A SURVEY OF FEW FIXED DOSE COMBINATION PRODUCTS USED IN WEST BENGAL

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THESIS

Submitted in partial fulfillment of the requirements for the Bachelor of Pharmacy in the Netaji Subhas Chandra Bose Institute of Pharmacy under Maulana Abul Kalam Azad University of Technology

2017

Chakdaha, Nadia

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CERTIFICATE

This is to certify that **Your name**, has carried out the project work on the subject entitled "A SURVEY OF FEW FIXED DOSE COMBINATION PRODUCTS USED IN WEST BENGAL" under our supervision. He had incorporated his finding into this thesis of above title being submitted by him in partial fulfillment of the requirement for the award of the Degree of **Master of Pharmacy** of Maulana Abul Kalam Azad University of Technology, Kolkata. We are satisfied that he has carried out this project work independently and with proper care and confidence.

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Dedicated to

Father & Mother

ACKNOWLEDGMENTS

The dissertation entitled “A survey of few fixed dose combination products used in West Bengal” is by far the most significant scientific accomplishment in my life and it would be impossible without the help of those people who supported me and believed in me. The satisfaction that accompanies the successful completion of any task would be incomplete without mentioning the name of people who made it possible with constant guidance, support and encouragement that crows all efforts with success.

Finally, I would like to express my appreciation for all the efforts to everyone who have directly or indirectly contribute their ideas and energies in successful completion of my project.

Date:-June, 2017 *YOUR NAME*

CONTENTS

ABBREVIATIONS

ARB	Angiotensin Receptor Blocker
AT1	Angiotensin II receptor type 1
AT2	Angiotensin II receptor type 2
FDC	Fixed Dose Combination
RAS	Renin Angiotensin System
PPAR	Peroxisome proliferator-activated receptor
CVD	Cardio Vascular Disease
NSAID	Non-Steroidal Anti-Inflammatory Drugs

Chapter 1

1. INTRODUCTION

1.1 Introduction

Dosage forms that contain more than one active ingredient are called fixed-dose combinations (FDCs). The fixed dose combinations (FDCs) are increasingly marketed in various names either to improve patient compliance of to get synergistic effect from two or more drugs in some special treatments. They are being used presently in the treatment of wide ranging therapeutic conditions and are particularly useful in the management of chronic conditions.

Antihypertensive drugs with different mechanisms of actions like *angiotensin receptor blocker* (ARB) -Telmisartan, Losartan, *beta1-adrenergic blocker* like Atenolol are often prescribed with Amlodipine, a long acting *calcium channel blocker* (CCB). Often it is found that the antihypertensive combinations produce better patient compliance.

Proton pump inhibitors like Omeprazole, Pantoprazole, Rabeprazole are available with antiemetic Domperidone as FDCs. Domperidone has other pharmacologi effects too.

Therefore there is a requirement of surveying the frequency of use of those two categories of drugs and their FDCs to study the use or misuse of those products as FDCs.

1.2 Aim of the project

To study the use of individual drugs and FDCs in West Bengal.

1.3 Objectives

- To survey the sale of antihypertensive drugs and their FDCs in six districts of West Bengal.
- To survey the sale of antiulcer drugs and antiemetic drugs and their FDCs in six districts of West Bengal.

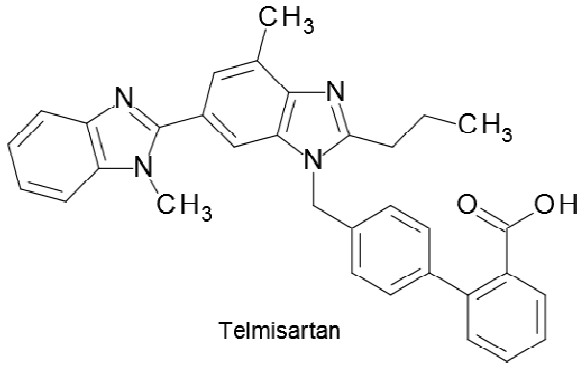
Chapter 2

2. LITERATURE SURVEY

2.1 TELMISARTAN

Telmisartan is angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. Telmisartan was discovered by Boehringer Ingelheim and was launched in the year 1999 as Micardis. (1) and Losartan was discovered by Merck & Co. Inc. as brand name Cozaar.

