MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Advances in Pharmacology and Clinical Trials
ISSN: 2474-9214

Pheochromocytoma: Therapeutic Agents against the Disease and Chromatographic Methods for their Determination in Biological Fluids

Mbah CJ*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nigeria

***Corresponding author:** Chika J Mbah, Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria, Email: chika.mbah@unn.edu.ng

Research Article

Volume 9 Issue 4

Received Date: November 24, 2024

Published Date: December 23, 2024

DOI: 10.23880/apct-16000252

Abstract

Pheochromocytoma is a neuroendocrine tumour of the adrenal medulla and manifests itself by sustained or paroxysmal hypertension due to excessive production of catecholamine's. The symptoms require medical diagnosis and because of hormones secreted such symptoms may include high blood pressure, headache, rapid heartbeat, and sweating. Biochemical tests to confirm elevated levels of metanephrine and normetanephrine (catecholamine metabolites), imaging studies (magnetic resonance imaging, computed tomography, scintigraphy) are generally used to diagnose the disease and its metastases. The purpose of the study was to summarize therapeutic agents used to treat pheochromocytoma and provide some of the liquid chromatographic analytical methods utilized to determine the therapeutic agents in biological fluids. The methodology involved literature review covering the title of the study. It was carried out by utilizing library scientific journals; scientific online databases such as Drug Bank, Embase, International Pharmaceutical Abstracts, Medline, PubChem, PubMed, Science Direct, and Scopus. These databases provided the required information. Results obtained revealed that treatment of the disease involved surgical removal of the tumour (gold-standard treatment), radiotherapy and chemotherapy (catecholamine blockade). Several analytical methods namely chromatographic, electrochemical, spectroscopic methods have been described to measure these therapeutic agents used to treat pheochromocytoma in biological fluids. In conclusion, treatment of pheochromocytoma involves therapeutic agents such as alpha1 (α1) adrenoceptor antagonists, beta (β)-adrenoceptor antagonists, calcium channel blockers, and anti-neoplastic agents. Amongst the chromatographic methods, hyphenated liquid chromatographic methods are of the most interest to analytical scientists.

Keywords: Pheochromocytoma; Surgery; Therapeutic agents; Biological fluids; Chromatographic analytical methods

Abbreviations

ACTH: Adrenocorticotropic Hormone; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; I123-MIBG-I123: Metaiodobenzylguanidine; NO: Nitric Oxide

Introduction

Pheochromocytoma is a neuroendocrine tumour of the adrenal gland affecting the chromaffin cells of the medullary portion of the gland and is characterized by the

excessive production and release of catecholamine's into the circulation [1].

Although the adrenal medulla is mostly affected by the disease (85%), other parts of the body that could experience the tumours (extra-adrenal pheochromocytomas) are neck, chest, base of the skull; middle ear, spermatic cord,.and urinary bladder.

The pathophysiology of the tumour indicates continuous or episodic increased release of catecholamine's such as epinephrine, norepinephrine, and dopamine [2].

Other hormones and peptides associated with the disease include adrenocorticotropic hormone, atrial natriuretic factor, calcitonin, growth hormone-releasing factor, parathyroid hormone-related peptide, somatostatin, serotonin, and vasoactive intestinal peptide.

The classical and most common symptom of pheochromocytoma is hypertensive crisis (due to tumoral excessive secretion of catecholamine's following alpha-adrenoceptor activation) which may last either a few minutes or a few hours of which the end is characterized by arterial hypotension [3]. The crisis (hypertensive paroxysm) which can be triggered by anaesthetics, intense physical effort, palpation of the lumbar region, smoking, surgery is associated with symptoms, such as anxiety, abdominal pain or chest pain, diaphoresis, severe headache, heart rhythm disorders, nausea, and visual disturbances [4,5].

Other symptoms may include acute myocardial ischemia (due to the increased oxygen demand), autonomic hyperreflexia, acrodynia ('pink disease'), cerebral vasculiti, hypercriticism (due to hyper secretion of adrenocorticotropic hormone, ACTH), hypocalcaemia (due to hyper secretion of calcitonin), hyperglycaemia without diabetes mellitus, and hypertensive encephalopathy [6,7].

Diagnosis of the disease may involve looking out for positive symptoms such as severe headache, diaphoresis, and heart rhythm disorders. Biochemical identification tests (some of which are specific and sensitive) are carried out for the presence of catecholamine's and their metabolites (namely metanephrines and normetanephrines) in plasma and urine [8]. In addition, other diagnostic tests such as measurement of plasma and urinary vanillylmandelic acid [7], biomarkers methoxytyramine (identification of malignant forms of pheochromocytoma) and chromogranin a (neuroendocrine tumours) are also conducted [9]. Furthermore, imaging evaluation namely computed tomography (CT), magnetic resonance imaging (MRI) could be carried out to establish the dimensions and localization of the tumour as well as identifying metastatic lesions [10]. Scintigraphy using I123 metaiodobenzylguanidine (I123-MIBG) is also utilized in the identification of catecholamine-producing tumours and their metastases [11]. The I123-MIBG is a highly specific test. Genetic tests can also be carried out on patients with family history of pheochromocytoma.

