

Drug-Related Problems in Hypertensive Patients with Multiple Comorbidities

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Abstract

Hypertensive patients with multiple comorbidities often received multiple medications to achieve target blood pressure and to treat other comorbidities which can lead to the occurrence of drug-related problems (DRP). The objectives of this study were to identify the DRPs and the most common drugs associated with DRPs in this population. The study was conducted prospectively involving hypertensive patients with multiple comorbidities at a tertiary care centre. Data were obtained from bed head tickets and from the interview with eligible patients. The assessment of DRPs was based on Pharmaceutical Care Network Europe Foundation (PCNE) Classification of DRP tools version 5.01. From the total of 80 patients, 88.8% of the patients had at least one DRP. A total number of 172 DRPs were identified with an average of 2.15 ± 1.5 DRPs per patient. The most frequent category of DRP was interactions (33.7%), followed by adverse reactions (23.9%), drug choice problems (14.5%), dosing problems (13.4%), others (8.1%) and drug use problems (6.4%). Antihypertensive agents were the most common drugs associated with DRPs in this population. Significant associations were found between elderly and the occurrence of adverse reactions, and between renal impairment with the occurrence of drug choice problems and over dosage problems. This study demonstrates that DRPs were frequently observed in hypertensive patients with multiple comorbidities. Thus interventions to resolve these problems are important to ensure the effectiveness and safety of the prescribed medications.

Keywords: Drug-Related Problems; Hypertension; Antihypertensive; DRP

Introduction

Hypertension is defined as persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater

and/or diastolic BP of 90 mmHg or greater [1]. In Malaysia, the overall prevalence of hypertension for subjects aged above 15 years was 27.8%. The prevalence of hypertension was significantly higher in male (29.6%),

compared to female (26.0%). Only 34.6% of the subjects with hypertension were aware of their hypertensive status, and 32.4% were taking antihypertensive medication. Amongst the latter group, only 26.8% had their blood pressure under control [2].

Cardiovascular disease is the most common cause of death in industrialised countries where hypertension is the most frequent treatable risk factor of the cardiovascular disease [3]. High blood pressure is highly associated with the risk of heart failure, stroke and kidney disease. The presence of additional risk factors such as smoking, diabetes and high cholesterol levels increases the cardiovascular risk from hypertension [2].

Most hypertensive patients suffer from other comorbidities which require the proper combinations of antihypertensives agents and other medications [4]. Some comorbidities such as diabetes and obesity are also associated with uncontrolled hypertension [5]. The majority of hypertensive patients require one or more antihypertensive agents in order to achieve this optimal blood pressure control [1]. Combination therapy with multiple medications can lead to the occurrence of DRP such as adverse effects of the drugs, drug-drug interaction, the inappropriate choice of drugs and also the inappropriate dose of drugs administered [6].

The occurrence of DRPs potentially interferes with desired health outcomes. Poor compliance and lack of persistence with medications for example, may lead to treatment failure. Patients who were highly compliant with antihypertensive therapy were 45% more likely to achieve blood pressure control than those with medium or low compliance [7]. DRPs may also result in reduced quality of life, and increased morbidity and mortality [8]. Lack of effect of the chosen drug can be a challenge in the patients' management, and often optimal levels of blood glucose, cholesterol or blood pressure are not achieved during drug treatment. This will increase the risk of morbidity and mortality [9].

DRP could also lead to the increased of treatment cost. In 1995, the cost associated with drug-related problems was estimated as \$76.6 billion [10]. This has increased to more than double with an estimated annual average of \$177.4 billion by the year 2000. Drug-related morbidity and mortality continue to pose a serious medical and economic problem for society. More attention should be directed towards developing solutions that could reduce preventable morbidity, mortality, and costs associated with DRPs [11].

Identification of DRPs among hospitalized hypertensive patients is critically important to ensure patients' safety and treatment optimization. Hence, this study was conducted to identify the types and number of drug-related problems that occur in warded hypertensive patients.

Methodology

Study Design and Setting

This was a prospective study conducted in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) after obtaining ethical approval from UKM Research Ethics Committee with the reference number of UKM 1.5.3.5/244/NF-043-2013.

