with severe drug interactions. One of them is amlodipine and simvastatin, which can increase the risk of rhabdomyolysis from statins. Pharmacists have an important role in monitoring the effects of drug interactions in hypertensive patients. Patients get the maximum therapeutic effect with minimal drug interactions or prevent drug interactions.

***Keywords*: Drug interactions, Hypertension, Antihypertensive, PDDIs, amlodipine, simvastatin.**

Abstrak

Hipertensi merupakan penyakit kronis yang pada umumnya memerlukan terapi kombinasi. Penggunaan kombinasi terapi antihipertensi dan terapi jangka panjang memerlukan pemantauan efek potensi interaksi obat. Penelitian ini bertujuan untuk mengetahui profil interaksi obat terkait tingkat keparahan dan mekanismenya. Metode penelitian deskriptif dan observasional resep di beberapa apotek di wilayah pesisir pantai Surabaya. Sampel pada penelitian adalah resep yang terdiri dari antihipertensi dengan obat lain. Hasil menunjukkan sebanyak 43% potensi interaksi obat-obat. Interaksi farmakodinamik sedikit lebih dominan (49%) dibandingkan farmakokinetik (45%), sedangkan tingkat keparahan interaksi obat yang paling tinggi yaitu ringan (49%), sedang (39%) dan berat (12%). Interaksi obat dengan tingkat sedang adalah amlodipine-metformin, yang dapat menurunkan efek farmakologis metformin. Oleh karena itu, apoteker perlu memantau kadar gula darah secara rutin. Interaksi serius memiliki kejadian terendah tetapi efeknya bisa berbahaya sehingga apoteker perlu memantau pasien yang menerima obat dengan interaksi dengan tingkat serius. Salah satunya adalah amlodipine dan simvastatin yang dapat meningkatkan risiko rhabdomiolisis akibat statin. Apoteker mempunyai peran penting dalam memantau efek interaksi obat pada pasien hipertensi. Pasien mendapatkan efek terapi yang maksimal dengan interaksi obat yang minimal atau mencegah interaksi obat.

***Kata Kunci*: Interaksi Obat, Hipertensi, Antihipertensi, Amlodipine, Simvastatin**

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Introduction

Potential drug-drug interactions (pDDIs) are events that could affect the effectiveness or safety of two or more medications that are taken concurrently [1]. One of the avoidable drug-related issues that run the risk of degrading the therapeutic effect, causing adverse drug reactions, and leading to treatment failure or even death is drug-drug interactions (DDIs), which account for about 22 percent of drug withdrawal and adverse drug reaction-related hospital admissions [2]. To reduce the associated risk and enhance clinical pharmaceutical safety, it is crucial to identify pDDIs. Age, comorbidities, polypharmacy, nutritional condition, and genetic make-up of an individual are a few factors that influence the occurrence of DDIs in populations [3,4]. DDIs should be taken seriously, especially in older patients with concomitant conditions. According to reports, patients using five prescriptions experienced a 50% increase in the likelihood of adverse drug responses, and patients taking eight medications experienced a 100% increase [5].

DDIs are very common in both inpatients and outpatients, particularly in the ICU, oncology, and hematology [6-11]. According to various research, the prevalence of pDDIs ranges from 16–96% [12,13]. The present study aims to obtain profile the actual occurrence of pDDIs in outpatient prescriptions and categorize the severity of the interactions due to the lack of research on the epidemiology of DDIs in the outpatients of pharmacies at coastal area of Surabaya. The objective of this study was to ascertain the prevalence of pDDIs in outpatients by screening the prescriptions. Additionally, we analyzed the association of pDDIs with variables in the prescriptions.

Material and Methods

This cross-sectional retrospective study was conducted in the outpatients of coastal area of Surabaya. The prescriptions for analysis were collected for three months. All of the study's outpatients, who were older than 18, were receiving at least two medications. Gender and prescribed medicines were all included in the data. Dosage forms which contain combination active ingredients were analyzed individually according to each ingredient. The clinical importance of pDDIs has been evaluated based on the Lexi-Interact in UpToDate, and they have been divided into five categories: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy adjustment), and X. (avoid combination). We used Stockley's Drug Interactions if the medications weren't listed in Lexi-Interact.

An Excel file from Microsoft Office was used to store the data. To examine the demographics of all outpatients, the quantity of medicines, and the severity of pDDIs, descriptive statistics were used. The values were shown using the proper percentages and figures.

Results and Discussion

A number of 340 prescriptions were examined for the presence of pDDIs. Table 1 presented clinical data about the study population. Female patients dominated 53% of the study population. No more than three drugs were most frequently administered for each patient, making up 62 percent of all prescriptions.

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Table 1. Demographic of hypertensive patients with pDDIs

		No of patients (%)	No of patients with pDDIs (%)
Sex	Male	160 (47)	48 (14)
	Female	180 (53)	97 (29)
Number of prescribed medicines	≤3	210 (62)	76 (22)
	4-5	115 (34)	54 (16)
	≥ 6	15 (4)	15 (4)
Theraapeutic Classes	ACEI	62 (18)	-
	CCB	278 (82)	10 (4)
	Antidiabetic	150 (44)	30 (20)
	Statin	24 (7)	24 (100)

In the prescriptions of pharmacies in the East Coast area, Surabaya, this retrospective study revealed that, of the 340 prescriptions screened by Lexi-Interact, 43 percent had at least one potentially dangerous drug interaction, with 49 percent, 39 percent, and 12 percent of these pDDIs falling into the risk categories of minor, moderate, and major, respectively. We determined that the risk of pDDIs was elevated by female gender, advanced polypharmacy.

