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RESEARCH ARTICLE

Analysis of drug-related problems in ischemic stroke in-patients in one Indonesian district hospital

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Abstract

Background: Ischemic stroke is one of the leading causes of death in Indonesia. Appropriate management, including the identification of drug-related problems (DRPs), is needed to prevent disability and death. **Objective:** This study aimed to analyse DRPs as defined by the Pharmaceutical Care Network Europe (PCNE). **Method:** This was a cross-sectional research using the medical records of in-patients with ischemic stroke aged >18 years. **Result:** Out of the 115 patients examined, 51.3% were male, and the mean age was 57.85 ± 10.539 years. Exactly 204 cases of DRPs and 175 causes appeared in 101 patients. A total of 58 patients experienced one-to-two problems, and 43 patients experienced more than two problems. The problems domain consists of therapeutic effectiveness (P1, 133(65.2%)), adverse effects (P2, 67(32, 84%)), and medical expenses (P3, 4(1, 96%)). The DRPs mostly involved antihypertension and antiplatelet. The most common cause was a new indication for treatment (C1.9, 51(29.14%)) and drug interactions (C8.1, 48(27.43%)). Multivariate analysis of patient characteristics showed that patients taking more than eight medications were more likely to experience more than two DRPs than those on one-to-four medications (OR 5.593; 95%, CI 1.015-30.812). **Conclusion:** Most patients experienced one-to-two DRPs with the highest being a potentially suboptimal treatment. Clinical pharmacists are expected to monitor therapy, especially in polypharmacy patients.

Introduction

Stroke is caused by a disruption in blood flow to the brain either due to blockage of blood vessels (Ischemic) or rupture of blood vessels (Haemorrhagic) in the brain, causing bleeding in the surrounding areas (Hui *et al*., 2023). In 2019, stroke was the second leading cause of death, accounting for 11.6% of all deaths (Feigin *et al*., 2021).

Providing drug therapy to patients with ischemic stroke requires special attention. Patients with ischemic stroke often have other comorbid conditions which require patients to take polypharmacy medications (Gallacher *et al*., 2014) a result, drug-related problems (DRPs) are likely to arise and cause therapeutic failure (Ministry of Health, 2019). The Pharmaceutical Care Network Europe (PCNE) defines DRPs as an event related to drug therapy which may adversely affect the therapeutic outcomes. DRPs are categorised into four domains, i.e. therapeutic effectiveness, undesired drug reactions, treatment costs and others (PCNE, 2010). Classification of DRPs facilitates documentation by healthcare professionals in the pharmaceutical service process for therapy monitoring and evaluation purposes.

In the UK, the proportion of preventable adverse drug reactions ranged from 12.35–37.96%, with cardiovascular system drugs being the most commonly affected medication class (Insani *et al*., 2021). Aleksic *et al*. also found that out of 696 ischemic stroke patients, at least one potential drug-drug interaction happened during hospitalisation, with most interactions including aspirin (Aleksic *et al*., 2019). Identification and analysis of drug-related problems (DRPs) are needed to prevent disability and death.

Methods

Design

This cross-sectional study used retrospective secondary data from one district hospital in Indonesia. The institutional review board from the district hospital approved the study with approval number 035/16.1/31.72/-1.862.9/2019.

Samples and data collection

All patients who were enrolled in this study were patients aged ≥18 years with a primary diagnosis of ischemic stroke hospitalised between February and April 2019. The exclusion criteria were patients for whom important data were not available. From the criteria, we were able to collect 101 patients' medical records. All clinical data were recorded after patients completed their treatment. Data of their demographic characteristics were collected. The medication profiles and therapeutic regimen for each medication were also documented.

Identification and classification of DRPs

Data entry, processing and tabulation were performed using Microsoft Excel. The DRPs were defined according to the PCNE version 6.02 (PCNE, 2010)which had been validated by the Ministry of Health, Indonesia. Identification of DRPs was based on a review of patients' conditions, prescriptions, and laboratory records. Information related to medication therapies, such as the recommended drug of choice, recommended dosages, frequency of administration, drug–drug interactions and adverse drug reactions were compared based on Indonesian guideline for the treatment of ischemic stroke (Ministry of Health, 2019), the standard pharmacotherapy textbooks and IBM Micromedex Web Applications Access. Two clinical pharmacists reviewed the determination of DRPs.