2.1.1 Structure and IUPAC Names



Telmisartan

***IUPAC Name*:**

2-[4-[[4-methyl -6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid (2)

Molecular Formula: $C_{33}H_{30}N_4O_2$

Molecular Weight: 514.629 g/mol

2.1.2 Pharmacokinetic Parameters

Table 2.1 Pharmacokinetic parameters of Telmisartan

Pharmacokinetic Information	**Telmisartan** (2)
Route of Elimination	> 97% through bile, <1% through urine
Volume of distribution	500 L
Total Clearance	Total plasma clearance = 800mL /min
Plasma protein binding	> 99.5%, mainly bound to albumin and α1-acid glycoprotein
Dose	40mg, 80mg orally
Plasma half life	24 hrs (3)
Bioavailability	42 – 58% orally

2.1.3 Mode of Action

Telmisartan is angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT1), with a binding affinity 3000 times greater for AT1 than AT2. In addition to blocking the Renin Angiotensin System (RAS), telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).(4) Telmisartan activates PPAR-δ receptors in several tissues. (5)

2.1.6 Drug-drug interaction

Telmisartan is contraindicated with drugs like:

- digoxin
- lithium
- a diuretic
- NSAIDs like aspirin, ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, or meloxicam, and others; or

2.2 LOSARTAN

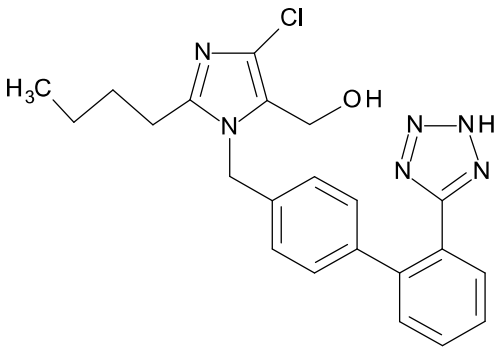
Losartan is angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. Losartan was discovered by Merck & Co. Inc. as brand name Cozaar.

2.2.1 Structure and IUPAC Name

[2-butyl-5-chloro-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]imidazol-4-yl]methanol

Molecular formula: $C_{22}H_{23}ClN_6O$

Molecular weight: 422.917 g/mol



Losartan

2.2.2 Pharmacokinetic Parameters

Table 2.2 Pharmacokinetic parameters of Losartan

Pharmacokinetic Information	**Losartan** (11)
Route of Elimination	After oral administration 35% through urine and 60% through feces. After IV administration 45% through urine and 50% through feces.
Volume of distribution	Unchanged drug 34L Active metabolite 12L
Total Clearance	Total plasma clearance = 600 mL/min [losartan] Total plasma clearance = 50 mL/min [active metabolite] Renal clearance = 75 mL/min [losartan] Renal clearance = 25 mL/min [active metabolite]
Plasma protein binding	> 98.7%, mainly bound to albumin
Dose	25mg, 50mg, 100mg orally
Plasma half life	Unchanged drug: 2 hrs. Active metabolite: 6-9 hrs
Bioavailability	Approximately 33% (Undergoes first-pass metabolism)

2.2.3 Mode of Action

Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than Losartan and acts as a non-competitive AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is 1,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion.

Chapter 3

3. COMBINATION THERAPY

3.1 Definition

Combination therapy or **polytherapy** is therapy that uses more than one medication. Typically, these terms refer to using multiple therapies to treat a single disease, and often all the therapies are pharmaceutical (although it can also involve non-medical therapy, such as the combination of medications and talk therapy to treat depression). 'Pharmaceutical' combination therapy may be achieved by prescribing or administering separate drugs. Dosage forms that contain more than one active ingredient are called **fixed-dose combinations**.

Polypharmacy is a related term, referring to the use of multiple medications (without regard to whether they are for the same or separate conditions/diseases). Sometimes "polymedicine" is used to refer to pharmaceutical combination therapy. Most of these kinds of terms lack a universally consistent definition, so caution and clarification are often advisable.