Discussion

The Management of the Disease Involves Three Options, Namely

Surgery: It entails open transperitoneal adrenalectomy or the laparoscopic approach. The removal of the tumours by open transperitoneal adrenalectomy is indicated when tumours are multiple, very large, or difficult to remove by laparoscopic procedure. The laparoscopic approach is less invasive and assists in curing and preventing the lesions [10]. Surgical approach is the mainstay of therapy for the majority of localized tumours. To avoid intra- and postoperative cardiovascular complications (such as negative hemodynamic events) preoperative antihypertensive therapy is required [12].

Radiotherapy: is a non-invasive procedure to manage phaeochromocytoma and is appropriate in locations with high surgical risk or when surgery is not applicable [13].

Chemotherapy: Therapeutic agents employed in the management of phaeochromocytoma can be subdivided into:

Pre-Operative Agents

Alpha-1(α1) Adrenoceptor Antagonists

These blockers are administered to prevent anaesthesia, adrenal venography, arteriography induced symptoms as well as hypertensive crises during surgery. Typical examples of these selective alpha-1 adrenergic receptor antagonists are prazosin, doxazosin, and terazosin [14]. They are first line therapeutic agents and antagonism produced by them is reversible. Prazosin is most frequently used in patients with indications of surgical resection of pheochromocytoma.

Beta (β)-Adrenoceptor Antagonists And Calcium Channel Blockers

They are given only after administration of α-adrenergic receptor blockers and to be added 2 or 3 days before surgery if the heart rate ex-ceeds 80 beats per minute [15]. Typical examples of beta-adrenoceptor antagonists are metoprolol, atenolol, bisoprolol, carvedilol, propranolol and labetalol [16]. Typical examples of calcium channel blockers are amlodipine, diltiazem, nicardipine, nifedipine, verapamil and can be administered as primary drugs in order to control hypertension or as adjunct antihypertensive therapy [17].

Intraoperative Agents: These agents are used intraoperatively (during surgery) to control hypertension

and tachycardia [18,19]. Typical examples are esmolol (beta-adrenoceptor blocker), sodium nitroprusside and nitroglycerine [18]. Intraoperative hypertension and hemodynamic instability occur depending on anesthetic drugs, tumoral dimensions, and plasma catecholamine levels.

Postoperative Agents: These agents control postoperative hypotension hence blood pressure and heart rate monitoring are vital after surgery. Typical examples are vasopressor agents [20].

Intravenous Chemotherapy: It is usually reserved for aggressive metastatic tumours that might cause pain or pressure on vital tissues or organs. Typical examples are cyclophosphamide, dacarbazine and vincristine [21].

Characteristics of these Therapeutic Agents

Amlodipine: It is a derivative of dihydropyridine. Chemically defined as 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. As a calcium channel blocker, amlodipine antagonizes the influx of extracellular calcium ions into myocardial and peripheral vascular smooth muscle cells. The inhibition gives rise to dilatation of the main coronary and systemic arteries, myocardial contractility decrease, blood flow and oxygen delivery to the myocardial tissue increase, and total peripheral resistance decrease. It can also inhibit the p-glycoprotein efflux pump resulting in modulation of multi-drug resistance activity.

Atenolol is an isopropylamino-propanol derivative. It is defined chemically as [4-[2-hydroxy-3-(propan-2-ylamino) propoxy]phenyl] acetamide, The drug acts as a peripheral, cardioselective β-blocker and has specificity for β1-adrenergic receptors without intrinsic sympathomimetic effects. It also has the ability to delay atrioventricular conduction and decrease in myocardial oxygen requirements.

Bisoprolol derivative of phenoxypropanol. The chemical name is 1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl)phenoxy]propan-2-ol. As a selective β1 adrenergic receptor antagonist it selectively and competitively blocks β1 adrenergic receptors in the heart, hence decreasing the heart rate and contraction resulting in cardiac output reduction and lowering of blood pressure. Furthermore, the drug prevents the release of rennin (a hormone) secreted by the kidneys to cause blood vessels constriction.

Carvedilol derivative of carbazole and propanol. It is chemically defined as 1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol. Carvedilol acts as a non-cardioselective β-blocker as well as blocker of α1 adrenergic receptors.

Cyclophosphamide derivative of phosphamide. Chemically it is N,N-bis(2-chloroethyl)-2-oxo-1,3,2λ5-oxazaphosphinan-2-amine. As an alkylating agent, it acts by alkylating the nucleophilic moieties of the biological cancer cells.

Dacarbazine: It is a triazene derivative. Chemically defined as, 4-(dimethylaminodiazenyl)-1H-imidazole-5-carboxamide. It acts by alkylating and cross-linking DNA resulting in disruption of DNA activity, cell cycle arrest, and apoptosis.

