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RESEARCH ARTICLE

Drug interactions in patients with hypertension at Persahabatan hospital in 2015

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Abstract

Introduction: Hypertensive disease can cause various complications, such as cardiovascular disease, stroke, diabetes mellitus, and kidney failure. To overcome these complications, patients are given polypharmacy therapy, which can potentially lead to drug interactions. **Aim:** The purpose of this study was to determine the potential incidence of drug interactions in hypertensive inpatients at the Persahabatan Hospital in 2015. **Methods:** The research is a descriptive study with retrospective data by purposive sampling technique using secondary data, medical records of hypertensive inpatients. The study of drug interactions was conducted theoretically, based on a literature study using Drug Interaction Facts 2014. **Results:** The results showed out of 174 hypertensive patients, 141 (81.0%) had potential drug interactions, with a total of 1444 cases. The highest drug interactions were at three levels of significance in 383 cases (26.5%), with 554 cases (38.4%) of pharmacodynamic mechanisms.

Introduction

Drug interactions involve the effect of one drug being altered by the presence of other drugs, food, drink, or other chemicals. Possible drug interactions appear when a patient is simultaneously given more than one drug, with the likelihood increasing depending on the concentration of the drug administered. Nowadays, with the increasing complexity of therapy, polypharmacy is widely used and has a great potential of causing drug interactions. Antihypertensive drugs can increase the likelihood of the occurrence of clinically significant drug interactions (Nidhi, 2012).

Based on the data from basic health research, the prevalence of hypertension in Indonesia in 2013 diagnosed by health workers showed that there was an increase from 7.6% in 2007 to 9.5% in 2013. This diagnosis was based on interviews, in which patients were asked if they had been diagnosed by health personnel or whether the patients were taking any hypertension medication/s. The prevalence of hypertension based on scientific measurements, however, showed a decrease from 31.7% in 2007 to 25.8% in 2013. The assumption of a decrease in the prevalence based on measurements is estimated because the gauges used in 2007 were no longer produced in 2013, or because public awareness had improved in 2013, which can be seen from the increase in the prevalence of hypertension diagnosed by health personnel based on interviews (Badan Penelitian dan Pengembangan Kesehatan, 2013).

A study conducted on inpatients suffering from hypertension, diabetes mellitus and hyperlipidaemia at Haji Hospital in Jakarta from January to June 2013 showed that potential interactions occurred in 48 patients (48.4%), while there were no interactions found in 49 patients (51.6%). The most common type of drug interaction mechanism was a pharmacokinetic type, at 73.9%, and the level of pharmacodynamic interaction was 26.1% (Jauhari, 2014). Another research at Dr Soeradji Tirtonegoro Klaten hospital from January to June 2009 showed that 55 patients had drug interactions, with a total of 104 cases. The number

of events based on the pharmacokinetic interaction mechanism was 28 (26.92%); pharmacodynamic interactions numbered 43 events (41.4%), while there were 33 incidents (31.7%) of unknown interaction mechanisms (Andriyanto, 2011).

The hypertensive disease can lead to various complications, such as cardiovascular disease, stroke, diabetes mellitus, and kidney failure (Baxter, 2008). To overcome these complications, patients are usually given polypharmacy therapy, which can potentially lead to drug interactions, which may increase the risk of toxicity or reduce the therapeutic effect of hypertensive drugs. In addition to overcoming the complications of hypertension, patients receiving polypharmacy therapy are also the presence of accompanying patient illnesses, which could potentially lead to drug interactions. It is, therefore, necessary to study drug interactions in hypertensive patients.

Methods

A cross-sectional design was used by accessing patients' medical records retrospectively and purposively. The data used were secondary data obtained from the search results of the potential of a drug interaction based on medical record status and therapy received as inpatients at Persahabatan Hospital during 2015. Sampling using the Krejcie and Morgan formula (Tatro, 2014). One hundred seventy-four patients met the inclusion and exclusion criteria.