Statistical analysis

Patients' characteristics and the number of DRPs were presented descriptively. Backward logistic regression was performed to search for factors affecting the number of DRPs. Analysis was done using IBM SPSS Statistics version 27.

Results

Patients' characteristics

More than half (51.3%) of the patients were male, and the mean age of total patients was 57.85 ± 10.539 years, with seven being the median number of medications. The comorbidities consist of hypertension (62.6%), diabetes mellitus (20.9%), dyslipidaemia (45.2%), epilepsy (3.5%), gout arthritis (3.5%), vertigo (6.1%), and dementia (0.9%). Patient characteristics can be seen in Table I.

Table I: Patient characteristics

Variables	Value† (n=115)
Age	
Mean ± SD	57.85 ± 10.539
18-59	69 (60)
≥60	46 (40)
Sex	
Male	59 (51.3)
Female	56 (48.7)
Comorbid	
1	61 (53)
>1	54 (47)
Number of medications	
Median (min-max)	7 (3-14)
1 to 4	13 (11.3)
5 to 8	65 (56.5)
>8	37 (32.2)
Length of stay	
Median (min-max)	5 (2-13)
<6	63 (54.8)
≥6	52 (45.2)
Drug related problems (code P)	
Median (min-max)	2 (0-8)
None	14 (12.2)
1-2 problems	58 (50.4)
>2 problems	43 (37.4)

†Categorical data: n (%); numerical data: mean ± SD for normal distributed data, median (min-max) for non-normal distributed data

Drug-related problems

There were 204 cases of DRPs that appeared in 101 patients. Data showed that 133 (65.2%) problems were related to the treatment effectiveness (P1) domain. The number of DRPs can be seen in Table II.

Table II: Percentage of drug-related problems based on PCNE V6.2 (n=204 problems)

Code	Primary problems	Total	Percentage (%)
P1	**Treatment effectiveness**	**133**	**65.20**
P1.1	No effect of drug treatment/therapy failure	0	0.00
P1.2	Effect of drug treatment not optimal	74	36.27
P1.3	Wrong effect of drug treatment	0	0.00
P1.4	Untreated indication	59	28.92
P2	**Adverse reactions**	**67**	**32.84**
P2.1	Adverse drug event (non-allergic)	54	26.47
P2.2	Adverse drug event (allergic)	4	1.96
P2.3	Toxic adverse drug event	9	4.41
P3	**Treatment costs**	**4**	**1.96**
P3.1	Drug treatment is more costly than necessary	0	0.00
P3.2	Unnecessary drug-treatment	4	1.96

The total number of causes of DRPs was 175 causes. The three highest number of causes were new indication for drug treatment presented (C1.9, 29.14%), other cause which was drug interaction (C8.1, 27.43%), and dosage regimen not frequent enough (C3.3, 13.71%). Table III shows the number of causes of DRPs. The DRPs mostly happened in patients taking antihypertension and antiplatelet (Figure 1).

Table III: Percentage of the causes of drug-related problems based on PCNE V6.2 (n=175 causes)

Code	Causes	Total	Percentage (%)
C1	**Drug Selection**	**79**	**45.14**
C1.1	Inappropriate drug (incl. contra-indicated)	6	3.43
C1.2	No indication of drug	0	0.00
C1.3	Inappropriate combination of drugs or drugs and food	22	12.57
C1.4	Inappropriate duplication of the therapeutic group or active ingredient	0	0.00
C1.5	Indication for drug treatment not noticed	0	0.00
C1.6	Too many drugs prescribed for indication	0	0.00
C1.7	More cost-effective drugs are available	0	0.00
C1.8	Synergistic/preventive drug required and not given	0	0.00
C1.9	New indication for drug treatment presented	51	29.14
C2	**Drug form**	**0**	**0.00**
C3	**Dose selection**	**24**	**13.71**
C3.1	Drug dose too low	0	0.00
C3.2	Drug dose too high	0	0.00
C3.3	The dosage regimen is not frequent enough	24	13.71
C3.4	Dosage regimen too frequent	0	0.00
C3.5	No therapeutic drug monitoring	0	0.00
C3.6	Pharmacokinetic problem requiring dose adjustment	0	0.00
C3.7	Deterioration/improvement of disease state requiring dose adjustment	0	0.00
C4	**Treatment duration**	**19**	**10.86**
C4.1	Duration of treatment too short	19	10.86
C4.2	Duration of treatment too long	0	0.00
C5	**Drug use process**	**0**	**0.00**
C.6	**Logistics**	**5**	**2.86**
C6.1	Prescribed drugs not available	5	2.86
C6.2	Prescribing error (necessary information missing)	0	0.00
C6.3	Dispensing error (wrong drug or dose dispensed)	0	0.00
C7	**Patient**	**0**	**0.00**
C8	**Other**	**48**	**27.43**
C8.1	Drug interaction	48	27.43
C8.2	No obvious cause	0	0.00