Studied Population

The sample size was calculated using Raosoft sample size calculator which provided a sample size of 207 patients. The studied population consists of hypertensive patients with multiple comorbidities who were admitted to the medical wards of UKMMC from September 2013 to November 2013. The inclusion criteria for the study population were patients with age of more than 18 years old, patients with current diagnosis of hypertension and patients who were currently taking at least one antihypertensive agent in the ward. Subjects with incomplete data were excluded from this study.

Data Collection

Data of the patients who fulfilled the criteria in this study were collected from bed head tickets (BHT) in the wards. The patients' background information, current medications, lab investigation results, progress note and any pharmaceutical care issues presence were noted. Interview was also conducted with subjects to obtain information regarding patients' medications compliance and also the patients' background information.

Identifications and Clarifications of DRPs

The classification of DRPs identified in this study was based on the Pharmaceutical Care Network Europe Foundation (PCNE) classification for drug-related problems version 5.01 [12]. Based on PCNE classification, DRPs are classified into six domains of problems including adverse reactions, drug choice problems, dosing problems, drug use problems and others. In this study, the DRPs were identified from the information collected from the BHT, with references to the established literatures such as Lexicomp's Drug Information Handbook, Micromedex and British National Formulary [13-15]. The

identification and clarification of DRPs were done together with a pharmacist who is also an academician.

Statistical Analysis

The data collected were analysed using the statistical software Statistical Package for Social Sciences (SPSS Inc., Chicago, IL), version 18. Continuous data were presented as mean \pm standard deviation while categorical data were presented as percentages. The association between two categorical variables was tested using the Chi-Square test of independence. Statistical significance was defined as p-value $<$ 0.05.

Results

Baseline Data

A total 86 hypertensive patients were screened for drug-related problems but six patients were excluded from this study due to missing information and no antihypertensive agents taken by the patients. Therefore, a total of 80 patients were included in this study. The demographic data and clinical characteristics of the patients are shown in Table 1. The mean \pm SD age of patient was 65.7 ± 10.2 years. The minimum and maximum ages of the patients were 24 and 82, respectively.

Characteristics	Frequency (Percentages, %)
Gender	
Male	41 (51.3)
Female	39 (48.8)
Age	
Non-elderly (< 65 years old)	33 (41.3)
Elderly (\geq 65 years old)	47 (58.8)
Race	
Malay	36 (45.0)
Chinese	33 (41.3)
Indian	10 (12.5)
Others	1 (1.3)
Duration of hypertension	
Less than 10 years	26 (32.5)
11-20 years	16 (20.0)
21-30 years	11 (13.8)
Unknown	27 (33.8)
Blood pressure	
Achieved target (\leq 140 mmHg)	39 (48.8)
Did not achieve target ($>$ 140 mmHg)	41 (51.3)
Comorbidities^a	
Renal impairment	41 (51.3)
Diabetes mellitus	60 (75.0)
Cardiovascular disease	50 (62.5)
Dyslipidemia	32 (40.0)
Stroke	16 (20.0)
Liver impairment	2 (2.5)
Bronchial asthma / COPD	14 (17.5)
Gouty arthritis	6 (7.5)

Table 1: Demographic and clinical characteristic of the patients (N = 80).

The number of medications taken per patient ranged from 3 to 15 with the mean \pm SD of 8.57 ± 3.0 . About 37.5% of the patients were on monotherapy for hypertension and the rest were on combination therapy. The most frequently used drug classes were calcium channel blockers, beta blockers and ACE inhibitors. Felodipine, bisoprolol and perindopril were the most widely used antihypertensive agents representing these classes, respectively. The dual therapy with highest frequency was ACE inhibitors with calcium channel blockers.

From the total of the 80 patients, 88.8% had at least one DRP. A total number of 172 drug-related problems (DRP) were identified with an average of 2.15 ± 1.5 DRPs per patient. The details of the DRP identified are shown in Table 2. The most frequent category of DRP was interactions (33.7%), followed by adverse reactions (23.9%). The drugs which were mostly associated with DRP were antihypertensives drugs. The details on the drugs/drug classes mostly associated with DRPs are shown in Table 3.

