JOURNAL OF BASHIR INSTITUTE OF HEALTH SCIENCES

RESEARCH ARTICLE

Drug interaction and rational drug therapy in hospitalized patients reported with stroke

[a]Fawad Ali Shah, [a]Muhammad Imran Khan, [b]Bashir Ahmad, [c]Shabir Hussain

[a]Department of Pharmacology, Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan.
[b]Pakistan Institute of Medical Sciences, Islamabad, Pakistan.
[c]Department of Pharmacology, Bannu Medical College, KPK, Pakistan.

*CORRESPONDENCE

Fawad Ali Shah
Email:
fwd_shah@yahoo.com
Phone:
+923460474193

ABSTRACT

Objective: The purpose of the current study was to determine prescription rationalities, any pharmacotherapy-based problems, and to determine drug interactions in patients with stroke. **Methods:** Patient case histories were determined using a standard questionnaire form having a patient tag, age, sex, past history, chief complaints, biochemical tests, treatment chart and other relevant information. Forty patients suffering from stroke and were on treatment were selected for the current study. The relevant information was recorded with respect to patient demographic data, disease incidence, drug interactions. **Results:** Most of the hospitalized patients were in the range of 51-60 (20% out of 40 patients) and 71-80 (22.5% out of 40 patients) years. The most frequent cause of hospitalization was Cerebro Vascular Accident (CVA) or stroke (57.5%). New drugs were added to the regimen of 37.5% of patients due to certain diseases. The dose was changed in the regimen of 17.5% of patients. In 7.5% patient dosage form was changed. 27.5% of patients were observed with the therapeutic alternative. Drug interactions were found in the prescription history of 30% of patients. **Conclusion**: Hence, it is concluded that most of the patients admitted to hospital with Cerebro Vascular Accident and stroke have irrational drug prescription and drug-drug interactions in their prescription history.
Keywords: stroke, drug interactions, rational pharmacotherapy, patients

INTRODUCTION

A stroke, previously known as a cerebrovascular accident (CVA), is the rapidly developing loss of brain function due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism), or a hemorrhage (leakage of blood) [1]. As a result, the affected area of the brain is unable to function, leading to inability to move one or more limbs on one side of the body, inability to understand or formulate speech, or an inability to see one side of the visual field [2] and as a result, it is the second cause of death worldwide [3].

While World Health Organization [4] defines it as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours". This definition was supposed to reflect the reversibility of tissue damage and was devised for the purpose, with the time frame of 24 hours being chosen arbitrarily. The 24-hour limit divides stroke from transient ischemic attack, which is a related syndrome of stroke symptoms that resolve completely within 24 hours [2].

The major causes are advanced age, hypertension (high blood pressure), previous stroke or transient ischemic attack (TIA), diabetes, high cholesterol, cigarette smoking [5] and atrial fibrillation [6] although the magnitude of atrial fibrillation is small, the evidence from the Medical Research Council trials is that 833 patients have to be treated for 1 year to prevent one stroke [7],[8]. High blood pressure is the most important modifiable risk factor of stroke which accounts for 35 to 50% of stroke [9], [2]. Other causes are heavy alcohol consumption [10]. Alcohol use could predispose to ischemic stroke and intracerebral and subarachnoid hemorrhage via multiple mechanisms (for example via hypertension, atrial fibrillation, rebound thrombocytosis and platelet aggregation and clotting disturbances) [11]. Also, drugs like cocaine, amphetamines and over-the-counter cough and cold drugs containing sympathomimetics can lead to stroke [12] [13] [14]. Sickle cell anemia, which can cause blood cells to clump up and block blood vessels, can also lead to stroke. A stroke is the second leading death cause of in people under 20 who suffer from sickle-cell anemia [15]. Obesity and an unhealthy diet are the other causes. [16].