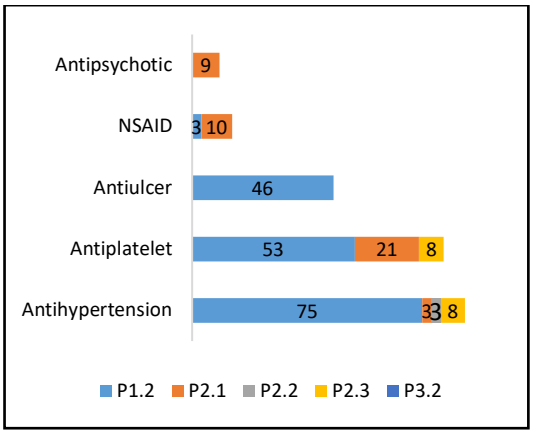

Figure 1: Number of DRPs based on related medications (top five)

Factors affecting the number of DRPs

In the bivariate analysis, the number of medications significantly affected the occurrence of patients experiencing above two problems. Multivariate analysis on age, sex, comorbid, number of medications, and length of stay demonstrated that the number of drugs significantly affected the increase in the number of DRPs (p = 0.009), with patients taking more than eight medications were more likely to experience above two DRPs than taking one-to-four medications (OR 5.593; 95%CI 1.015-30.812).

Discussion

The main finding of the study is that the total amount of DRPs was 204 in 101 patients. Therefore, the average DRPs per patient was 0.49, with most patients encountering one-to-two DRPs. The effect of drug treatment not optimal (P1.2) predominates the DRPs. This finding is similar to a study in China stating that the average number of DRPs per patient with ischemic stroke was 1.3, with the most common problem being P1.2 (57.9%) (Tian *et al*., 2023).

Problems related to suboptimal drug effects were observed in 74 patients, which was dominated by causes of dosage regimen not frequent enough and drug interactions. These problems mostly occurred in patients taking antihypertension, antiplatelet, and/or antiulcer. Thirty-three patients were co-prescribed amlodipine and clopidogrel, which may potentially reduce the antiplatelet effect of clopidogrel by inhibiting CYP3A (Gremmel *et al*., 2010). Based on the analysis of prescriptions and nursing notes, amlodipine and clopidogrel therapy were administered at different times. Amlodipine was administered at midnight, while clopidogrel was administered at noon. Despite the time gap in drug administration, interaction is still possible because of the relatively long half-life of amlodipine (30-50 hours) (Bulsara & Cassagnol, 2023). Therefore, patients who are co-administered with amlodipine and clopidogrel should be closely monitored. Monitoring should be related to the effectivity of clopidogrel. Platelet function test used in research to identify clopidogrel responder is platelet aggregometry with adenosine 5'-diphosphate (ADP) (Bouman *et al*., 2010) yet it is not widely accepted in practice. Feasible monitoring is by assessing the patient's symptom or the occurrence of recurrent stroke. Furthermore, five patients experienced potential interaction between omeprazole and clopidogrel that can decrease the antiplatelet effect of clopidogrel. Omeprazole inhibits CYP19A2, which prevents the production of the active metabolite of clopidogrel (Vaduganathan & Bhatt, 2015). The same monitoring should be performed for these patients.

