International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-4, 2015 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Evaluation of Drug-Drug Interactions between Active Pharmacological Ingredients of Fixed Dose Combinations of Cardiovascular System Enlisted in CDSCO List

Gor AP[1], Dalal KB*[2], Ganguly BP[3]

[1]*Associate Professor, Dept. of Pharmacology, Pramukhswami Medical College, Karamsad, Gujarat, India.*
[2]*Final Year Resident, Dept. of Pharmacology, Pramukhswami Medical College, Karamsad, Gujarat, India.*
[3]*Professor & Head, Dept. of Pharmacology, Pramukhswami Medical College, Karamsad, Gujarat, India.*

Manuscript No: IJPRS/V4/I4/00228, Received On: 24/12/2015, Accepted On: 28/12/2015

ABSTRACT

Drug-drug interaction between active pharmacological ingredients is a significant criterion for evaluation of rationality of fixed dose combinations (FDCs). Being combination therapy is useful as treatment of cardiac disorders, there have been umpteenth cardiovascular FDCs marketed in India. Aim of this study was evaluation of drug-drug interactions of cardiovascular FDCs enlisted in CDSCO list from 2009 to 2015. According to inclusion criteria, 51 such cardiovascular FDCs from CDSCO were selected for analysis. Scientific evidence for cardiovascular FDCs was assessed using accessible electronic and print sources like Medscape and standard textbooks and descriptive statistics was applied. Maximum numbers of FDCs 19 (37.25%) were enlisted in CDSCO from 2010. All fixed dose combinations 51 (100%) from cardiovascular system were having oral dosage form. Fixed dose combinations 40 (78.43%) were having 2 active pharmacological ingredients. There were 17 (33.33%) combinations found to be Pharmacodynamic drug interaction whereas 3 combinations were having pharmacokinetic interactions between active pharmacological ingredients (APIs). There have been many numbers of FDCs approved by CDSCO in comparison with WHO essential medicine list and national list of essential medicines. Adverse DDIs between API of FDCs can increase morbidity and economic burden of patients. To lower the frequency of potential interactions, it could be necessary to make a careful selection of therapeutic alternatives and in cases without other options, patients should be continuously monitored to identify adverse events.

KEYWORDS

Fixed dose combinations, Drug-drug interactions, Cardiovascular

INTRODUCTION

A drug interaction can be defined as an interaction between a drug and another substance that prevents the drug from performing as expected. This definition applies to interactions of drugs with other drugs (drug-drug interactions (DDIs), as well as drugs with food (drug-food interactions) and other substances.[1]

***Address for Correspondence:**
Dalal Krunal B
Department of Pharmacology,
Pramukh Swami Medical College,
Shree Krishna Hospital, Karamsad – 388325, Gujarat, India
E-Mail Id: dalalkrunal@yahoo.co.in

Adverse DDIs is a major cause of morbidity and mortality. Hence, DDIs are important hazards to the health of millions of patients, they have to be tackled, and it is the need of the hour. In 2014, 53% of the deaths were due to chronic diseases of which 29% was cardiovascular diseases (CVD). By 2020, CVD will be the largest cause of deaths in India.[2] Trend of prescribing multiple drugs has been increasing in cardiovascular diseases. Combination therapy can be two or more agents administered separately or in a fixed-dose combination (FDC), and the latter

seems to be more popular in clinical practice based on its advantages in terms of convenience, cost, compliance, efficacy and aggressive effects.[3] Drug interaction between active pharmacological ingredients (APIs) is a very important criterion for rationality assessment.[4] Although many cardiovascular FDCs marketed till date, interactions between API has not been studied carefully which may be the reason for increasing adverse drug reaction. So our aim of this study was evaluation of drug-drug interactions of cardiovascular FDCs enlisted in CDSCO list.

MATERIAL AND METHODS

It is a descriptive study based on FDCs of cardiovascular drugs enlisted in Central Drug Standard and Control Organization (CDSCO) 2009 to 2014. Ethical approval was taken from the Institutional Human Research Ethics Committee prior to study.

Inclusion Criteria

All FDCs of cardiovascular system enlisted in CDSCO from 2009 to 2014 were selected for analysis.[5]

Exclusion Criteria

Fixed dose combinations having topical dosage forms were excluded.

According to inclusion criteria, 51 such cardiovascular FDCs from CDSCO were selected for analysis. The following were recorded from each combination: (1) Dosage form (2) Number of Active Pharmacological Ingredient (API) (3) Pharmacodynamic (PD) and pharmacokinetic (PK) parameters of APIs of combination (4) PK & PD interaction.