Various other risk factors include, a small blood pressure reduction (5 to 6 mmHg systolic, 2 to 3 mmHg diastolic) would result in 40% fewer strokes [17]. Lowering blood pressure has been conclusively shown to prevent both ischemic and hemorrhagic strokes [18] [19]. High cholesterol levels have been inconsistently associated with (ischemic) stroke [18]. Statins have been shown to reduce the risk of stroke by about 15% [20]. Patients with diabetes mellitus are 2 to 3 times more likely to develop stroke, and they commonly have hypertension and hyperlipidemia. Intensive disease control has been shown to reduce microvascular complications such as nephropathy and retinopathy but not macrovascular complications such as stroke [21] [22]. A stroke could soon be the most common cause of death worldwide [3]. Advanced age is one of the most significant stroke risk factors. 95% of strokes occur in people age 45 and older, and two-thirds of strokes occur in those over the age of 65 [23]. A person's risk of dying if he or she does have a stroke also increases with age. However, stroke can occur at any age, including in childhood. Family members may have a genetic tendency for stroke or share a lifestyle that contributes to stroke. Higher levels of the Von Willebrand factor are more common amongst people who have had ischemic stroke for the first time [24]. The results of this study found that the only significant genetic factor was the person's blood type. Having had a stroke in the past greatly increases one's risk of future strokes. Men are 25% more likely to suffer strokes than women, [25] yet 60% of deaths from stroke occur in women [26].

In Pakistan, it is believed to be even higher. Despite being a major public health problem, stroke has been ignored by health care authorities. More reliable data are needed to establish the precise burden of stroke in Pakistan. We do know it is the commonest reason for getting admitted to a neurology ward in our country. We also know that high blood pressure, the major risk factor for stroke, is very common in Pakistan. A national health survey revealed that more than 30% population above age 45 is suffering from high BP, most of who are undiagnosed and uncontrolled. Also, 12% population above age 15 is suffering from high cholesterol, and there are more than 5 million diabetics in Pakistan (#6 in world ranking). It is estimated that there will be 13 million diabetics in Pakistan by 2020 (#4 in the world). The estimated stroke incidence in Pakistan is close to 250 per 100,000 populations, which means that there are 350,000 new stroke patients every year in this country. Out of all ethnic groups, Pashtuns have the highest prevalence of high blood pressure and stroke [27].

METHODOLOGY

Data were recorded on a prescribed history form designed by the concerned department. Copy of a blank history form is attached herewith. Respective Ward Physician diagnosed all the cases. Earlier students were trained about taking the relevant histories. Ethical consent form was approved both by hospital administration and RIPS Research Ethical committee. Patients data was protected to ensured.

RESULTS AND DISCUSSION

 The result is obtained by observing 40 patients who were suffering from different diseases. The majority of patients were admitted to the ward with the complaint of stroke which is 57.5% of the total patients. Mostly these patients have developed stroke as a result of previous disease complications, particularly hypertension and diabetes. Hypertension and diabetes also made a high ratio in concurrent diseases. In 30% of patients, drug interactions were noted. Several patients also complaint about ADRs. New drugs were regularly added to the already existing regimen on regular basis. These interventions include a change in dose, change in dosage form, the addition of new drug as well as a therapeutic alternative.
 The patient demographic data, disease incidence rate, intervention and drug interactions are summarized as follows.

Table1. Patient demographic data.

S.no	Age group	No. of patients	*Percentage
1	11—20	05	12.5
2	21—30	03	7.5
3	31—40	01	2.5
4	41—50	06	15.0
5	51—60	08	20.0
6	61—70	05	12.5
7	71—80	09	22.5
8	81—90	03	7.5

*Percentage of total patients (n=40).

Table 2. Disease Incidence Rate.

	Cause of hospitalization	No of patients	*Percentage
Main Causes Of Hospitalization	Acute renal failure	02	5.0
	Anemia	01	2.5
	Ascites	01	2.5
	Bronchitis	01	2.5
	Cerebro vascular accident	23	57.5
	Congestive cardiac failure	01	2.5
	Diabetes Mellitus	02	5.0
	Hepatitis	01	2.5
	Hypertension	01	2.5
	Hypovolemic shock	01	2.5
	Ischemic heart diseases	01	2.5
	Malaria	01	2.5
	Nephrotic syndrome	01	2.5
	Parkinsonism	01	2.5
	Respiratory tract infections	01	2.5
	Ulcer	01	2.5
Concurrent Diseases	Asthma	01	2.5
	Cerebro Vascular Accident	02	5.0
	chronic obstructive pulmonary diseases	01	2.5
	Congestive cardiac failure	03	7.5
	Diabetes millitus	06	15.0
	Hepatits c	01	2.5
	Hypertension	12	30.0
	Ischemic heart diseaes	01	2.5
	Myocardial infarction	02	5.0
	Nephrotic syndrome	01	2.5
	Parkinsonism	01	2.5
	Pneumonia	01	2.5
	Respiratory tract infections	02	5.0
	Tansient ischemic attack	01	2.5
	Urinary tract infetions	01	2.5
	Asthma	01	2.5
	Cerebro vascular accident	02	5.0
	Chronic obstructive pulmonary diseases	01	2.5

*Percentage of total patients (n=40).