Code	Problems	Frequency (Percentage, %)
Adverse reactions		41 (23.9)
P1.1	Side effect suffered (non-allergic)	40 (23.3)
P1.2	Side effect suffered (allergic)	1 (0.6)
Drug choice problem		25 (14.5)
P2.1	Inappropriate drug (not most appropriate for indication)	8 (4.6)
P2.4	Contra-indication for drug	13 (7.6)
P2.6	No drug prescribed but clear indication	4 (2.3)
Dosing problem		23 (13.4)
P3.1	Drug dose too low or dosage regime not frequent enough	9 (5.2)
P3.2	Drug dose too high or dosage regime too frequent	14 (8.2)
Drug use problem		11 (6.4)
P4.1	Drug not taken/ not compliance to medications	11 (6.4)
Interactions		58 (33.7)
P5.1	Potential interaction	54 (31.4)
P5.2	Manifest interaction	4 (2.3)
Others		14 (8.1)
P6.2	Insufficient awareness / knowledge of health and diseases (possibly leading to future problems)	11 (6.4)
P6.4	Therapy failure	3 (1.7)

Table 2: Drug related problems in hypertensive patients with multiple comorbidities (n = 172).

Problems	Drugs/drug classes
Adverse reactions	Diuretics
Drug choice problem	Antihypertensives
Dosing problem	Antihypertensives
Drug use problem	Antihypertensives Antiplatelets
Interactions	Clopidogrel
Others	Aspirin

Table 3: Drugs/drug classes mostly associated with DRPs.

Adverse Reactions

In this study, a total of 41 adverse reactions were reported. One case of side effects caused by allergic reactions to drug was reported and the rest of the adverse reactions cases were non-allergic related side effects. The most reported adverse reactions identified were electrolyte imbalances. These include hypokalemia, hypomagnesaemia and hyponatremia and were associated with the use of furosemide and hydrochlorothiazide. Two cases of hypokalemia were

reported as the adverse reactions of antiasthmatic drugs and another one case was hyperkalemia caused by perindopril. The second most frequent adverse reactions were hypoglycemia, which was related to the use of antidiabetics. Four cases of acute kidney injury were reported as adverse reactions of NSAIDs and oral antidiabetic agents. The adverse reactions associated with other antihypertensives agents were hypotension which was related to the use of amlodipine, bisoprolol, valsartan and perindopril. Several cases of bradycardia and pedal oedema were also reported which were associated with the use of beta blockers and amlodipine, respectively. The only case of allergic reactions towards perindopril was identified. Other adverse reactions reported were diarrhoea (antibiotics, colchicine), increase in ALT (lovastatin) and bicytopenia (clopidogrel).

Drug Choice Problems

From the total of 25 drug choice problems identified, there were 8 problems associated with inappropriate drug choice, 13 problems associated with contraindications and 4 problems which involved drugs not prescribed for certain clear indications. The most common drug that was inappropriately used was perindopril which was used in patient with renal impairment with creatinine clearance less than 30 ml/min. There were also cases of the use of aspirin in patient with renal impairment who had creatinine clearance of less than 10 ml/min. The most cases identified for contraindication problems were the use of metformin in patient with chronic kidney failure. Other cases of contraindicated drugs problem involved the use of ezetimibe-lovastatin combination in patients with active liver disease and the use of gliclazide in ketoacidosis patient. The problems of no drug prescribed for clear indication involved patients who received no treatment for established anemia.

Dosing Problems

A total of 23 dosing problems were identified in this study. Dosing problems included doses of medications prescribed which were either too high or too low. Nine cases of drug being prescribed with subtherapeutic dosing were identified. The most common drugs that were prescribed at low dose were antihypertensives such as amlodipine, perindopril and metoprolol resulting in uncontrolled blood pressure and hypertensive emergency. There were 14 cases of drugs being prescribed with excessive dosing. The most common drugs that were prescribed at high dose were rosuvastatin and ranitidine, particularly in patients with renal impairments.

