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MONTELUKAST AND LEVOCETERIZINE FIXED DOSE COMBINATION-AN EVIDENCE REVIEW

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ABSTRACT

Indian pharma market is flooded with various fixed drug combinations. Among them, one of the widely used FDC is montelukast + levocetirizine. This is prescribed for the patients of any age group (paediatrics, adults and geriatric) and used as a long term therapy for the treatment of conditions such as prophylaxis, acute and chronic types of asthma, relief of symptoms of seasonal and perennial allergic rhinitis, prevention of exercise induced bronchoconstriction and chronic idiopathic urticaria. It is very essential to check the rational use of this FDC. Generally fixed dose combinations create confusions among physicians, because it contains more than one drug in various doses and it is very difficult to remember all these details and another issue with the FDCs are that the entire FDC cannot be used if the patient is contraindicated to any of the drug in the FDC. And patient specific dose calculation is also difficult with FDCs. There are very less clinical trial data available about the safety and efficacy of this agent. Objective of this review article is to check the rational use of montelukast levocetirizine FDC. To achieve the objective, all the literatures related to montelukast levocetirizine FDC were collected and analysed. The study concluded that some differences are there in the pharmacokinetic parameters of both these agents includes duration of action. In dosing also, levocetirizine dose can vary from 2.5m^{g} to 10mg once daily whereas montelukast dosing is 10mg. Rationality of this FDC can be further supported by more clinical trial data to conform the rationality of these FDC.

KEYWORDS: ***Montelukast, levocetirizine, Rationality, Safety,Efficacy***

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INTRODUCTION

Rational drug use defined by WHO "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and the lowest cost to them and to their community"[1]. Fixed dose combination can be defined as a single dosage form which includes two or three active pharmaceutical ingredients, manufactured and distributed in fixed doses. FDCs of drugs are important for public health perspective and commonly used for treatments of pain and inflammation, hypertension, diabetes mellitus, tuberculosis, malaria, HIV etc[2]. Thousands of FDCs are available in India[3]. FDCs have advantages like they offer a simple dosage schedule which improves patient complaints and therefore improves treatment outcome. However FDCs have certain disadvantages like FDCs can confuse physician because it contain multiple ingredients and doses. Since fixed dose combination contain more than one drug and it may cause therapeutic confusion that every patient may not need all the drugs in an FDC and in case if any of these drugs in the FDC is contraindicated to a patient causes the entire FDC unfit for the therapy. Every patient is unique and characteristic such as weight, age, co-morbidities will demand individualised dose calculation which is not possible for FDCs. The rationality of FDCs should be based on certain aspects such as the drugs in the combination should act by different mechanisms, the pharmacokinetics must not be widely different and the combination should not have supra-additive toxicity of the ingredients. And most FDCs have the demerits like dosage alteration of one drug is not possible without alteration of the other drug. Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation and by simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually[4].

Approval of FDCs in India

FDC in India is treated as new drug as per the rule 122E of drugs and cosmetic rule. This is because of the fact that by combining two or more drugs the safety efficacy and bioavailability of the individual API may change. DCGI (Drug controller general of India) is the licensing authority notified under section21 (b) of drugs and cosmetic act. The rationality of FDC is examined in the office of DCGI as per the provision of schedule Y before its market authorisation in the country. The applicant pharmaceutical company should submit exhaustive information justifying the rational of the FDC is in question. The examination process also involves external experts in their relevant field including pharmacologist. The safety and efficacy is later ascertained by conducting clinical trial and bioequivalence studies. Once the data from clinical study has been found satisfactory by the DCGI, permission to manufacture and market the FDC is granted[4, 5, 6, and 7]. Indian pharma market is flooded with various irrational FDCs; recently the Health Ministry banned 344 FDCs through a gazette notification. These include several common cough syrup solutions, analgesics and antibiotic combination, many of which are sold over the counter. The reason for banning FDC is the irrational use of drugs in the market[8].There are millions of unapproved, unsafe, dangerous and even lethal drugs being sold in the Indian market. It is mandatory for FDCs to get an approval from the CDSCO (Central drugs standard control organisation) since 1961; however, there are still a large proportion of unapproved FDC drugs often sold over the counter in the country. One such example is selling a combination of the antibiotics cefixime and azithromycin without an approval from the central government. This combination is not approved for sale in major pharmaceutical market including US, UK, Germany, France and Japan. After the ban, the company was forced to immediately stop the manufacture and sale of its powerful antimicrobial agent. In 2007, the CDSCO banned from sale of about 294 FDCs because they had never been approved by the central regulation but had been granted manufacturing/ distributing licenses by state drug authorities, and the list was published in 2014.[9, 10] Unofficially it has been found that about 1000's of drugs are under constant vigilation and they are at an increased risk of being banned. For thetime being they are given a warning which may be taken back if the rationality of these drugs is not improved. About 344 FDC's were banned in India by the health ministry in the year 2016 including fixed dose combination of Levocetirizine+ Montelukast+ Acebrophyline. Montelukast and levocetirizineis one of the widely used FDC in India, which is used as a long term therapy in all age population (Infants, children, adults and geriatrics) for the treatment of conditions such as prophylaxis, acute and chronic types of asthma, relief of symptoms of seasonal and perennial allergic rhinitis, prevention of exercise induced bronchoconstriction and chronic idiopathic urticaria. However the studies about the rationality behind the FDC is not available in India and hence