It is apparent from the table that the prevalence of diseases increases with aging and so patients above 40 years of age encountered more diseases with the highest incidents of diseases is seen particularly in individuals among 51-60 (20%) and 71-80 (22.5%). This highest incident in such age group people is because of adaptation of sedentary lifestyle, continuous exposure to the unhygienic environment, lack of awareness of diseases and health education. Therefore, it is the need of time that such activities should be arranged that produces mass awareness as well as patient awareness about their health. Since lifestyle modifications are an important risk factor for all most every disease, therefore it should be given particular emphases and should be focused on a priority basis.

It is evident from Table II that 23 cases (comes out to be 57.5%) of strokes as a major cause of hospitalization were seen out of 40 cases. Mostly these patients were above 50 years of age and the stroke was observed as a complication of already existing disease (mostly hypertension and in some cases diabetes) and at the same time hypertension and diabetes were observed as a major concurrent disease i.e. 30% and 15% respectively. Since hypertension is both primary and secondary, so again counseling, awareness should be produced.

Table 3: Interventions.

Types of intervention	Details	Case No	No of patients	*Percentage
Change in dose	Inj Transaminases BD to TDS to have good control	37	07	17.5
	Nitroglycerin changed from 2.6 to 6.5mg to provide a better vasodilation effect.	31		
	Inj Lasix OD changed to BD to have a good result	25		
	Tab Sofvasc 5mg changed to 10 mg to lower BP.	05		
	Tab Sinemet changed from TDS to BD because other antibiotics are also been added to the regimen.	04		
	Inj Metomide changed from OD to BD to further accelerate its effect.	01		
	Tab Zestril changed from 5 mg to 10 mg to lower BP.	14		
Change in dosage form	Tab Panadol changed to Iv state to provide an abrupt effect.	09	03	7.5
	Inj Metranidazol changed to tab because patient s getting recovered.	27		
	Inj Gravinite changed to Syp Gravinite because patient showing response.	35		
Therapeutic alternative	Ceftriaxone changes to Cefixime because ceftriaxone is mostly available in hospital and is given free of cost to patients, but now it is lacking in hospital.	40A	11	27.5
	Tab Bredin to tab amlodipine and relaxin changed to Dosek, doctors give no specific reasons.	16		
	Inj Cebac changed to inj Ceftriaxone because it is available in hospital.	17		
	Inf Levite changed to Leflox, given no specific reasons.	23		
	Tab Loprin to tab Clopidogrel And then to Norplat to get a good response and to have a psychological effect	10		

	Tab Loprin changed to Progrel to have a good response since it is better tolerated.	04		
	Ceftriaxone changed to Cefixime; quantity is lacking in hospital.	09		
	Inj Sonnet to inj Ceftriaxone, because it is available free of cost to the patient.	13		
	Inj Anzol is changed to inj Zantac because anzol is doubtable.	28		
	Inj Hyzonate changed to inj Decadron because Decadron is better tolerated and gives good response.	37, 25		
Addition of new drug	Syp Hydryllin to relieve cough.	40 A	15	37.5
	Inj Decadron and syp Gravinite to relieve fluid accumulation and vomiting resp.	35		
	Inj Novidate is added to provide better antibiotic cover	34		
	Tab Clarithro, tab Safvasc and inj Lasix were added to provide antibiotic cover, decrease BP, and to prevent LVF resp.	33		
	Tab Sinemet and Xenox added to overcome Parkinson effect and to cause sleep resp.	29		
	Oint Polyfix, syp liac added for treatment of bedsore and to relieve constipation resp.	07		
	Cap Spril is added to provide better antibiotic cover	09		
	Inf Dubatrex added for inotropic support	22		
	Tab Daonil and Progril were added to provide glycemic control.	14		
	Inj Maxolone to facilitate stomach emptying	13		
	Syp Pulmonal and inj Leflox added for bronchodilation & for antibiotic cover resp	28		
	Tab Sustac added for vasodilation	26		
	Inj Detamol to counteract fever	02		
	Tab Noclot added as antiplatelet	01		
	Mannitol and decadron added to relieve brain edema	03		
Without intervention		14 24 30	03	7.5

*Percentage of total patients (n=40).