Scientific evidence for cardiovascular FDCs was assessed using accessible electronic and print sources of drug information like Medical journals, standard Pharmacology and Medicine text books, Pharmacopoeias, Formulary, Cochrane database, Pub Med etc.[6-11]

Statistical Analysis

Descriptive statistics in terms of frequency counts and percentages were used for variables.

RESULTS AND DISCUSSION

There were 51 fixed dose combinations of cardiovascular system selected from CDSCO list from 2009 to 2014 for evaluation of drug-drug interactions between active pharmacological ingredients (Table 1). Maximum numbers of FDCs 19 (37.25%) were enlisted in CDSCO from 2010 followed by 13 (25.49%) from 2009 and 2010 each. None of FDC was enlisted from 2012 (Figure 2).

All fixed dose combinations 51 (100%) from cardiovascular system were having oral dosage form. Maximum fixed dose combinations 40 (78.43%) were having 2 active pharmacological ingredients followed by 8 (15.68%) combinations were having 3 API, 2 (3.92%) were with 4 API whereas only one combination was having 5 API (Table 1).

Table 1: Demographic Data of Fixed Dose Combinations of Cardiovascular System Drugs from CDSCO2009 to 2014

Sr. no.	Demographic parameter		CDSCO n (%)
1	Total numbers of FDCs (API Combinations)		51
2	Dosage forms of FDCs	Oral	51 (100)
		Parenteral	0 (0)
3	Numbers of API included in FDCs	2	40 (78.43)
		3	8 (15.68)
		4	2 (3.92)
		5	1 (1.96)

In cardiovascular system, out of 51 combinations 20 FDCs were found having drug-drug interactions. There were 17 (33.33%) combinations were found to be Pharmacodynamic drug interaction whereas 3 combinations were having pharmacokinetic interactions between active pharmacological ingredients (Figure 2).

Few potential drug-drug interactions between active pharmacological ingredients of cardio-vascular fixed dose combinations were shown in table 2.

Table 2: Potential interactions between active pharmacological ingredients of FDCs

Sr no.	Fixed dose combinations (Strength in mg)	Effect	Type
1	Amlodipine 5/2.5+ Hydrochlorothiazide 25/12.5 + Olmesartan 40	Hypotension	Pharmacodynamic
2	Telmisartan 20 + Amlodipine 2.5+ Hydrochlorothizide 6.25	Hypotension	Pharmacodynamic
3	Rosuvastatin5/5/5/10/10/10/20 + Fenofibrate67.5/145/160/67.5/145/160/160	Increase chances of myalgia	Pharmacodynamic synergism
4	Metoprolol 25 +Telmisartan 40	Increase potassium level	Pharmacodynamic synergism
5	Niacin 1000 + Laropiprant 20	Increase blood, lymph and respiratory ADRs	Pharmacokinetic
6	Amlodipine 5/2.5 + Valsartan 320 /80 + HCTZ 12.5 /12.5	Hypotension	Pharmacodynamic
7	Metoprolol 25/50+ Olmesartan 20/20	Increase potassium level	Pharmacodynamic synergism
8	Aspirin 75 + Simvastatin 10/20+ Lisinopril 5/10 + Atenolol 25/50	Increase renal dysfunction and potassium level	Pharmacodynamic antagonism
9	Telmisartan 40/80 + Indapamide 1.5/1.5	Hypotension	Pharmacodynamic synergism
10	Atorvastatin10 + Ramipril 5 + Aspirin 75/150 + Metoprolol 25	Increase renal dysfunction and potassium level	Pharmacodynamic antagonism
11	Atorvastatin 5 + Fenofibrate 145	Increase chances of myalgia	Pharmacodynamic synergism
12	Aliskiren 150/160 + Valsartan 300/320	Increase risk of Hypotension, hyperkalemia and renal impairment	Pharmacodynamic and pharmacokinetic
13	Simvastatin 20 + Ramipril 5 + Atenolol 50 + HCTZ 12.5 + Aspirin 100	Increase renal dysfunction and potassium level	Pharmacodynamic antagonism and Pharmacokinetic
14	Losartan 100 + HCTZ 25	Hypotension	Pharmacodynamic synergism
15	Prasugrel 10 + Aspirin 75	Increase risk of bleeding	Pharmacodynamic synergism