an assessment is required as it will help clinician to get an evidence based analysis about this FDC and thereby improves the patient compliance. Hence the awareness of society towards this FDC can be improved. The use of Montelukast in the case of reversal of bronchospasm in acute asthma attacks is not approved by the FDA.

METHODS

This was an evidence review conducted with an aim to check the rationality of Montelukast + levocetirizine FDC. The study period was 3 months. Materials and methods used in the study were as follows:

Identifying the scope of the work

Montelukast levocetirizine FDC is one of the widely prescribed fixed drug combinations in India. It is widely prescribed for paediatric patients also. Hence, it was very important to check the available evidence to confirm the rationality of the same.

Collection of data

All the open access articles about montelukast and levocetirizine in Medline & Pub-med were collected. Drug Information Software Lexicomp was used to study the PK/PD of both the drug. Detailed pharmacokinetic and pharmacodynamic data were collected separately for both levocetirizine and montelukast from Lexicomp.

Analysing the data

Pharmacokinetic and pharmacodynamic parameters of both these drugs were compared using the data from software Lexicomp to check whether it is justified to give both these agents as an FDC. All the available literature were analysed to check whether the rationality of this FDC was proven in any of the clinical trial conducted in India.

DISCUSSION

Pharmacology of montelukast and levocetirizine

The pharmacokinetic and pharmacodynamic properties of Monteleukast and levocetirizine are compared in the following Table-1.

Table 1

Pharmacology of Montelukast and levocetirizine (Reference: Lexicomp)

Characteristics	Monteleukast	Levocetirizine
THERAPEUTIC CLASS	Leukotriene Receptor Antagonist	Histamine H1 Antagonist
ABSORPTION	Rapid	rapid and extensive
DISTRIBUTION	Volume of distribution : 8 to 11 L	Vd (1-2 yrs)oral sol:0.37±0.06 L/kg (6-11yrs) oral tab: 0.4±0.02 L/kg adults :0.4 L /kg
METABOLISM	extensively hepatic via CYP3A4,2C8& 2C9	minimal (<14%)via aromatic oxidation, N & O dealkylation(CYPA4) and taurine conjugation
EXCRETION	Faeces:86%, urine< 0.2%	urine 85.4%, faeces 12.9% clearance- children(1-2 yrs) oral sol: 1.05± 0.1 ml /min/kg children-(6-11yrs) oral tab 0.82±0.05ml/min/kg adults-0.63ml/kg/min
TIME TO PEAK	Tab 10mg- 3-4 hrs(fasting) chewable tablet-4mg(2- 5 yrs) 2 hrs(fasting) chewable tablet 5mg 2-2.5hrs(fasting) granules 2.3±1 hrs (fasting) and 6.4±2.9hrs with high fat meal	children 1-2 yrs oral sol(range 1-6 hrs) 6-11 yrs oral tab 1.2 ±0.2 hrs adults oral sol 0.5 hrs tab 0.9 hr
DURATION OF ACTION	>24 hrs	24 hr