It is apparent from Table III, that new medications were added to the already existing regimen of 37.5% of patients. The dose was changed in 17.5% of patients. In 7.5% of patients, the dosage form was changed. In 27.5% of patients, the concept of therapeutic alternative was observed.

Table 4. Drug Interactions.

S.No	Drug interaction	consequences	reference
1	Digoxin + Furosemide	Furosemide increases digoxin toxicity because it causes hypokalemia [39].	case 25,40A
3	Decadron + Glimepiride	Decadron antagonizes the effect of Glimepiride [40].	case 1
5	Decadron + Nimodipine	Nimodipine effect antagonize by Decadron [40].	case 3
6	Kempro + levodopa	Kempro decreases absorbtion of Levodopa [40].	case 4
7	Ziscar + decadron	Ziscar effect antagonize by Decadron [40].	case 8
8	Lasix + Hyzonate	Risk of hypokalemia [39].	case 15
9	Ramipace + Decadron	Ramipace effect antagonize by Decadron [40].	case 22
10	Angiocard + Decadron	Angiocard effect antagonize by Decadron [40].	case22
11	Lasix + Loprin	Risk of nephrotoxicity by concurrently giving both the drugs [40].	case 19
12	Zestril + decadron	Zestrl effect antagonize by Decadron [40].	case 16
13	Decadron + Dounil	Dounil effect antagonize by Decadron [40].	case 23

It is clear from the table that 30% of patients encountered drug interactions (n=40). The interactions that are mostly overlooked by the doctors in the medical ward are the concurrent use of Decadron with any other vasodilator (Calcium Channel Blockers, ACE Inhibitors). So, doctors must have adequate knowledge so to minimize the incidence of a drug interaction.

CONCLUSION
Clinical Pharmacist has major roles as he can best educate the patient about their medications as well as a disease state. At the same time, Pharmacists can be beneficial to the doctors as well, because most doctors overlook the onset of ADRs and drug interactions due to either their busy schedule or by other reasons. To overcome the side effects and to avoid potential drug interactions is an important element of treatment therapy, which cannot be bypassed. Patient compliance can be achieved only if they know about the proper use of their medications and this can be achieved only if there is a qualified Pharmacist with full use of the authority of their responsibilities.

LIMITATIONS
Since the purpose of the project was to determine rationalities in prescription particularly of a stroke patient and to determine pharmacotherapy-based problems. 99% of prescription was rational and no as such irrationality was observed. Although some shortcomings were there due to lack of resources but it can be easily overcome by the appointment of a Clinical Pharmacist at the Ward level. Apart from it, the data collected was from specific community and doesnot address the national wise sampling.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest which can adversely effect the current study.

AUTHOR CONTRIBUTION
FAS collected and analyzed the data and revised the final version of the manuscript, BA helped in data analysis and drafting of the manuscript. While, MIK along with SH helped in study design, critical revision of the manuscript submission.

FUNDING SOURCE
No funding source to be mentioned.

REFERENCES
[1]. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochimica et Biophysica Acta
        2009;1802(1):80–91.
[2]. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;371 (9624):1612–23.
[3]. Feigin VL. Stroke epidemiology in the developing world. Lancet 2005;365 (9478):2160–1.

[4]. Stroke Mount Sinai Hospital, New York

[5]. World Health Organisation (1978). Cerebrovascular Disorders Geneva: World Health Organization. ISBN 9241700432.

[6]. Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. Stroke 2003;34(12):2995–8.

[7]. Brain Basics: Preventing Stroke. National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders/stroke/preventing_stroke.htm.

[8]. Shuaib A, Hachinski VC . Mechanisms and management of stroke in the elderly. CMAJ 1991;145(5):433–43.

[9]. Sam J. Thrombosis of the cerebral veins and sinuses. The New England Journal of Medicine 2005;352(17):1791–8.