Combination therapy is frequently prescribed by physicians to treat and manage a plethora of medical conditions; however, without thorough monitoring, various problems can arise. In some cases, patients must try several different combinations of drugs before finding the best therapy to successfully treat a medical condition. Pharmacists can be instrumental in ensuring that combination drug therapy is used appropriately by screening for potential drug–drug interactions, contraindications, or both, and by making therapeutic recommendations aimed at achieving optimal response without increasing the potential for adverse drug reactions. Pharmacists also can identify possible cases of polypharmacy, especially among elderly patients and those with multiple medical conditions. Combination drug therapies can offer additive benefits that target multiple pathologic processes.

3.2 Rationale for Combination Therapy

- Combination drug therapy can be used initially or added gradually if the therapeutic response with monotherapy is not as expected.
- Fixed dose combination therapy provides the convenience of administering fewer pills to a patient to take daily and reduced potential for medication errors. Thus it

enhance the patient compliance and simpler drug regimens may increase the likelihood of patient adherence to the dosage regimen.

- Medication costs may also decrease when drugs are combined in fixed-dose combination formulations.
- Combined agents also may minimize the adverse effects of each individual agent.

3.3 Uses of combination therapy

Conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria, and HIV/AIDS. One major benefit of combination therapies is that they reduce development of drug resistance, since a pathogen or tumor is less likely to have resistance to multiple drugs simultaneously. Artemisinin based monotherapies for malaria are explicitly discouraged to avoid the problem of developing resistance to the newer treatment.

Table 3.1 Examples of combination drug regimens for common medical conditions (33)

Condition	Possible drug combinations
Heart failure	Diuretic + beta-blocker + ACEI/ARB ± Aldosterone blocker ± digoxin
Post myocardial infarction	Aspirin, beta-blocker, ACEI/ARB, statin
Hypertension (> stage 1)	Combination of at least 2 of te following agents: ACEI/ARB, CCB, diuretic, beta-blocker.

* ACEI=Angiotensin Converting Inhibitor; ARB=Antiotensin II receptor Blocker; CCB=Calcium channel blocker.

Chapter 4

4. EXPERIMENTAL

4.1 Survey questionnaire

A questionnaire represented in Appendix-1 was prepared with information of a medical shop and its address. The shop owner was asked about the number of strips of a certain drug or fixed combination product (FDC) sold per day. Data regarding two categories of drugs and their FDCs were placed in the form. First category contains individual and FDCs of antihypertensive drug combination and the second was proton pump inhibitors with an antiemetic drug domperidone. Finally the name of the interviewee, his/her signature, contact number and the date of interview was finally taken to ascertain the authenticity of the survey.

4.2 Study population

Medicine shops of six districts of West Bengal were selected at random. The districts were North 24 Parganas, Burdwan, Hoogly, Howrah, Murshidabad and Nadia. Survey was carried out in 20 shops of North 24 Parganas, 2 shops of Burdwan, 18 shops of Hoogly, one shop of Howrah, 7 shops of Howrah and 5 shops of Nadia district respectively.

Chapter 5

5. RESULTS AND DISCUSSION

5.1 Survey result of antihypertensive drugs and their FDCs sold per day

The number of strips of antihypertensive drugs – Telmisartan, Losartan, Atenolol and Amlodipine sold per day is displayed in Table 5.1. The mean and standard deviation (SD) values are also determined. The mean values, when plotted as a histogram it is evident that in this six districts of West Bengal individual Amlodipine sale is highest at 10 strips per day. The individual drugs- Telmisartan, Losartan, Atenolol and their combination products are found to be same in Figure 5.1.