Diltiazem: A derivative of benzothiazepine. It is chemically defined as [(2S,3S)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate. The drug acts by blocking voltage-sensitive calcium channels in the blood vessels, thus preventing calcium levels increase. It can also interfere with the release of calcium from the sarcoplasmic reticulum and blocks the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes. Its actions lead to the main coronary and systemic arteries dilatation, myocardial contractility decrease, peripheral arterial resistance decrease, cardiac output decrease and improved oxygen myocardial tissue delivery.

Doxazosin: It is a quinazoline derivative. Chemically defined as [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-(2,3-dihydro-1,4-benzodioxin-3-yl)methanone. As a selective α1-adrenergic receptors antagonist, the drug inhibits α1-adrenergic action on the vascular smooth muscles leading to a decrease in vascular resistance.

Esmolol: A phenylpropionic acid derivative. The chemical name is methyl 3-[4-[2-hydroxy-3-(propan-2-ylamino) propoxy]phenyl]propanoate. It acts as a cardioselective β-blocker used in parenteral forms in the treatment of arrhythmias and severe hypertension.

Labetalol is a benzamide derivative. Chemically defined as 2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl] benzamide. As a selective α1-adrenergic antagonist and non-selective β-adrenergic antagonist, it competitively binds to α1-adrenergic receptors in vascular smooth muscle, thus inhibiting the vasoconstriction in peripheral blood vessels as well as adrenergic stimulation of endothelial cell function. The drug also decreases adrenergic stimulation by binding to β-receptors in the bronchial and vascular smooth muscle.

Metoprolol is a phenoxypropanol derivative. Defined chemically as 1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-

ylamino)propan-2-ol. It acts as a cardioselective competitive β1-adrenergic receptor antagonist thus decreasing the rate and force of myocardial contraction, resulting in a diminished cardiac output. The drug also acts by decreasing rennin secretion thus decreasing sympathetic activation, including vasoconstriction, aldosterone secretion.

Nicardipine a derivative of nitrophenyl-pyridine. Chemically defined as 5-O-[2-[benzyl(methyl)amino] ethyl] 3-O-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. It acts as a potent calcium channel blocker thus inhibiting coronary and peripheral arteries contraction that results in lowering of heart muscle oxygen requirements and arterial contraction decrease.

Nifedipine is a dihydropyridine derivative. Defined chemically as dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. As a calcium channel blocker, it acts by inhibiting the transmembrane influx of extracellular calcium ions into myocardial and vascular smooth muscle cells, resulting in the main coronary and systemic arteries dilatation and myocardial contractility decrease. It can also inhibit efflux pump P-glycoprotein.

Nitroglycerine is a derivative of glycerol. Chemically defined as 1,3-dinitrooxypropan-2-yl nitrate. As a vasodilator, the drug reduces the preload (decreasing left ventricular volume by dilating the veins) and afterload (reducing arteriolar resistance) following its conversion into nitric oxide (NO) in smooth muscles of the blood vessels resulting in decrease of myocardial oxygen demands. The drug also acts by causing coronary artery dilatation, thus improving myocardial blood distribution.

Prazosin is a piperazine derivative. Chemically, it is defined as [4-(4-amino-6,7-dimethoxyquinazolin-2-yl) piperazin-1-yl]-(furan-2-yl)methanone. The drug acts on large resistance vessels (arterioles) as an α1-adrenergic receptor blocker resulting in a decrease in total systemic vascular resistance. It can also decrease bladder sphincter tone, thus permitting the opening of the bladder into the urethra to relieve the urinary conditions linked with benign prostatic hypertrophy.

Propranolol is a naphthalene derivative. Defined chemically as 1-naphthalen-1-yloxy-3-(propan-2-ylamino) propan-2-ol. It acts competitively as a nonselective β-adrenergic receptor antagonist. This action causes negative chronotropic and inotropic effects resulting in cardiac output reduction.

Sodium Nitroprusside: It is a pentacyanide derivative. Chemically defined as disodium iron(4+) nitroxyl anion pentacyanide dehydrate. The drug acts as vasodilator thus it is used intravenously for severe hypertension, hypertensive emergencies and heart failure treatment.

Terazosin: It is a piperazine derivative. The chemical name is [4-(4-amino-6,7-dimethoxyquinazolin-2-yl) piperazin-1-yl]-(oxolan-2-yl)methanone. It acts as a nonselective α1-adrenergic receptor antagonist resulting in its use in the treatment of hypertension and benign prostatic hypertrophy.

Verapamil: It is a derivative of phenylalkylamine. Chemically defined as 2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile. The drug is a calcium channel blocker and its mechanism of action is similar to other calcium channel antagonists previously described.

Vincristine is a diazapentacyclic tetraene derivative. Chemically it is methyl (1R,9R,10S,11R,12R,19R)-11-acetyloxy-12-ethyl-4-[(13S,15S,17S)-17-ethyl-17-hydroxy-13-methoxycarbonyl-1,11 diazatetracyclo[13.3.1.04,12.05,10]nonadeca-4(12),5,7,9-tetraen-13-yl]-8-formyl-10-hydroxy-5-methoxy-8,16-diazapentacyclo[10.6.1.01,9.02,7.016,19]nonadeca-2,4,6,13-tetraene-10-carboxylate.