Sample population

The population comprised inpatients diagnosed with hypertension at Persahabatan Hospital. The sample consisted of the medical records of hypertensive patients at the hospital in 2015 who met the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria included inpatients 1) male and female; 2) diagnosed with hypertension at Persahabatan Hospital in 2015; 3) aged over 18; 4) medical records were complete, clear and legible; and 5) had received at least two drug treatments and hypertension drugs. The exclusion criteria included inpatients 1) diagnosed with hypertension, who were suffering from malignant diseases such as cancer; 2) pregnant women, and 3) patients were dead.

Data analysis

After collecting the data, the researchers conducted a descriptive analysis by screening the drug interactions using Drug Interaction Facts 2014 (Tatro, 2009). The percentage of patients with potential drug interactions based on significance level and interaction mechanism was illustrated.

Results and discussion

Drug interactions

The following is the patients' drug interaction data based on the Drug Interaction Facts 2014. As shown in Table I, it was found that the total number of patients with potential drug interactions was 141 (81.0%). In comparison, those without potential drug interactions were 33 (19.0%) out of the total of 174.

Table I: Number of patients

Type of patients	Number of patients (n: 174)	Percentage
Patients with potential drug interactions	141	81.0%
Patients without potential drug interactions	33	19.0%

Percentage of drug interactions based on level of significance

As can be seen in Table II, the total number of potential drug interactions was 1,443, with the most cases at Level 3 of significance, at 383 (26.5%).

Table II: Drug Interactions Based on Level of Significance

Level of significance	Number of cases (n: 1,443)	Percentage
Level 1	323	22..4%
Level 2	213	14.8%
Level 3	383	26.5%
Level 4	212	14.7%
Level 5	312	21.6%

Level of significance grade 1

The highest percentage of drug interaction occurs within the significance Level 1 group was those between spironolactone and ACE inhibitors, with a total of 62 cases; spironolactone-captopril, with 59 cases (18.3%); spironolactone-lisinopril, with two cases (0.6%); and ramipril-spironolactone, with one case (0.3%). The level of significance of the interaction between spironolactone with the ACE inhibitor group is at the level of significance of 1, with a major degree of

interaction and documented *probable*, which means this effect is potentially life-threatening, capable of causing permanent damage, and is highly likely to occur, but is not clinically proven (Tatro, 2009).

The combination of spironolactone and ACE inhibitors results in increased serum potassium concentrations in high-risk patients (renal failure) and an unknown interaction mechanism (Tatro, 2009). The recommended procedure is to monitor kidney function and potassium serum concentrations in patients who were receiving this drug combination and reduce dosage if necessary (Tatro, 2009). Combinations of these drugs should be avoided for patients with a glomerulus filtration rate of less than 30 mL/min (Baxter, 2010).

Level of significance grade 2

Drug interaction with the highest level of significance at Level 2 was aspirin with the ACE inhibitor group, with a total of 85 cases, consisting of 81 cases of captopril-aspirin (38.0%), three cases of aspirin-lisinopril (1.4%), and one case of ramipril-aspirin (0.5%). ACE inhibitors with aspirin interact with mechanisms by which aspirin inhibits the prostaglandin-mediated synthesis of vasodilatation. The significance level interaction of these drugs is at Level 2, with a moderate degree of interaction and documented suspected, which means that the effect may lead to deterioration of the patient's clinical status, therefore requiring additional therapy, and a prolonged hospital stay is possible, some data support, but more studies are required for verification. Effects resulting from drug interactions include cases of the effects of ACE inhibitors being reduced. In this case, the recommended procedure is to monitor blood pressure and the patient's hemodynamic parameters, to decrease the aspirin dose to below 100 mg/day, to switch to non-aspirin antiplatelet, or to replace the ACE inhibitors with angiotensin receptor blockers (Tatro, 2009).