Drug Use Problems

The only drug use problem identified in this study was the drug not taken or non-compliance problems, with the total of 11 cases identified (6.4%). The non-compliance cases occurred prior and during the admissions. Among these cases, the patients had uncontrolled blood pressure, recurrent stroke, unstable angina and hyperglycemia as the results of non-compliance to medications. The most frequent drugs involved were antihypertensives drugs and antiplatelets.

Drug Interactions

In this study, a total of 58 major drugs interactions were identified which consists of 54 potential interactions and 4 manifested interactions. This mainly involved clopidogrel with 28 cases. Clopidogrel has potential interaction with other anticoagulants (fondaparinux, enoxaparin), antiplatelet (aspirin) and proton pump inhibitors (esomeprazole, omeprazole). The manifested interactions identified in these drugs combinations were metoprolol with digoxin, and diltiazem with bisoprolol which resulted in bradycardia, hydrochlorothiazide and antiasthmatic drug which caused hyperkalemia, and warfarin with piperacillin which caused over warfarinisation and bleeding.

Others

The problems under the 'others' category of DRP that were identified in this study were therapy failure and insufficient awareness of health and disease. There were 11 cases of insufficient awareness of health and disease which could lead to future problems and 3 cases of therapy failure reported. All the therapy failure cases involved patients with recurrent stroke due to aspirin failure.

Factors such as elderly and renal impairment were found to have a statistically significant association with DRPs. There were significant associations between elderly and adverse reactions ($p = 0.001$). There were also significant associations between renal impairment and drug choice problems ($p = 0.016$) or overdose problems ($p = 0.048$).

Discussion

Studies regarding drug-related problems in hypertensive patients are very limited. To date, several studies on DRP using PCNE classification system have been conducted in Malaysia including a study on patients with diabetes mellitus type 2 and hypertension by Zaman Huri & Fun Wee and a study on patients with diabetes,

hypertension or hyperlipidemia conducted by Chua, et al. [16,17]. There are recent international studies which also used the same version of the instrument such as the research conducted by Chan, et al. and Eichenberger, et al. [18,19] but none of the studies focus on DRPs in hypertensive patients specifically.

The average of DRPs per patient and the percentages of patients had at least one DRP in this study showed discrepancy with other previous studies. In our study, there was an average of 2.15 ± 1.5 DRPs per patient with 88.8% of the patients had at least one DRP. When comparing with other recent study on DRPs with almost similar population, the average number of problem identified by Zaman Huri & Fun Wee [16] was 1.9 ± 1.2 DRPs per patient with 90.5% of the patients had at least one DRP. This discrepancy may be due to the different methods and references to identify DRPs. For example, The Modified Beers criteria have been used by Zaman Huri & Fun Wee [16] to identify the appropriateness of the use of drugs in the elderly patients. In addition, our study also utilized Micromedex as the reference for drug interactions which may contribute to the differences in classification and frequency of drug interactions identified. Study populations and settings may contribute to these differences as well. Study by Chua, et al. [17] looking at the pharmaceutical care issues in patients with diabetes, hypertension and hyperlipidemia in Malaysia via interview revealed that 53.7% had at least one DRP or pharmaceutical issue. The prescriptions were used instead of medical records or bed head tickets to gain information in the study conducted by Eichenberger, et al. [19] thus the absence of laboratory values may affect the number of DRPs being identified.

Electrolyte disturbances caused by diuretics are the most common adverse reactions identified in this study. Electrolytes disturbances are commonly reported in patients who use diuretics for the treatment of hypertension [20]. This finding differs from Zaman Huri & Fun Wee and Chua, et al. [16,17] where they reported that the most reported adverse reaction was hypoglycemia induced by antidiabetics. These differences may be due to the different study populations and study method. The study conducted by Zaman Huri & Fun Wee [16] focused more on diabetic populations hence the incidence of hypoglycemia will be significant since all subjects received antidiabetic therapy. Chua, et al. [17] used interview method thus the renal and electrolyte profiles of the patients were not available. Further analysis from our result showed that there was a significant association between elderly patients and adverse reactions. Therefore, it is recommended that the prescriber be aware with the potential adverse reactions that may

occur, especially when treating the elderly who are prone to significant deleterious effects.