The drug acts by interfering with the formation of the mitotic spindle following its irreversibly binding to microtubules and spindle proteins in S phase of the cell cycle and, resulting in the arrest of tumour cells in metaphase. It can also depolymerize microtubules, interferes with cellular respiration, nucleic acid and lipid biosynthesis.

Due to low therapeutic indices or low plasma concentration levels of these agents, monitoring of their plasma concentration levels becomes imperative. The monitoring can be accomplished by determining plasma drug concentrations using analytical methods that are highly accurate, precise, sensitive, selective and specific. Although a number of analytical methods namely chromatographic, electrochemical and spectroscopic methods might have been used to measure these agents in biological fluids, the present study will provide only some of the liquid chromatographic methods (hyphenated and non-hyphenated) that have been utilized to determine their concentration levels in various biological matrices. Hyphenation is interfacing a chromatographic technique and one or more spectroscopic detection techniques. Hyphenated methods have the selectivity and sensitivity with high accuracy to determine therapeutic agents at low drug concentration in biological fluids.

Biological fluids assist to maintain body homeostasis. Whole blood, serum or plasma, urine, saliva and

cerebrospinal fluid are biological fluids very often analyzed. The present study summarizes therapeutic agents used in the management of pheochromocytoma and some liquid chromatographic analytical methods employed to measure their concentrations in biological fluids. The analytical methods include:

Amlodipine determined in (a) plasma [22-24] by hyphenated system, [25] by non- hyphenated system, (b) serum [26] by non- hyphenated system.
Atenolol determined in (a) whole blood by non-hyphenated system, (b) plasma [27-29] by hyphenated system, [30] by non- hyphenated system, (c) urine by non- hyphenated system.
Bisoprolol determined in (a) plasma [31-33] by hyphenated system, [34,35] by non-hyphenated system.
Carvedilol determined in (a) whole blood [36,37] by non-hyphenated system, (b) plasma [38-40] by hyphenated system, [41-43] by non- hyphenated system, (c) urine [43] by non- hyphenated system.
Cyclophosphamide determined in (a) plasma [44,45] by hyphenated system, [46] by non-hyphenated system, (b) urine [47] by hyphenated system.
Dacarbazine determined in (a) plasma [48,49] by non-hyphenated system.
Diltiazem determined in (a) serum [50] by non- hyphenated system.
Doxazosin determined in (a) plasma [51] by hyphenated system, [52-55] by non-hyphenated system, (b) serum [56] by hyphenated system.
Esmolol: determined in (a) plasma [57,58] by non-hyphenated system.
Labetalol: determined in (a) serum [59] by hyphenated system, (b) urine [60] by hyphenated system by non-hyphenated system.
Metoprolol: determined in (a) plasma [61-63] by hyphenated system, [64] by non-hyphenated system, (b) urine [64] by non- hyphenated system.
Nicardipine: determined in (a) plasma [65] by non-hyphenated system.
Nifedipine: determined in (a) plasma [66-68] by hyphenated system, [69] by non- hyphenated system, (b) serum [70] by non- hyphenated system (c) urine [71] by non- hyphenated system, (d) amniotic fluid [72] by hyphenated system.
Prazosin: determined in (a) plasma [73] by non-hyphenated system, (b) serum [74] by non-hyphenated system.
Propranolol: determined in (a) plasma [75] by hyphenated system.
Terazosin: determined in (a) plasma [76] by non-hyphenated system.
Verapamil: determined in (a) plasma [77-79] by hyphenated system, [80,81] by non- hyphenated system (c) serum [82] by non- hyphenated system, (d) urine [82] by non-hyphenated system.
Vincristine determined in: (a) whole blood by hyphenated system [83], (b) plasma [84-86] by hyphenated system.

Conclusion

Surgical removal of the tumour represents the gold-standard treatment for pheochromocytoma patients. The symptomatology in the disease is given by the predominant type of catecholaminergic secretion. Imaging scans may be used in metastases or when radiation is not an option. The α-receptor antagonists are they first-line treatment in order to reduce incidence of intraoperative cardiovascular complications.

Hypotension, the most common complication after tumour removal is to be avoided by use of vasopressor agents and/or vascular volume replacement with fluids intravenously administered. Several analytical methods such as chromatographic, electrochemical, and spectroscopic methods have been used to determine therapeutic agents used to treat pheochromocytomas in biological fluids. Of all the analytical methods, hyphenated liquid chromatographic method is the technique of choice for analytical scientists probably due to its high accuracy, sensitivity and selectivity.