Level of significance grade 3

At this level, the drug interaction with the greatest significance was furosemide with ACE inhibitors, with 183 cases comprising 176 cases (46.0%) of furosemide-captopril, two cases (0.5%) of ramipril-furosemide, and five cases (1.3%) of lisinopril-furosemide. Furosemide with ACE inhibitors interacts with the interaction mechanism by which the ACE inhibitors inhibit angiotensin II production, so the effects of furosemide are reduced (Tatro, 2009). In addition, furosemide increases the nephrotoxicity of ACE inhibitors (Lacy *et al*., 2009). The significance level interaction of these drugs is at Level 3, with a minor degree of interaction and documented suspected, which means the effect may be undetectable, but should not significantly affect the outcome of therapy and may occur, some data exists to support this, but more studies are needed (Tatro, 2009). The recommended procedure is to monitor the electrolyte and weight levels of patients receiving this combination (Tatro, 2009). British National Formulary recommends that inpatients taking furosemide at doses greater than or equal to 80 mg per day should consider temporarily suspending diuretics or lowering diuretic doses before adding ACE inhibitor therapy or that ACE inhibitor doses should start at very levels to avoid orthostatic hypotension (Baxter, 2008).

Level of significance grade 4

Drug interaction with the highest significance at Level 4 was $CaCO_3$ with proton pump inhibitors, with 59 cases, including 39 cases (18.4%) of $CaCO_3$-omeprazole and 20 cases (9.4%) of $CaCO_3$-lansoprazole. The significance level interaction of $CaCO_3$ with proton pump inhibitors is Level 4, with a moderate and intermediate degree and documented *possible*, which means the effect may lead to worsening of the clinical status of patients, the need for additional therapy, and likely lengthening of the stay in the hospital, but the data on this is very limited. The mechanism of the interaction of $CaCO_3$ with proton pomp inhibitors means the absorption of $CaCO_3$ is decreased so that the effect of $CaCO_3$ therapy is also reduced. The recommended procedure is to increase the dose of $CaCO_3$, especially in elderly patients (Tatro, 2009).

Level of significance grade 5

The highest level of drug interaction at Level 5 was furosemide-aspirin, with 160 cases (51.3%). The significance level of this interaction is level 5, with a minor interaction degree and documented *possible*, which means the resulting effect undetectable, but should not significantly affect the outcome of therapy and may occur, but the data is very limited. The mechanism of furosemide-aspirin interaction is unknown in cases when the furosemide effect is weakened in cirrhotic, and no clinical intervention is needed in response to the interaction between these two drugs. However, patients with cirrhosis and ascites who require furosemide need to be paid attention to aspirin usage (Tatro, 2009).

Percentage of a drug interaction based on the drug interaction mechanism

The drug interaction mechanism consists of pharmacokinetic and pharmacodynamic processes. Pharmacokinetic interactions involve the absorption, distribution, metabolism, and excretion of drugs. In

contrast, pharmacodynamic interactions involve the interaction of one drug with another, affecting the workplace (receptor) and leading to physiological disorders (Baxter, 2008).

As shown in Table III, drug interactions based on drug interaction mechanism of total drug interactions as many as 1,443 cases of drug interaction is the most of the mechanism of pharmacodynamic interaction as much as 554 cases (38.4%).

Table III: Drug Interactions Based on Interaction Mechanism

Interaction mechanism	Number of cases (n: 1,443)	Percentage
Pharmacokinetic	425	29.5%
Pharmacodynamic	554	38.4%
Combined Pharmacokinetic and Pharmacodynamic	41	2.8%
Unknown	423	29.3%

Drug interactions with pharmacokinetic interaction mechanisms

The greatest number of drug interactions with the pharmacokinetic mechanism was related to spironolactone-aspirin, with 81 cases (19.1%). The significance level of this interaction is level 3, with a minor degree of interaction and documented suspected, which means the resulting effect undetectable, but should not significantly affect the outcome of therapy and may occur, some data support, but more studies are needed (Tatro, 2009).

Spironolactone-aspirin interacts with the mechanism in which salicylate (aspirin) inhibits tubular renal secreting canrenone, which is an active metabolite of, meaning the diuretic action of spironolactone is reduced. However, data suggest that low-dose aspirin decreases the effect of spironolactone is still not studied (Tatro, 2009). It is possible that low-dose aspirin has benefits greater than being cardioprotective and reducing the effects of spironolactone in hypertensive and coronary artery disease patients (Baxter, 2008). The recommended procedure is to monitor blood pressure and sodium levels in chronic patients receiving spironolactone and salicylate (aspirin). An increase in the dose of spironolactone may be needed to restore its therapeutic effect (Tatro, 2009).