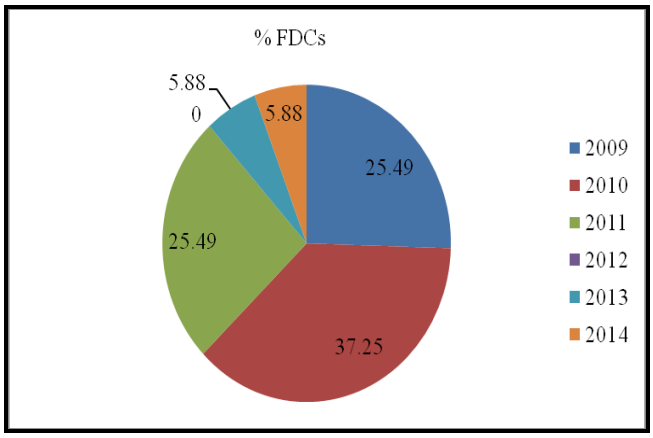

Figure 1: Distribution of FDCs of Cardiovascular Drugs According to Year Wise

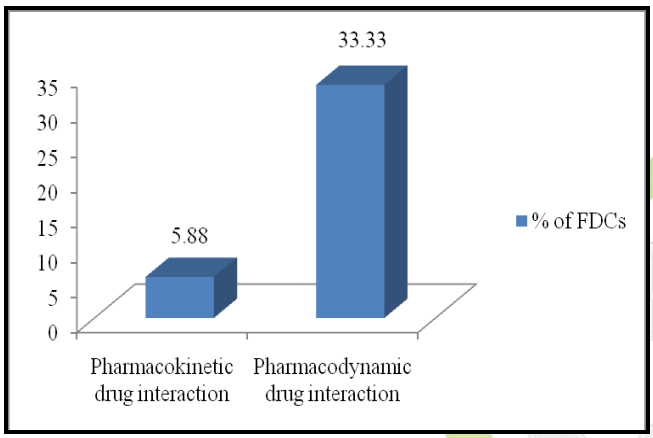

Figure 2: Evaluation of PK and PD Interactions of Active Pharmacological Ingredients in Cardiovascular Fixed Dose Combinations

Drug-drug interactions [DDIs] are becoming serious issue with complex drug therapies. DDIs can result in anything from minor morbidities up to fatal consequences. Studies have shown that up to 11% of outpatients experience symptoms associated with DDIs and DDIs are responsible for up to 2.8% of hospital admissions.[12] DDIs cause 4.8% of the hospitalizations in the elderly people.[13] They are attributed to polypharmacy, noncompliance of the patients, and deterioration because of illnesses or secondary infections.[14]

According to standard textbooks and references, we found that there was a possibility of having PK interaction with 3 (5.88%) combinations and PD interactions with 17 (33.33%) combinations from cardiovascular system. Most of other studies on evaluation of drug-drug interactions of fixed dose combinations were related to prescribing pattern of combinations in different set up and diseases.[4,15] The combination of ARB/ACE inhibitor and hydrochlorothiazide has advantage of improved efficacy since numerous previous studies have demonstrated that activation of renin angiotensin – aldosterone system (RAAS) by hydrochlorothiazide enhances the effects of agents acting through blockade of this pathway. When the patient is salt loaded the BP becomes volume dependent and the antihypertensive effect of the agents acting through RAAS is decreased. This effect can be resolved with the addition of diuretic as the BP becomes more rennin dependent.

The addition of losartan ameliorates the hypokalemia associated with the use of hydrochlorothiazide diuretics.[16] But this combination produces first dose postural hypotension which should be monitored.[10]In present study we have found such FDCs like Losartan 100 + HCTZ 25, Amlodipine 5/2.5 + Valsartan 320 /80 + HCTZ 12.5 /12.5 and Amlodipine 5/2.5 + Hydrochlorothiazide 25/12.5 + Olmesartan 40 were approved by CDSCO (Table 2).

Fenofibrate and rosuvastatin increases effects of each other by pharmacodynamic synergism. Fenofibrate may further increase risk for rhabdomyolysis when added to optimal statin regimen to further decrease TG and increase HDLs.[10,17] There were four different dose strength of FDC Fenofibrate + Rosuvastatin enlisted in CDSCO list.[5]

Although synergism with Beta blocker and ARB combination, it increases risk of fetal compromise if given during pregnancy. In addition this FDC increases potassium level.[10,18] Examples of such combinations were approved by CDSCO in this study like Metoprolol 25 + Telmisartan 40 and Metoprolol 25/50+ Olmesartan 20/20.

The need for simultaneous use of low-dose aspirin and anticoagulant or antiplatelet prasugrel agents are common for patients with cardiovascular disease; but this combination increases risk of bleeding by acting on same pathway.[10,19]

In this study we evaluated two combinations having four active pharmacological ingredients i.e. Atorvastatin10 + Ramipril 5 + Aspirin 75/150 + Metoprolol 25 and Simvastatin 20 + Ramipril 5 + Atenolol 50 + HCTZ 12.5 + Aspirin 100 (Table 2). Although there has been no defined rule for the permissible maximum number of constituents in the FDCs, any FDC containing >3 ingredients should be looked at watchfully as US FDA states that there is no rationale of combining >3 ingredients and chances of interactions would become increases.[20] Aspirin decreases effects of atenolol/lisinopril by pharmacodynamic antagonism. NSAIDs decrease synthesis of vasodilating renal prostaglandins, and thus affect fluid homeostasis and may diminish antihypertensive effect. In addition atenolol and aspirin both increase serum potassium.[10]