References

1. Barakat MT, Meeran K, Bloom SR (2004) Neuroendocrine tumours. Endocr Relat Cancer 11(1): 1-18.

2. Lehnert H (2004) Pheochromocytoma. Pathophysiology and clinical management, Karger Basel.

3. Galetta F, Franzoni F, Bernini G, Fallawi P, Angelo Carpi, et al. (2010) Cardiovascular complications in patients with pheochromocytoma: a mini-review. Biomed Pharmacotherapy 64(7): 505-509.

4. Lenders JW, Duh QY, Eisenhofer G, Anne PGR, Stefan KGG, et al (2014) Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 99(6): 1915-1942.

5. Lenders JW, Eisenhofer G, Mannelli M, Pacak K (2005) Phaeochromocytoma. Lancet 366(9486): 665-675.

6. Samuel MZ, Vitaly K, Karel P (2011) Hypertension in pheochromocytoma: characteristics and treatment. Endocrinol Metab Clin North Am 40(2): 295-311.

7. Kizer JR, Koniaris LS, Edelman JD (2000) Pheochromocytoma crisis, cardiomiopathy and hemodynamic collapse. Chest 118(4): 1221-1223.

8. Lenders JW, Pacak K, Walther MM (2002) Biochemical diagnosis of pheochromocytoma: Which test is best?

JAMA 287(11): 1427-1434.

9. Eisenhofer G (2012) Screening for pheochromocytomas and paragangliomas. Curr Hypertens Rep 14(2): 130-137.

10. Timmers HJ, Taieb D, Pacak K (2012) Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. Horm Metab Res 44(5): 367-372.

11. Martucci VL, Pacak K (2014) Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. Current problems in cancer 38(1): 7-41.

12. Tauzin-Fin P, Sesay M, Gosse P, Ballanger P (2004) Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. Br J Anaesth 92(4): 512–517.

13. Jansen TTG, Timmers H, Marres HAM, Kaanders J, Kunst HPM (2018) Results of a systematic literature review of treatment modalities for jugulotympanic paraganglioma, stratifed per Fisch class. Clin Otolaryngol 43: 652-661.

14. Prys-Roberts C, Farndon JR (2002) Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World J Surg 26(8): 1037-1042.

15. Weingarten TN, Welch TL, Moore TL, Walters GF, Whipple JL, et al (2017) Preoperative levels of catecholamine's Clinical and Translational Oncology 1 3 and metanephrines and intraoperative hemodynamics of patients undergoing pheochromocytoma and paraganglioma resection. Urology 100: 131-138.

16. Shao Y, Chen R, Shen Z, Teng Y, Huang P, et al. (2011) Preoperative alpha blockade for normotensive pheochromocytoma: Is it necessary? J Hypertens 29(12): 2429-2432.

17. Agrawal R, Mishra SK, Bhatia E, Anjali M, Gyan C, et al. (2014) Prospective study to compare peri-operative hemodynamic alterations following preparation for pheochromocytoma surgery by phenoxybenzamine or prazosin. World J Surg 38(3): 716-723.

18. Hariskov S, Schumann R (2013) Intraoperative management of patients with incidental catecholamine producing tumours: A literature review and analysis. J Anaesthesiol Clin Pharmacol 29(1): 41-46.

19. Benay CE, Tahiri M, Lee L, Evangelia T, Amin M, et al. (2016) Selective strategy for intensive monitoring after pheochromocytoma resection. Surgery 159(1): 275-282.

20. Manea M, Marcu DR, Bratu OG, Stanescu AM, Stoian AP (2019) Pheochromocytoma – clinical manifestations, diagnosis and current perioperative management. J Mind Med Sci 6(2): 244-247.

21. Manger WM (2006) Diagnosis and management of pheochromocytoma – recent advances and current concept. Kidney Int 70: S30-S35.

22. Lv C, Wei C , Bu F , Chen R , Wang X , et al. (2013) Determination of amlodipine in human plasma by LC-MS/MS and its bioequivalence study in healthy Chinese subjects. Pharmacology and Pharmacy 4: 191-200.

23. Sirikatitham A, Panrat K, Tanmanee N (2008) Determination of amlodipine in human plasma by electrospray ionization LC-MS/MS method: validation and its stability studies 30(4): 455-462.

24. Ma Y, Qin F, Sun X, Lu X, Li F (2007) Determination and pharmacokinetic study of amlodipine in human plasma by ultra-performance liquid chromatography-electrospray ionization mass spectrometry. J Pharm Biomed Anal 43: 540-545

25. Zarghi A, Foroutan SM, Shafaati A, Khoddam A (2005) Validated HPLC method for determination of amlodipine in human plasma and its application to pharmacokinetic studies. Farmaco 60(9): 789-792.

26. Bahrami G, Mirzaeei S (2004) Simple and rapid HPLC method for determination of amlodipine in human serum with fluorescence detection and its use in pharmacokinetic studies, J Chromatogr B: Biomed Sci Appl 36(1): 163-168.

27. Dias E, Hachey B, McNaughton C, Nian H, Yu C, et al. (2014) An LC-MS assay for the screening of cardiovascular medications in human samples J Chromatogr B Anal Technol Biomed Life Sci 937: 44-53.