Drug interactions with pharmacodynamic interaction mechanisms

The most significant drug interaction with the pharmacodynamic mechanism was furosemide with ACE inhibitors, with 183 cases (33.0%), consisting of 176 cases (31.8%) of furosemide-captopril, two cases (0.4%) of ramipril-furosemide, and five cases (0.9%) of lisinopril-furosemide. Furosemide with ACE inhibitors interacts with the mechanism by which the inhibitors inhibit angiotensin II production, so the effects of furosemide are reduced (Tatro, 2009). In addition, furosemide increases the nephrotoxicity of ACE inhibitors. The interaction significance level of these two drugs is level 3, with a minor degree of interaction and documented suspected. The recommended procedure is to monitor the electrolyte and weight levels of patients receiving this combination (Tatro, 2009).

Drug interactions with combined pharmacokinetic and pharmacodynamic interaction mechanisms

Drug interaction based on the combined pharmacokinetic and pharmacodynamic interaction mechanism only included 41 cases of aspirin-insulin. The significance level of this interaction was 2, with a moderate degree of interaction and is documented probable, which means that the effect could lead to deterioration of the patient's clinical status, the need for additional therapy, and a possible prolonged stay at the hospital; it is very likely to occur, but has not been clinically proven. The interaction mechanism of insulin-aspirin means the basal concentration of insulin is increased, and the acute response of insulin to glucose increases, so the insulin effect is also increased. The recommended procedure is to monitor blood glucose concentrations and decrease insulin doses if necessary (Tatro, 2009).

Drug interactions with unknown interaction mechanisms

The highest number of drug interactions with an unknown mechanism was that of furosemide-aspirin, with 160 cases (37.8%). The significance level of these two drug interactions is 5, with a minor degree of interaction and documented possible, which means the resulting effect undetectable, but should not significantly affect the outcome of therapy, but the data are very limited. The mechanism of furosemide-aspirin interaction is unknown in cases when the furosemide effect is weakened in cirrhosis and ascites patients. In general, no clinical intervention is needed in response to the interactions of these two drugs. However, in patients with cirrhosis and ascites who require furosemide, they need to be paid attention to aspirin usage (Tatro, 2009).

Conclusion

Hypertension inpatients at Persahabatan Hospital in 2015 consisted of 95 (54.6%) men and 79 (45.4%) women. Those with potential drug interactions numbered 141 (81.0%), with those with no potential drug interactions 33 (19.0%). The total number of drug interaction cases was 1,443. In terms of significance of interaction, 323 cases (22.4%) were at level 1; 213 cases (14.8%) at level 2; 383 cases (26.5%) at level 3; 212 cases (14.7%) at level 4; as and 312 cases (2162%) at level 5. Interaction based on the pharmacokinetic mechanism comprised 425 cases (29.5%), with 554 cases (38.4%) based on the pharmacodynamic mechanism; 41 cases (2.8%) based on the combined pharmacokinetic and pharmacodynamic mechanism; and 423 cases (29.3%) on unknown mechanisms. It is necessary to study drug interactions in other hospitals as a comparison in order to improve hospital pharmacy services in the field of clinical pharmacy, especially in relation to drug interactions. In addition, experimental studies on drug interactions are needed, for which documented doubts and further evidence is necessary.

References

Andriyanto, O. (2011). Identifikasi Drug Related Problems (DRPs) Kategori Interaksi Obat Pada Pasien Hipertensi di Instalasi Rawat Inap RSUP Dr. Soeradji Tirtonegoro Klaten Periode Januari-Juni 2009. Surakarta: Universitas Muhammadiyah Surakarta. Available at: http://eprints.ums.ac.id/12649/

Badan Penelitian dan Pengembangan Kesehatan (2013). *Riset Kesehatan Dasar (RISKESDAS)*, 5. Jakarta: Kementerian Kesehatan Republik Indonesia. Available at: https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/

Baxter (2008). *Stockley's Drug Interaction* (8th ed., pp. 3, 9, 22, 37, 954). London: Pharmaceutical Press. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2464810/

Baxter (2010). *Stockley's Drug Interaction*, 4. London: Pharmaceutical Press.