Table 5.1 Average number of strips of antihypertensive drugs and their FDCs sold per day

District	Telmisartan	Losartan	Atenolol	Amlodipine	Telmi sartan + Amlodipine	Losartan + Amlodipine	Atenolol + Amlodipine
24 Pgs(N)	4.5	3.9	2.5	9.5	3.7	2.4	3.2
Burdwan	7.0	2.5	5.5	15.0	4.0	1.5	6.5
Hoogly	5.0	4.4	3.6	10.5	4.2	3.7	3.9
Howrah	8	5	5	10	6	6	10
Murshidabad	1.7	1.4	1.3	4.1	2.0	2.0	0.7
Nadia	7	4.4	3.4	11.4	2.4	3.4	2.6
Mean	**5.5**	**3.6**	**3.5**	**10.1**	**3.7**	**3.2**	**4.5**
SD	**2.29**	**1.37**	**1.57**	**3.52**	**1.43**	**1.62**	**3.29**

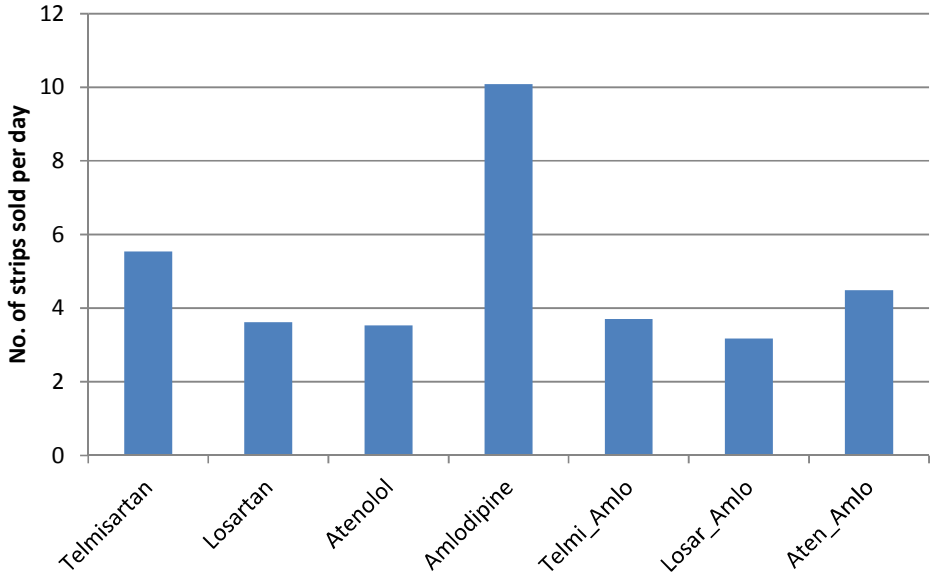


Figure 5.1 No. of strips of different antihypertensive drugs and their FDCs sold per day

The number of strips of antihypertensive drugs – antiulcer and antiemetic drugs and their FDCs per day is displayed in Table 5.2. The mean and standard deviation (SD) values are also determined. The mean values, when plotted as a histogram (Figure 5.2) it is evident that in these six districts of West Bengal the sale of individual proton pump inhibitors and their FDCs with Domperidone are significantly high. There is a correlation between the individual drugs and their FDCs, except Domperidone. FDCs with the antimemetic drug Domperidone was found to be rarely sold (3.3 strips per day) compared to FDCs containing it.

CHAPTER 6: CONCLUSION

Dosage forms that contain more than one active ingredient are called fixed-dose combinations (FDCs). They are used for better patient compliance. However the FDCs cannot be used indiscriminately.

In case of antiulcer drugs combined with an antiemetic drug like domperidone is found to be sold similarly high number in contrast to their individual counterpart. Use of antiemetic agent Domperidone is extremely low compared to its FDCs. Therefore there is every possibility of precipitation of side effects of Domperidone if the FDCs containing it is prescribed indiscriminately.

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APPENDIX -1

SURVEY FORM FOR MEDICAL SHOP

Name of the Medical Shop _____

Address: _____

SALE (Strips / day)

Telmisartan	Losartan	Atenolol	Amlodipine	Telmisartan + Amlodipine	Losartan + Amlodipine	Atenolol + Amlodipine

Omeprazole	Pantoprazole	Rabeprazole	Domperidone	Omeprazole + Domperidone	Pantoprazole + Domperidone	Rabeprazole + Domperidone

Name of Interviewee _____ Signature _____ Contact No. _____ Date: _____

END