28. Puntb AM, Steinstra NA, Van Kleef MEA, Lafeber M, Spiering W, et al (2019) Screening of cardiovascular agents in plasma with LC-MS/MS: A valuable tool for objective drug adherence assessment. J Chromatogr B1121: 103-110.

29. Lwin E, Gerber C, Song Y, Leggett C, Ritchie U, et al. (2017) A new LC-MS/MS bioanalytical method for atenolol in human plasma and milk. Bioanalysis 9(7): 517-530.

30. Spanakis M, Niop I (2013) Determination of atenolol in human plasma by HPLC with fluorescence detection: Validation and application in a pharmacokinetic study J Chromatogr 51(2): 128-132.

31. Peste G, Bibire N, Apostu M, Vlase A, Oniscu C (2009) A

new liquid chromatography-tandem mass spectrometry method for determination of bisoprolol in human plasma samples. J Biomed Biotech: 1-8.

32. Liu M, Zhang D, Sun Y, Wang Y, Liu Z, et al. (2007) Liquid chromatographic-electrospray tandem mass spectrometric determination of bisoprolol in human plasma. Biomed Chromatogr 21: 508-513.

33. Ding L, Zhou X, Guo X, Song Q, He J, et al. (2007) LC-ESI-MS method for the determination of bisoprolol in human plasma. J Pharm Biomed Anal 44: 520-525.

34. Ulu ST, Zeynep A (2012) An HPLC method for the determination of bisoprolol in human plasma and its application to a pharmacokinetic study. J Chromatographic Sci 50(7): 615-619.

35. Oniscu C, Vlase CV, Peste G (2007) A new high performance liquid chromatographic method for determination of bisoprolol in plasma samples. Roumanian Biotechnological Letters 12(1): 3079-3084.

36. Saito M, Kawana J, Ohno T, Kanako M, Mihara K, et al. (2006) Enantioselective and highly sensitive determination of carvedilol in human plasma and whole blood after administration of the racemate using normal-phase high-performance liquid chromatography. J Chromatogr B 843(1): 73-77.

37. Kim S, Lee SH, Lee H (2012) Rapid and sensitive carvedilol assay in human plasma using a high-performance liquid chromatography with mass/mass spectrometer detection employed for a bioequivalence study. Am J Anal Chem 1(3): 135-143.

38. Yang E, Wang S, Kratz J, Cyronak MJ (2004) Stereoselective analysis of carvedilol in human plasma using HPLC/MS/MS after chiral derivatization. J Pharm Biomed Anal 36(3): 609-615.

39. Jeong DW, Kim YH, Ji HY, Youn YS, Lee KC, et al. (2007) Analysis of carvedilol in human plasma using hydrophilic interaction liquid chromatography with tandem mass spectrometry. J Pharm Biomed Anal 44(2): 547-552.

40. Zakrzewski-Jakubiak M, de Denus S, Leblanc MH, White M, Turgeon J (2010) Enantioselective quantification of carvedilol in human plasma by HPLC in heavily medicated heart failure patients. J Pharm Biomed Anal 52: 636-641.

41. Zarghi A, Foroutan SM, Shafaati A, Khoddam A (2007) Quantification of carvedilol in human plasma by liquid chromatography using fluorescence detection: application in pharmacokinetic studies. J Pharm Biomed Anal 44(1): 250-253.

42. Machida M, Watanabe M, Takechi S, Kakinoki S, Nomura A (2003) Measurement of carvedilol in plasma by highperformance liquid chromatography with electrochemical detection. J Chromatogr B 798(2): 187-191.

43. Peccinini RG, Ximenes VF, Cesarino EJ, Lanchote VL (2008) Stereoselective analysis of carvedilol in human plasma and urine using HPLC after chiral derivatization. Biopharmaceutics & Drug Disposition 29(5): 280-288.

44. Ekhart C, Gebretensae A, Rosing H, Rodenhuis S, Beijnen JH, et al. (2007) Simultaneous quantification of cyclophosphamide and its active metabolite 4-hydroxycyclophosphamide in human plasma by high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry. J Chromatogr B 854(1-2): 345-349.

45. Martins I, Souza JO, Sanson AL, Vieira EP, Giusti-Paiva A (2009) Simultaneous determination of cyclophosphamide and ifosfamide in plasma using SPE HPLC-UV methods. Lat Am J Pharm 28(1): 41-46.

46. Kasel D, Jetter A, Harlfinger S, Gebhardt W, Fuhr U (2004) Quantification of cyclophosphamide and its metabolites in urine using liquid chromatography/ tandem mass spectrometry. Rapid Commun Mass Spectrom 18(13): 1472-1478.

47. Barbieri A, Sabatini L, Indiveri P, Bonfiglioli R, Lodi V, et al. (2006) Simultaneous determination of low levels of methotrexate and cyclophosphamide in human urine by micro liquid chromatography/electrospray ionization tandem mass spectrometry. Rapid Commun Mass Spectrom 20(12): 1889-1893.