Dipiro (2009). Pharmacotherapy Handbook (7th ed., pp. 10-11,176). England: Mc-Graw-Hill Companies.

Dipiro (2014). *Pharmacotherapy A Pathophysiologic Approach*, 9. England: Mc-Graw-Hill Education. *Available at:* https://accesspharmacy.mhmedical.com/book.aspx?bookID=1861

Drugs.com. (2016, December 12). *Available at:* www.drugs.com/drug_interactions.php

Gitawati, R. (2008). *Interaksi Obat dan Beberapa Implikasinya.* Artikel. Pusat Penelitian dan Pengembangan Biomedis dan Farmasi, 178. Jakarta : Badan Penelitian dan Pengembangan Kesehatan. *Available at:* http://ejournal.litbang.kemkes.go.id/index.php/MPK/article/view/1086

Irza, S. (2009). *Analisis Faktor Risiko Hipertensi Pada Masyarakat Nagari Bungo Tanjung, Sumatra Barat*. Skripsi. Fakultas Farmasi Universitas Sumatra Utara, 42. Medan : Fakultas Farmasi Universitas Sumatra Utara.

Jauhari. (2014). Interaksi Obat Pada Pasien Hipertensi, Diabetes Melitus, dan Hiperlipidemia Rawat Inap di Rumah Sakit Haji Jakarta Periode Januari-Juni 2013. Jakarta : Universitas Muhammadiyah Prof. Dr. Hamka. *Available at:* http://lib.uhamka.ac.id/ffs/opac/themes/libri/detail.jsp?id=3110&lokasi=lokal

Kementerian Hukum dan Hak Asasi Manusia. (2009). *Undang-Undang Republik Indonesia Nomor 44 tentang Rumah Sakit* (p. 2-3). Jakarta: Kementerian Hukum dan Hak Asasi Manusia

Kementerian Kesehatan Republik Indonesia. (2008). *Peraturan Menteri Kesehatan Republik Indonesia Nomor 269/MENKES/PER/III/2008 Tentang Rekam Medik*. Jakarta: Kementerian Kesehatan Republik Indonesia. Available from: https://ngada.org/menkes269-2008.htm

Kementerian Kesehatan Republik Indonesia. (2016). *Peraturan Menteri Kesehatan Republik Indonesia Nomor 25 Tahun 2016 tentang Rencana Aksi Nasional Kesehatan Lanjut Usia Tahun 2016-2019, p. 22-23*. Jakarta: Kementerian Kesehatan Republik Indonesia

Koda Kimble, M.A and Young, L. (2013). B.K, Aldredge (Ed(s)). *Applied Therapeutics The Clinical Use of Drugs*, (10th ed). USA: Wolter Kluwer Health

Krejcie and Morgan. (1970). *Determining Sample Size for Research Activities, Educational and Psychological Measurement* (30, pp. 607-610)

Lacy et al. (2009). *Drug Information Handbook A Comprehensive Resource for all Clinicians and Healthcare Professionals* (17th ed, p. 60). Ohio: Lexi-comp

Mozayani and Raymon. (2012). Buku Ajar Interaksi Obat Pedoman Klinis dan Forensik. (pp. 412). Jakarta: Penerbit Buku Kedokteran EGC. Available at: https://egcmedbooks.com/buku/detail/32/buku-ajar-interaksi-obat-pedoman-klinis-forensik

Mulyani et al. (2015). *Hubungan Jumlah Obat yang Diresepkan dengan Potensial Penggunaan Obat yang Tidak Tepat Pada Pasien Penyakit Ginjal Kronik di RS PKU Muhammadiyah Yogyakarta*. Pharmaciana Universitas Ahmad Dahlan, 154. Yogyakarta; Universitas Ahmad Dahlan. *Available at:* http://journal.uad.ac.id/index.php/PHARMACIANA/article/view/2063