HALF LIFE ELIMINATION	2.7-5.5 hrs, mild to moderate hepatic impairment 7.4 hrs, slightly longer in elderly patient	Children 1-2 yrs oral sol 4.09± 0.67 hrs children 6-11 yrs oral tab 5.7± 0.2hrs adults approximately 8-9 hrs. renal impairment- half-life increased by 1.4,2, 2.9 & 4 fold, slightly shorter in women than in men
PLASMA PROTEIN BINDING	>99%	91-92%
AUC(area under plasma drug conc.vs. time curve)	Hepatic impairment- increased 41%	Patient with all stage of renal impairment AUC increased by 1.8, 3.2, 4.3, & 5.7
INDICATIONS	Prophylaxis and chronic treatment of asthma, relief of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis prevention of exercise? induced bronchoconstriction	Chronic idiopathic urticaria, perennial allergic rhinitis(6months and older), seasonal allergic rhinitis(>2yrs)
CONTRAINDICATIONS	Hypersensitivity	hypersensitivity, ESRD, haemodialysis, 6 months -11yrs age infants and children with renal impairment
DOSING	Allergic rhinitis, asthma (patients with both also)-10mg once daily bronchoconstriction, exercise induced (prevention) oral 10mg at least 2 hrs prior to exercise (additional dose should not be administered within 24 hrs) chronic urticaria& NSAID induced urticaria oral 10mg 0nce daily.	perennial and seasonal allergic rhinitis oral 5mg once daily(some experience relief of symptoms with 2.5 mg once daily) chronic idiopathic urticaria oral 5mg once daily(some experience relief of symptoms with 2.5 mg once daily)
TIME OF ADMINISTRATION	evening	evening
DOSING IN PAEDIATRIC	ASTHMA: (oral) 1-2 yrs -4mg once daily in the evening 2-6 yrs 4mg once daily in the evening 6-15 yrs 5mg once daily in the evening > 15 yrs 10mg once daily in the evening BRONCHOCONSTRICTION exercise induced(prevention) (oral) 6-15 yrs- 5mg at least 2 hrs prior to exercise ≥15 yrs 10mg once daily at least 2 hr prior to exercise PERRENIAL ALLERGIC RHINITIS: 6months to 2 yrs 4mg once daily ,2-6 yrs 4mg once daily, 6-15 yrs 5mg once daily ,≥15 yrs 10mg once daily SEASONAL ALLERGIC	PERRENIAL ALLERGIC RHINITIS, CHRONIC URTICARIA(oral) 6 months - 5yrs 1.25 mg once daily in the evening(max dose -1.25 mg per day) 6-11yrs 2.5mg once daily in the evening(max dose- 2.5mg per day) ≥12 yrs and adolescence- adult dose.

	RHINITIS (oral) 2-6 yrs 4mg once daily ,6-15 yrs 5mg once daily, adolescence ≥15 yrs 10 mg once daily.	
DOSING IN RENAL IMPAIRMENT	no dosage adjustment necessary	children ≥12 yrs , adolescents and adults CrCl 50 -80 ml /min: 2.5mg once daily , CrCl 30-50ml/min 2.5 mg once every other day, CrCl 10-30 ml /min 2.5 mg twice weekly(every 3-4 days), CrCl<10ml/min, haemodialysis,6months -11yrs children with renal impairment patients use is contraindicated
DOSING IN HEPATIC IMPAIRMENT	mild to moderate: no dosage adjustment necessary severe impairment: has not been studied	no dosage adjustment necessary
ADMINISTRATION	patient with asthma and both asthma and allergic rhinitis single dose in the evening, allergic rhinitis may individualise administration time	oral: administer in the evening without regards to meal
STORAGE	room temp 25 0C (77 0F) protect from moisture and light, store in original package, granules must be used within 15 min of opening packets	store at 20- 25oC (68-77 0F)

Both the drugs montelukast and levocetirizine comes under the immunosuppressant of which montelukast is a Leukotriene receptor antagonist and levocetirizine is a histamine H1 antagonist. The metabolism is extensively hepatic via CYP3A4, 2C8 and 2C9 in case of montelukast and is minimal (<14%) via aromatic oxidation, N and O dealkylation (CYPA4) and taurine conjugation in case of levocetirizine. The excretion is through urine and faces in both the cases. The duration is greater than 24 hours in case of montelukast and 24 hour in case of levocetirizine. Dosing of montelukast for the indications is 10mg once daily, whereas in levocetirizine the dose varies from 2.5mg to 5mg once daily, hence when they are made into a fixed drug combination the appropriate dosing required for the patient may not be achieved.The FDC of Levocetirizine + Montelukast available in Indian market is montelukast 10mg+ levocetirizine 5mg. When dose adjustment for renal impairment is taken montelukast does not require a dose adjustment whereas levocetirizine requires it. Dose adjustment in case of hepatic impairment whether required or not is fully studied in case of montelukast for severe hepatic impairments. Table -2, Table -3.