48. Malik MZ, Ahmad M, Muahammad S (2013) Rapid and simultaneous determination of adriamycin, bleomycin, vinblastine and dacarbazine in plasma of Hodgkin's lymphoma patients by a reversed phase HPLC method. J Chil Chem Soc 58(2): 1674-1677.

49. Safgren LS, Joel M, Rios RR, Ames MM (2001) Validated high-performance liquid chromatographic assay for simultaneous determination of dacarbazine and the plasma metabolites 5-(3-hydroxymethyl-3-methyl-1-triazeno) imidazole-4- carboxamide and 5-(3-methyl-1-triazeno) imidazole-4-carboxamide. Journal of Chromatography B 754(1): 91-96.

50. Sultana N, Arayne MS, Shafi N, Siddiqui FA, Hussain A (2010) Development of a RP-HPLC method for the simultaneous analysis of diltiazem and statin:

Application in pharmaceuticals and human serum. Anal Methods 2(10): 1571-1576.

51. Al-Dirbashi OY, Aboul-Enein HY, Jacob M, Al-Qahtani K, Rashed MS (2006) UPLC-MS/MS Determination of doxazosine in human plasma. Anal and Bioanal Chem 38: 1439-1443.

52. Ji HY, Park EJ, Lee KC, Lee HS (2008) Quantification of doxazosin in human plasma using hydrophilic interaction liquid chromatography with tandem mass spectrometry. J Separation Sci 31(9): 1628-1633.

53. Sripalakit P, Nermhom P, Saraphanchotiwitthaya A (2005) Improvement of doxazosin determination in human plasma using high-performance liquid chromatography with fluorescence detector. J Chromatogr Sci 43(2): 63-66.

54. Sripalakit P, Nermhom P, Saraphanchotiwitthaya A (2006) Validation and pharmacokinetic application of a method for determination of doxazosin in human plasma by high-performance liquid chromatography. Biomed Chromatogr 20(8): 729-735.

55. Wongsinsup C, Taesotikul W, Kaewvichit S, Sangsrijan S (2007) Simple method of extraction and determination of doxazosin mesylate in human plasma by high-performance liquid chromatography with fluorescence detector. CMU J Natur Sci 6(2): 231-240.

56. Chytil L, Strauch B, Cvačka J, Marešová V, Widimský J, et al. (2010) Determination of doxazosin and verapamil in human serum by fast LC-MS/MS: application to document non-compliance of patients. J Chromatogr B 878(30): 3167-3173.

57. Fung L, Bykowski-Jurkiewicz C, Sarver JG, Erhardt PW (2010) Determination of esmolol and metabolite enantiomers within human plasma using chiral column chromatography. J Chromatogr B 878(26): 2449-2452.

58. Tang Y, He Y, Yao T, Zeng S (2004) Simultaneous determination of the enantiomers of esmolol and its acid metabolite in human plasma by reversed phase liquid chromatography with solid-phase extraction. J Chromatogr B 805(2): 249-254.

59. Wu J, Lord HL, Pawliszyn J, Kataoka H (2000) Polypyrrole-coated capillary in tube solid phase microextraction coupled with liquid chromatography-electrospray ionization mass spectrometry for the determination of β-blockers in urine and serum samples. Journal of Microcolumn Separations 12(4): 255-266.

60. Gergov M, Robson JV, Duchoslav E, Ojanpera I (2000) Automated liquid chromatography-tandem mass spectrometric method for screening β-blocking agents in urine. J Mass Spectrom 35(7): 912-918.

61. Narmada P, Bhujanga Rao AKS, Jogi KV (2013) Determination of metoprolol in human plasma by liquid chromatography tandem-mass spectrometry. Int J Pharm Phytopharmacol Res 3(2): 117-120.

62. Venkateswarlu P, Kumar BN, Seshaiah K, Prasad W (2010) Selective and sensitive method for the determination of metoprolol in human plasma using liquid chromatography coupled with tandem mass spectrometry. Acta Pharm 60: 177-184.

63. Jensen BP, Sharp CF, Gardiner SJ, Begg EJ (2008) Development and validation of a stereoselective liquid chromatography-tandem mass spectrometry assay for quantification of S-and R-metoprolol in human plasma. J Chromatogr B 865(1-2): 48-54.

64. Yilmaz B, Asci A, Arslan S (2010) Determination of metoprolol in human plasma and urine by high-performance liquid chromatography with fluorescence detection. J Sep Sci 33(13):1904-1908.

65. Fernandes CM, Veiga FJB (2003) A simple method for nicardipine hydrochloride quantification in plasma using solid-phase extraction and reverse-phase high performance liquid chromatography. Biomed Chromatogr 17(1): 33-38.

66. Liliya S, Logoyda L (2020) LC-MS/MS method development and validation for the determination of nifedipine in human plasma. Biointerface Research in Applied Chemistry 10(5): 6189-6196.