Regarding the drug choice problem, our results were in agreement with studies conducted by Zaman Huri & Fun Wee and Chua, et al. [16,17] in terms of inappropriate use of drugs and contraindication to drugs problems. Antihypertensives and metformin were the drugs most commonly associated with both problems, respectively. In addition, the problem of 'drug not prescribed' which was identified mostly among patients with anemia in current study, had also being reported in the study conducted by Koh, et al. [21]. The high frequency of drug choice problems which was the third most occurring DRP highlighted the need for the drugs to be prescribed more cautiously especially among patients with renal impairment.

In this study, overdose problem was more frequently observed compared to subtherapeutic dosage problems. The percentage of dosing problems reported in the study conducted by Chua, et al., Chan, et al. and Eichenberger, et al. [17-19] were lower compared to our's. This may be due to the lack of information and assessment of the renal functions, hepatic functions and blood pressure measurement of patients involved. The subtherapeutic dosing problems mainly involved antihypertensive drugs which caused the patients to have uncontrolled blood pressure. Based on the study conducted by Grigoryan, et al. [22], half of the patient with resistant hypertension involved in the study had uncontrolled blood pressure due to suboptimal dose of antihypertensive and drugs combinations. Reiner, et al. [23] stated that rosuvastatin, the drugs that most implicated to overdosing problems in this study is not recommended to be given to patient with renal impairment. This is due to the risk of toxic effect on kidney which can worsen the kidney function of patient with pre-existing renal disease [24]. Since there were significant associations between renal impairment patients with overdose problems and drug choice problems in this study, the choice of drugs and the dose of drugs to be prescribed to renal impairment patients must be carefully determined to ensure effectiveness of treatment, minimize drugs adverse reactions and prevent drug-induced nephrotoxicity [25]. The only drug use problems identified in this study was non-compliance to medications. The reasons for non-compliance included patient forgot to take medications, patients refused to take medications and patients did not take medications due to unwell. Non-compliance to medications has been reported to be highly associated with uncontrolled blood pressure in hypertensive patients [26]. Therefore, it is the role of the pharmacists to improve the compliance of patients towards medications. This is supported by a

study conducted by Fikri-Benbrahim *et al.* which showed that pharmacist' interventions were associated with significant improvement in compliance of hypertensive patients towards antihypertensive medications [27].

Interactions were the most common DRPs in our findings and this is similar to the study conducted by Eichenberger, *et al.* [19]. In this study, the drugs that were mostly involved in drug interactions were clopidogrel and aspirin, which was similar to the findings in study conducted by Zaman Huri & Fun Wee but different from the findings of the study conducted by Koh, *et al.* in Singapore [16,21]. The discrepancy was probably due to the different hospital practices and prescribing patterns across different countries. The most common drug interactions identified in this study were the potential drug interactions between antiplatelets and anticoagulants. The study conducted by Delaney, *et al.* [28] reported that drug combinations involving antiplatelets and anticoagulants are associated with a high risk of gastrointestinal bleeding.

The issues classified under the problems of insufficient awareness or knowledge included patients' lack of knowledge about their medications and patients' lack of self-management in terms of diet and hygiene. In this study, all the cases of treatment failure involved the failure of aspirin treatment on prevention of stroke leading to recurrent stroke. Aspirin resistance is one of several possible explanations for the treatment failure of aspirin [29]. Change in medications or addition of regimens must be done to overcome this problem. Combination of aspirin with clopidogrel therapy appears safe and effective to overcome the issues of aspirin failure [30].

There were however several limitations pertaining to our study. Although patient interview was conducted to obtain information regarding compliance to medications and medical history, not all patients were eligible to be interviewed as a few subjects were unconscious. Our study also included a small sample size due to time limitation factor.

Conclusion

Based on this study, the most common DRPs identified were interactions, adverse drug reactions and drug choice problems. Among the DRPs identified, the drugs that were most associated with DRPs were antihypertensives. This study demonstrates that DRPs are frequently observed in hypertensive patients with multiple comorbidities thus interventions to resolve these problems are important to

ensure the effectiveness and safety of medications taken by hypertensive populations.

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