Nidhi, S. (2012). Concept of Drug Interaction. *Review Article. Department of Pharmacognosy*, 120. Jakarta: JSS College of Pharmacy. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897029/

Nurhayati. (2013). *Interaksi Obat Antihipertensi pada Pasien ASKES Penderita Hipertensi yang Dirawat di Ruang ICU RSPAD Gatot Subroto Periode Januari-Maret 2011*. Jakarta : Fakultas Farmasi dan Sains Universitas Muhammadiyah Prof. Dr. HAMKA. *Available at*

http://lib.uhamka.ac.id/ffs/opac/themes/libri/detail.jsp?id=3526&lokasi=lokal

Parekh, R. (2012). *Rhabdomyolysis: Advances in Diagnosis and Treatment.* Emergency Medicine Practise, 14(3), pp. 5-6, 8. North Carolina

Priyanto. (2009). *Farmakoterapi dan Terminologi Medis* (pp. 188-191, 195-202) Depok: *LESKONFI*. *Available at:* https://onesearch.id/Record/IOS3107.46333/Description

Rachman, F. (2011). *Berbagai Faktor yang Berhubungan dengan Kejadian Hipertensi pada Lansia di RS Dr. Kariadi Semarang*. Karya Tulis Ilmiah. Semarang: Fakultas Kedokteran Universitas Diponegoro

Rahajeng and Tuminah. (2009). *Prevalensi Hipertensi dan Determinannya di Indonesia*. Artikel Penelitian. Pusat Penelitian Biomedis dan Farmasi Badan Penelitian Kesehatan, 585. Jakarta: Departemen Kesehatan RI. Available at: https://www.academia.edu/21468378/Prevalensi_Hipertensi_dan_Determinannya_di_Indonesia

Robins et al (2007). *Buku Ajar Patologi,* 61 (2), 367. Jakarta: Penerbit Buku Kedokteran *EGC.* Available at: http://lib.fkik.untad.ac.id/index.php?p=show_detail&id=942&keywords=

Setyanda et al. (2015). *Hubungan Merokok dengan Kejadian Hipertensi pada Laki-laki Usia 35-65 Tahun di Kota Padang*. Artikel Penelitian, 435. Padang: Fakultas Kedokteran Universitas Andalas. Available at: http://jurnal.fk.unand.ac.id/index.php/jka/article/view/268

Solih EIN. (2015). *Evaluasi Ketepatan dan Interaksi Obat pada Pasien Hipertensi dengan Komorbiditas di Rawat Inap Rumah Sakit AL Dr. Mintohardjo Periode Januari-Juni 2013*. Jakarta: Fakultas Farmasi dan Sains Universitas Muhammadiyah Prof. Dr. HAMKA

Sukandar et al (2008). *ISO Farmakoterapi* (120th ed., pp. 128-130). Jakarta: PT ISFI Penerbitan. *Available at:* https://opac.perpusnas.go.id/DetailOpac.aspx?id=717085

Sunaryanti, S.S. (2011). *14 Penyakit Paling Sering Menyerang dan Sangat Mematikan* (pp. 55-60). Jakarta: Flashbooks. *Available at:* https://onesearch.id/Record/IOS3605.INLIS000000000020760

Tatro, D.S. (2014). *Drug Interaction Facts*, p. XIVXV. USA: Wolters Kluwer Health

Tjay and Rahardja. (2015). *Obat-Obat Penting Khasiat, Penggunaan, dan Efek Efek Sampingnya*, 7, 545. Jakarta: PT. Elex Media Komputindo. *Available at:* https://books.google.co.id/books?id=TN8QxBMHW6IC&printsec=frontcover#v=onepage&q&f=false

Waty and Hasan. (2012). *Prevalensi Penyakit Jantung Hipertensi pada Pasien Gagal Jantung Kongestif di RSUP H. Adam Malik*, 1(1). Medan: Fakultas Kedokteran Universitas Sumatra Utara