Table 2
Adverse drug reactions of montelukast (Reference: Lexicomp Software)

System	Problems
Children ≥ 15 years and adults	
Central nervous system	Headache (18%), dizziness (2%), fatigue (2%), fever (2%)
Dermatologic	Skin rash (2%)
Gastrointestinal tract	Dyspepsia (2%), gastroenteritis (2%), toothache (2%)
Hepatic	Increased serum astAST (2%), increased serum alt ALT(≥1%)
Neuromuscular and skeletal	Weakness (2%)
Respiratory	Nasal congestion (2%), cough (≥1%), epistaxis (≥1%), sinusitis (≥1%), upper respiratory tract infection (≥1%)
Children 2 to ≤14 years	
Central nervous system	Fever, headache
Dermatologic	Dermatitis, eczema, skin rash, urticaria
Gastrointestinal tract	Abdominal pain,dyspepsia, gastroenteritis, nausea
Infection	Influenza, varicella, viral infection
Ophthalmic	Conjunctivitis
Otic	Otalgia,otitis
Respiratory	Laryngitis, pharyngitis, pneumonia, rhinorrhea, sinusitis, upper respiratory tract infection
Children 6 to 23 months	
Respiratory	Cough, otitis media, pharyngitis, rhinitis, tonsillitis, upper respiratory tract infection, wheezing

Table 3
Adverse drug reactions of levocetirizineReference: Lexicomp)

System	Problems
Gastrointestinal	Diarrhoea (infants: 13%, children: 4%)
Central nervous system	Drowsiness (3% to 6%), fatigue (adolescents and adults: 2% to 3%)
Otic	Otitis media (children: 3%)
Respiratory	Nasopharingitis(adolescents and adults:4% to 6%),cough(children:3%),epistaxis(children:2%),pharyngitis(adolescents and adults: 1% to 2%)

Miscellaneous	Fever (children: 4%)
Neuromuscular and skeletal	Weakness
Limited to important or life-threatening (<1%)	
Aggressive behavior, agitation, anaphylaxis, angioedema, arthralgia, convulsions, depression, dysuria, fixed drug eruption, hallucination, hepatitis, hypersensitivity reaction, increased serum bilirubin, increased serum transaminase, movement disorder (including dystonia and oculogyric crisis), myalgia, palpitations, paresthesia, pruritus, skin rash, suicidal ideation, syncope, tachycardia, urinary retention, urticaria, visual disturbances	

A research article entitled as 'fixed dose combinations- to prescribe or not to prescribe: A dilemma of medical profession' by MayankPrakash Nigam et al., described clearly that Levocetirizine + Montelukast FDCs usage is irrational in case of asthma because Levocetirizine, an anti histaminic has no role in asthma. Montelukast can be recommended only as an alternative to inhale steroids in mild persistent asthma. There is no indication for Levocetirizine and Montelukast together in asthma. Usage of this FDC is rational in case of allergic rhinitis.