Less frequent dosing was observed in the case of ranitidine injection with the regimen of 50 mg IV twice daily. However, IV ranitidine should be administered at a dosage of 50 mg every six to eight hours to treat peptic ulcer (Micromedex, 2023). Less dosing may not resolve patient's ulcer because of the potential of drug concentration below the therapeutic windows. However, the twice daily dosage usually is used for treatment with oral ranitidine and might be still effective for acute treatment of mild dyspepsia. Therefore, further monitoring of patient's outcome therapy receiving IV twice daily needs to be done by the healthcare provider.

In this study, untreated indications were observed in 63 cases that covered patients with symptomatic conditions or abnormal laboratory value, such as headache or cough and dyslipidaemia. Statin is strongly recommended for secondary prevention of stroke with evidence of dyslipidaemia or atherosclerosis (Ministry of Health, 2019). Unfortunately, due to the nature of the observational study, it was impossible to confirm whether the above conditions are caused by certain medications, the symptoms of diseases, or other factors like the unwillingness of the patients to take the medications. For dyslipidaemia, it was also unclear whether patients are contraindicated to use statins.

Some of the non-allergic adverse drug events (ADEs) in this research were caused by inappropriate drug combinations while alternatives were available. Often, after a thorough risk-benefit analysis, patients still need the combinations; thus, monitoring is imperative. We identified 52 potential cases of ADEs, with four of them involving dual antiplatelet therapy. A study by Kurniawati *et al*. showed that 76% of patients with antiplatelet combination therapy experienced

gastrointestinal bleeding, compared to 24% of patients with single therapy (Kurniawati *et al*., 2023). A combination of antiplatelet therapy was associated with an increased incidence of bleeding compared to single antiplatelet therapy (Brown *et al*., 2021).

As a preventive measure against bleeding caused by aspirin 80 mg of, the physician had prescribed enteric coated formulation and both drugs were administered at different times. Aspirin was administered in the morning, while clopidogrel was administered at noon; however, four patients still developed bleeding. This may be attributable to the considerable inter-individual variability with respect to the effect of drug interactions (Bultas, 2013). Genetic profiling of patients is one of the means to minimise the drug adverse effects and interactions between drugs (Hahn & Roll, 2021). However, it cannot be performed as a routine procedure owing to limited access and prohibitive costs. Our findings call for close monitoring of patients for bleeding caused by antiplatelet combination.

Potential interactions between ischaemic and non-ischaemic stroke drugs in this study were observed between glimepiride and aspirin. According to Patel *et al.*, aspirin and glimepiride interact in the distribution phase (Patel *et al*., 2014). Low-dose aspirin preferentially binds to the glimepiride binding site on albumin, which increases the effect of glimepiride and can cause hypoglycaemia (Patel *et al*., 2014). Therefore, monitoring of blood glucose levels is recommended. Non-stroke drug interactions occurred between simvastatin and fenofibrate. The concomitant use of fibrous acid derivatives and HMG-CoA reductase inhibitors potentially cause rhabdomyolysis, although the rhabdomyolysis was not clinically detected yet in this study. Concurrent use of these drugs should be avoided unless the potential benefit of reducing lipid levels is greater than the increased risk of side effects and should be monitored (Wiggins *et al*., 2016). Patients with high risk of rhabdomyolysis should be monitored for signs of muscle-related side effects and serum creatine phosphokinase (CPK) (Stanley *et al*., 2023). The use of hydrophilic statin, such as rosuvastatin and pravastatin, also could be an alternative better than lipophilic statin since it shows the lower risk of rhabdomyolysis in patients (Di Stasi *et al*., 2010; Safitri *et al*.,2021)

A potentially toxic drug event was observed in one patient with type 2 diabetes mellitus who had a GFR (Glomerural Filtration Rate) of 20 mL/min. The patient was prescribed metformin 250 mg twice daily. The use of metformin was inappropriate because it is contraindicated in patients who have a Glomerular Filtration Rate (GRF) <30 mL/min due to metformin-associated lactic acidosis (MALA) (Lazarus *et al*., 2018).

Conclusion

Most patients encountered one-to-two DRPs, with the highest being a potentially suboptimal treatment. Patients taking multiple medications were more likely to experience more DRPs, therefore clinical pharmacists are expected to do therapy monitoring.

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