Aliskiren + Valsartan (Table 2). Either increases toxicity of the other by pharmacodynamic synergism. Dual blockade of renin-angiotensin system increases risks of hypotension, hyperkalemia, and renal impairment.[18]

CONCLUSION

Thus it can be concluded that the majority of pharmacodynamic interactions between API of CVS fixed dose combinations which even increases morbidity. Continuing education of prescribers and use of electronic support tools may help abate the problem, and follow up may be needed to ascertain the clinical consequences of important interactions. Patients with cardiovascular diseases and those who are prescribed multiple medications need to be monitored more closely as these are at a higher risk of potential DDIs.

REFERENCES

1. Chavda, N. B., Solanky, P. P., Baria, H., Naik, R., & Bharti, K. (2015). Study of potential drug–drug interaction between prescribed drugs in patients attending outpatient department of medicine at tertiary-care hospital in south Gujarat region. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(3).
2. Fact sheet on CVDs. Available from: http://www.who.int/cardiovascular_diseases/en/
3. Woodcock, J., Griffin, J. P., & Behrman, R. E. (2011). Development of novel combination therapies. *New England Journal of Medicine*, *364*(11), 985-987.
4. Manjula Devi, A. S., Sriram, S., Rajalingam, B., Alfet Raju, A., Varghese, R. S., & Venkata Phani, A. (2012). Evaluation of the rationality of fixed dose combinations of cardiovascular drugs in a multispecialty tertiary care hospital in Coimbatore, Tamilnadu, India. *Hygeia Journal for Drugs and Medicines*, *4*, 51-58.
5. Fixed dose combinations approved by DCGI (i) since 1961 till November, 2014.Available from: http://www.cdsco.nic.in/writereaddata/FDCapproved_dcgi(1)_2013.pdf
6. Jadav, S. P., & Parmar, D. M. (2011). Critical appraisal of irrational drug combinations: A call for awareness in undergraduate medical students. *Journal of Pharmacology & pharmacotherapeutics*, *2*(1), 45.
7. Policy guidelines for approval of fixed dose combinations (fdcs) in India. Available from: http://www.mohfw.nic.in/WriteReadData/l892s/6404452866Kokate%20Report.pdf
8. Sharma, H. L., Sharma, K. L. (2013). Principals of pharmacology. 2nd ed. Hyderabad: *Paras Medical Publisher.*
9. Tripathi, K. D. (2013). Essentials of medical pharmacology.7thed. New Delhi: *Jaypeebrothers medical publishers (P) LTD.*
10. Drug interaction checker. Available from: http://www.drugs.com/drug_interactions.html
11. Usp, D. I. (2003). Drug information for the health care professional. *Antidepressants*, *26*, 296-314.

12. Aparasu, R., Baer, R., & Aparasu, A. (2007). Clinically important potential drug-drug interactions in outpatient settings. *Research in Social and Administrative Pharmacy*, *3*(4), 426-437.

13. Doucet, J., Chassagne, P., Trivalle, C., Landrin, I., Pauty, M. D., Kadri, N., & Bercoff, E. (1996). Drug-drug interactions related to hospital admissions in older adults: A prospective study of 1000 patients. *Journal of the American Geriatrics Society*, *44*(8), 944-948.

14. Seymour, R. M., & Routledge, P. A. (1998). Important drug-drug interactions in the elderly. *Drugs & Aging*, *12*(6), 485-494.

15. Soherwardi, S., & Chogtu, B. (2012). Surveillance of the potential drug-drug interactions in the medicine department of a tertiary care hospital. *Journal of Clinical and Diagnostic Research*, *6*(7), 1258-1261.

16. Panda, J., Tiwari, P., & Uppal, R. (2006). Evaluation of the rationality of some FDCs: Focus on antihypertensive drugs. *Indian Journal of Pharmaceutical Sciences*, *68*(5), 649.

17. Sharma, H. L., Sharma, K. L. (2013). Principals of pharmacology. 2nd ed. Hyderabad: *Paras Medical Publisher*, 324-35.

18. Sharma, H. L., Sharma, K. L. (2013). Principals of pharmacology. 2nd ed. Hyderabad: *Paras Medical Publisher*, 258-276.

19. Sharma, H. L., Sharma, K. L. (2013). Principals of pharmacology. 2nd ed. Hyderabad: *Paras Medical Publisher*, 655-671.

20. Hussein, S. H. (1996). *Cough mixtures*. Available from: http://www.prn2.usm.my/mainsite/bulletin/sun/1996/sun39.html.