Literature review

Vipangupta et al., (2010)[11] This randomized study was done at the outpatient department of Gian Sagar Medical College and Hospital, District Patiala in people aged between 18-60 years old of both sexes with a clinical history of perennial allergic rhinitis for at least 1 year, to compare the effectiveness of montelukast combined with levocetirizine once daily to levocetirizine alone for a 6-week treatment course of allergic rhinitis. They randomised patients as control group (Levocetirizine) and treatment group (Montelukast+ Levocetirizine). Duration of study was 6 weeks. Study concluded that the total daytime nasal symptom, composite symptom and night time nasal symptom scores showed a significant change in treatment group than in the control group. Patients in both groups reported with nausea, dizziness, fatigue, headache, somnolence, restlessness, dry mouth, fever and weakness but none of the adverse event reported was severe that required termination of treatment. Prateek Nayak et al., (2013)[12] A randomized, open label, prospective, comparative, multi centric study was conducted to compare the efficacy and safety of Montelukast and fexofenadine fixed dose combination vs Montelukast and Levocetirizine fixed dose combination in allergic rhinitis. This study was conducted at 4 sites (Mumbai, Chennai, two cites of Bangalore) in 100 subjects divided as two group, 62 in Montelukast+Levocetirizine group and 56 in Montelukast+Fexofenadine group by administering the drugs once daily for 14 days. This study concluded that montelukast+fexofenadine showed better improvement in symptoms of allergic rhinitis compared to Montelukast + Levocetirizine. Samidh shah et al., (2015)[13] analysed the rationality of antimicrobial and respiratory fixed dose combinations available in Indian market. Antimicrobial and respiratory FDCs enlisted in Indian drug review in 2010 and 2013 were analysed. Each FDC was assessed forthe number of active pharmacological ingredients, approved by regulatory authority, listing in world health organisation (WHO) essential medicine list (EML) or national list of essential medicine and there efficacy, safety, pharmacokinetic and pharmacodynamic interactions and advantages of each FDC were also analysed by evidence based literature search. Each criterion was scored one for positive, minus one for negative or unfavourable observation. The total score for the tool was 12 and the score greater than or equal to 7 was considered rational. The study concluded that FDCs of Montelukast with antihistaminic was found to be rational due to its enhanced and complimentary pharmacological and clinical effects leading to a reduction in the day and night time symptoms effectively in patients of allergic rhinitis. Even though FDCs score for Montelukast + Levocetirizine was ≥ 7 it was not enlisted in WHO EML, 2013. Angelika batta et al., (2015)[14] a retrospective observational study carried out at the outpatient medicine department of mahathma Gandhi medical hospital, jaipur by collecting 500 prescriptions for 6 months duration showed that often prescribed medications were FDC for asthma patients. The study reports that out of 60 FDCs prescribed only three were enlisted in the Esssential Medicine List of WHO. Levocetirizine, an anti histaminic has no role in asthma as the main mediators are Leukotriene and platelet activating factor. In mild and persistent asthma cases Montelukast is recommended only if inhaled steroids cannot be prescribed for some suitable

reasons. In this study, 42 prescriptions had this irrational combination of Montelukast and Levocetirizine. Mohini Scahin Mahatme et al., (2019)[15]A prospective, randomized, double- blind, parallel, active controlled, comparative four week trial in 70 patients with allergic rhinitis (AR) concluded that the mean change of total nasal symptom score (TNSS) was significant in Montelukast-fexofenadine group as compared to montelukast-levocetirizine group. However, the cost effectiveness ratio was less in Montelukast-Levocetirizine group than in Montelukast-fexofenadine group. Kiran Bylappa et al., (2018)[16] A double blind, and randomized, parallel group, comparative study was conducted to evaluate the efficacy of the FDC, Montelukast 10 mg and Levocetirizine 5 mg verses monotherapy of both drugs in patients with seasonal allergic rhinitis. Out of 274 patients 92 of them were in the FDC treatment group, 92 in Montelukast 10 mg group and 90 of them in Levocetirizine 5 mg group for a total duration of 16 days; which reported that, improvement in symptoms of allergic rhinitis was seen greater in patients in the FDC treatment group compared to patients in Montelukast 10 mg or Levocetirizine 5 mg monotherapy treatment group.

CONCLUSION

Montelukast +Levocetirizine FDC is widely prescribed in India and is not approved/available in the US & various countries in the European continent. The pharmacological and pharmacokinetic parameters of these agents do not match to make a combination with fixed doses as the duration of action is greater than 24 hours in case of Montelukast and is 24 hours only, in case of Levocetirizine. Normal Dosing of Montelukast is 10mg once daily, whereas in Levocetirizine the dose varies from 2.5mg to 5mg once daily. Hence when these are made into a fixed dose combination the appropriate dose required for a patient may not be achieved. Neither there are studies, which justify these differences in pharmacokinetic parameters between these agents. Majority of the available clinical trial data are about the combination therapy of both these agents, where Levocetirizine is used in different doses as per the patient needs and no trial data was available across various countries/continents for the fixed drug combination. Rationality of Levocetirizine + Montelukast FDC cannot be explained with the available insufficient data and so we conclude that this combination is irrational, till there are some randomised controlled trials to prove this otherwise.

AUTHORS CONTRIBUTION STATEMENT

Mr.A.Anandhasayanam conceived the presented idea. He provided intellectual content and guided the entire work. Ms. P. Saranya, Ms.Nanisha Zachariah did the literature search. Mr.Tamilselvan and Mrs.BituChullikkattil collected datas from Lexicimp software. Data analysis and interpretation was a collective work of the entire team. Ms.P.Saranya prepared the manuscript with others under the supervision of Mr.A.Anandhasayanam, who made corrections and he supervised the entire study.

CONFLICT OF INTEREST

Conflict of interest declared none.

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