[10]. Reynolds K, Lewis B, Nolen JD, et al. Alcohol consumption and risk of stroke: a meta-analysis. JAMA 2003;89(5):579–88.

[11]. Gorelick PB. Alcohol and stroke. Stroke; a Journal of Cerebral Circulation 1987;18(1):268–71.

[12]. Sloan MA, Kittner SJ, Rigamonti D, Price TR. Occurrence of stroke associated with use/abuse of drugs. Neurology 1991;41(9):1358–64.

[13]. Estover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. Archives of General Psychiatry 2007;64(4):495–502.

[14]. Cantu C, Arauz A, Murillo-Bonilla LM, López M, Barinagarrementeria F. Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs. Stroke 2003;34(7):1667–72.

[15]. National Institute of Neurological Disorders and Stroke (NINDS) (1999). "Stroke: Hope Through Research". National Institutes of Health. http://www.ninds.nih.gov/disorders/stroke/detail_stroke.htm

[16]. Stroke Risk Factors. American Heart Association. 2007. http://www.AmericanHeart.org/presenter.jhtml?identifier=4716. Retrieved January 22, 2007.

[17]. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335(8693):827–38.

[18]. Saty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289(19):2534–44.

[19]. "Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration". Lancet 346 (8991-8992): 1647–53.

[20]. O'Regan C, Wu P, Arora P, Perri D, Mills EJ . Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am. J. Med 2008;121(1):24–33.

[21]. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group". Lancet 352 (9131): 837–53.

[22]. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366(9493):1279–89.

[23]. Senelick Richard C., Rossi, Peter W., Dougherty, Karla (1994). Living with Stroke: A Guide for Families. Contemporary Books, Chicago. ISBN 0809226073

[24]. Bongers T, de Maat M, van Goor M et al. High von Willebrand factor levels increase the risk of first ischemic stroke: influence of ADAMTS13, inflammation, and genetic variability. Stroke 2006;37(11):2672–7.

[25]. National Institute of Neurological Disorders and Stroke (NINDS) (1999). "Stroke: Hope Through Research". National Institutes of Health. http://www.ninds.nih.gov/disorders/stroke/detail_stroke.htm

[26]. Linda, Ed., Singleton, LaFayette, MD, Johnson, Kir   k A. (1993). Black Health Library Guide to Stroke. Henry Holt and Company, New York.

[27]. google search ;Stroke society of Pakistan.

[28]. Shuaib A, Hachinski VC . Mechanisms and management of stroke in the elderly. CMAJ 1991;145(5):433–43.

[29]. Stam J. Thrombosis of the cerebral veins and sinuses. The New England Journal of Medicine 2005;352(17):1791–8.

[30]. Saver JL. Time is brain - quantified. Stroke 2006;37(37):263–6

[31]. Available at http://www.nps.org.au/health_professionals/publications/prescribing_practice_review/current/nps_prescribing_practice_review_44

[32]. The National Institute Of Neurological Disorders And Stroke Rt-Pa Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. New England Journal of Medicine 1995;333(24):1581–7.

[33]. The European Cooperative Acute Stroke Study (ECASS), Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. New England Journal of Medicine 2008;359(13):1317–1329. http://content.nejm.org/cgi/content/short/359/13/1317.

[34]. Dubinsky, R; Lai SM. Mortality of stroke patients treated with thrombolysis: analysis of nationwide inpatient sample. Neurology 2006;66(11):1742–1744.

[35]. "Position Statement on the Use of Intravenous Thrombolytic Therapy in the Treatment of Stroke". American Academy of Emergency Medicine. http://www.aaem.org/positionstatements/thrombolytictherapy.shtm

[36]. Lee M, Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. Stroke 2010;41(5):932–7.

[37]. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent   stroke in patients who have nonvalvular atrial fibrillation. Ann. Intern. Med 2007;146 (12):857–67

[38]. Aciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant   treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke 2007;38(2):423–30.

[39]. Betram G Katzung, Parmely W. Drugs used in heart failure. In, Bertram G Katzung. Basic and Clinical Pharmacology, 9th edition. Singapore, The McGraw-Hill Companies, 2007;201-13.

[40]. Interactions. In, John Martin (ed). British National Formulary, 57th edition. London, BMJ Goup and RPS Publishing, 2009;708-89.