The most frequent potential clinical effect of category C and D pDDIs was strengthened pharmacological actions, which decrease effect antihypertensive agents. Data revealed that 55 (28%) prescriptions had between 2 and 5 pDDIs per prescription, and 51 prescriptions (34%) included multiple pDDIs, some of which were up to six. Table 2 displays the distributions of those prescriptions.

Table 2. Distribution of the gender and number of prescribed medicine with number of pDDIs per precriptions

		No of pDDIs per prescriptions (%)					
		1	2	3	4	5	6
Sex	Male	30 (8)	15 (4)	10 (2)	0 (0)	5 (1)	0 (0)
	Female	70 (21)	35 (10)	20 (6)	30 (9)	15 (4)	15 (4)
Number of prescribed medicines	≤3	99 (40)	16 (7)	5 (2)	0 (0)	0 (0)	0 (0)
	4-5	20 (8)	30 (12)	31 (13)	5 (2)	10 (4)	5 (2)
	≥ 6	0 (0)	5 (2)	9 (4)	5 (2)	5 (2)	0 (0)

In a community pharmacy chain in Qatar, 31.9 percent of prescription had pDDIs, according to a retrospective observational research by Afraa Abbas et al. (Abbas, 2022). In Ireland, a prospective cohort study by John E Hughes et al. revealed that 22.65% of the population had been exposed to pDDIs (Hughes, 2021). A 63.5 percent prevalence of prescriptions with two or more medications had at least one pDDI, according to an restrospective study conducted in Bandung (Reeyan, 2021). The difference in pDDI prevalence between these studies may be due to the study's design, drug prescribing habits, screening method, pDDI definition, and other factors.

In contrast with other findings, a larger percentage of pDDIs were discovered in the male population. However, there are conflicting findings about how gender affects pDDIs. Male gender was linked to a decreased risk of pDDIs, according to a cross-sectional study done in China (Ren, 2020). In addition, some investigations reported no appreciable sex-related difference (Haq, 2020). The study design and the greater longevity of women may be to blame for the contradictory results (Wastesson, 2016).

As predicted, the results of the logistic regression analysis demonstrated that polypharmacy (the use of more than three medications per prescription) was a risk factor for the occurrence of pDDIs, which was consistent with the results of the pilot study by Fabiola Medina-Barajas et al. of pediatric hospitalized patients. The growing number of prescription drugs had been found in several studies to be a risk factor for developing drug interactions (Bojuwoye, 2022).

In our investigation, amlodipine + metformine was the popular interactions that occurred. Amlodipine-induced hyperglycemia may result from reduced insulin release or from the drug's blockage of GLUT-1 receptors (Gari, 2017). The therapeutic outcomes of the identified pDDIs that occurred most frequently were

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decreasing effects of lowering blood pressure. The most frequent interactions in the hypertensive patients, according to a previous study, were amlodipine and atenolol, amlodipine and metronidazole, aspirin and atenolol, and enalapril and aspirin. These interactions have the potential to cause renal function deterioration, decrease antihypertensive effects, increased risk hypotension and hyperkalemia, among this discrepancy can be caused by DDI's screening process and various drug prescribing patterns (Subramanian, 2018).

Table 3. Moderate pDDIs

Drugs	No of patients (%)	Effect of pDDIs	Management pDDIs
Amlodipine - Metformin	30 (21)	Effects of metformin decrease	Monitoring blood glucose closely
HCT – Mefenamic acid	20 (14)	Mefenamicacid increases and HCT decreases potassium level	Monitoring serum potassium
Amlodipinine - Dexamethasone	5 (3)	Effects of amlodipine decrease	Monitoring blood pressure

This study is the first to examine the prevalence of pDDIs among outpatients in the eastcoast area of Surabaya. Our study did have certain restrictions, though. First off, because it was a retrospective study, pDDIs' actual clinical effects were not examined. Additionally, because this was a single-center trial, it is possible that the treatment plans and patient profiles cannot be generalized. Second, each patient's information was only allowed on one prescription document. We were unable to gather complete data, including age, use of vitamins, OTC medications, and herbal remedies, which may have led to an underestimating of pDDIs. Third, there are various DDI databases that differ in the severity grading and the inclusion of pDDIs (Benoist, 2018). However, to calculate the prevalence of pDDIs, a single screening database was used. It is advised that two or more screening databases be utilized to assess pDDIs in order to increase the detection's accuracy.

Table 4. Major pDDIs

Drugs	No of patients (%)	Effect of pDDIs	Management pDDIs
Amlodipine - Simvastatin	18 (12)	Risk of rhabdomyolysis increases	Use simvastatin maximum 20 mg/day or use alternative drug

Clinical recommendations often apply to a single disease. However, the combined effect of numerous clinical recommendations is infrequently taken into account (Dumbreck, 2015). Therefore, it is essential to create therapeutic standards pertaining to the common pDDIs, as well as their potential negative effects and management approaches. Additionally, by including clinical pharmacists in the healthcare team and deploying computerized warning systems with smart DDI databases, this study will increase awareness of the significance of routinely screening pDDIs.

Conclusions

This study showed that category B interactions were the most typical pDDIs in outpatients, followed by the category C. Risk variables that were significantly linked to the development of pDDIs included gender and polypharmacy. Further, as prospective clinical outcomes of the pDDIs in our investigation, increased risk of rhabdomyolisis was most frequently seen. Implementing appropriate techniques, such as computer-based warning systems of pDDIs, close monitoring, and based on clinical guidelines, is therefore important in order to prevent or minimize these significant pDDIs. When it comes to keeping an eye on how drug interactions affect hypertension patients, pharmacists play a critical role.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Supplementary Materials

No supplementary materials.

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