67. Ismail KM, Rao MVL, Rao AB (2017) Estimation of nifedipine in K2EDTA human plasma using UHPLC-MS/MS method. Int J Res in Pharm Chem 7: 577-584.

68. Baratam SR, Janjanam KC, Ratna VJ (2018) Determination of nifedipine in human plasma by high performance liquid chromatography tandem mass spectrometry and its validation. World J Pharm Pharmaceut Sci 7: 678-691.

69. Abou-Auda HS, Najjar TA, Al-Khamis KI, Al-Hadiya BM, Ghilzai NM, et al. (2010) Liquid chromatographic assay of nifedipine in human plasma and its application to pharmacokinetic studies. J Pharm Biomed Anal 22(2): 241-249.

70. Gil-Agustí MT, Carda-Broch S, Monferrer-Pons L, Esteve-Romero JS (2006) Photostability studies for micellar liquid chromatographic determination of nifedipine in serum and urine samples. Biomed Chromatogr 20(2):

154-160.

71. Thulasamma P, Venkateswarlu P (2011) RP-HPLC method for the quantitative determination of nifedipine in dosage forms, human milk and urine. Res J Pharm and Technol 5(3): 322-327.

72. Filgueira GCO, Filgueira OAS, Carvalho DM, Marques MP, Moises ECD, et al. (2015) Analysis of nifedipine in human plasma and amniotic fluid by liquid chromatography-tandem mass spectrometry and its application to clinical pharmacokinetics in hypertensive pregnant women. J Chromatogr B 1(993): 20-25.

73. Hye-Sun G, In-Koo C (2006) Simplified HPLC method for the determination of prazosin in human plasma and its application to single-dose pharmacokinetics. J Appl Pharmacol 13(2): 90-94.

74. Sultana N, Shah SN, Hasan N, Arayne SM (2013) Simultaneous determination of prazosin and NSAIDs in bulk, pharmaceutical formulations and human serum by novel RP-HPLC method. Scientific Reports 2(4): 1-8.

75. He H, Li L, Zhao L, Sun N, Zhang M, et al. (2018) An improved HPLC-MS/MS method for simultaneous quantification of propranolol and its two phase I metabolites in plasma of infants with hemangioma and its application to a comparative study of plasma concentrations. RSC Advances 8: 37286-37294.

76. Cheah PY, Yuen KH, Liong ML (2000) Improved highperformance liquid chromatographic analysis of terazosin in human plasma. J Chromatography B 745(2): 439-443.

77. Singhal P, Yadav M, Winter S, Guttikar S, Patel D, et al. (2012) Enantiomeric separation of verapamil and its active metabolite, norverapamil, and simultaneous quantification in human plasma by LC-ESI-MS-MS. J Chromatogr Sci 50(9): 839-848.

78. Hedeland M, Fredricksson E, Lennernas H, Bondesson U (2004) Simultaneous quantification of the enantiomers of verapamil and its N-demethylated metabolite in human plasma using liquid chromatography-tandem mass spectrometry. J Chromatogr B 804: 303-311.

79. Borges NCC, Mendes GD, Barrientos-Astigarraga RE, Galvinas P, Oliveira CH et al. (2005) Verapamil quantification in human plasma by liquid chromatography coupled to tandem mass spectrometry. An application for bioequivalence study, J Chromatogr B 827: 165-172.

80. Ivanova-Petropulos V, Zendelovska D, Stefova M, Stafilov T (2008) HPLC method for determination of verapamil in human plasma after solid-phase extraction. J Biochem Biophys Methods 70(6):1297-1303.

81. Sawicki W (2001) A validated method for the determination of verapamil and norverapamil in human plasma. J Pharm Biomed Anal 25: 689-695.

82. Rambla-Alegre M, Gil-Agusti MT, Capella-Peiro ME, Carda-Broch S, Esteve-Romero JS (2006) Direct determination of verapamil in urine and serum samples by micellar liquid chromatography and fluorescence detection. J Chromatogr B Anal Technol Biomed Life Sci 839(1-2): 89-94.

83. Damen CWN, Rosing H, Schellens JHM, Beijnen JH (2009) Application of dried blood spots combined with high-performance liquid chromatography coupled with electrospray ionisation tandem mass spectrometry for simultaneous quantification of vincristine and actinomycin-D. Anal Bioanal Chem 394(4): 1171-1182.

84. Corona G, Casetta B, Sandron S, Vaccher E, Toffoli G (2008) Rapid and sensitive analysis of vincristine in human plasma using on-line extraction combined with liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom 22: 519-525.

85. Murry D, Classon R, Mark SS (2004) LC/MS method for the determination of vinblastine and vincristine in human plasma. AAPS J Pharm Sci 5: 81-85.

86. Dennison JB, Renbarger JI, Walterhouse DO, Jones DR, Hall DS (2008) Quantification of vincristine and its major metabolite in human plasma by high performance liquid chromatography/tandem mass spectrometry. Therapeutic Drug Monitoring 30(3): 357-364.