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A Review on Toxicological Study of Montelukast Impurities or Related Product

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Review Article

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ABSTRACT

Toxicology of impurities in Montelukast or related products is of increasing concern in pharmaceutical industries. To analyze impurity effects of Montelukast used in asthma therapy. There are 6 impurities qualified using RP-HPLC analysis on commercial products available. Among other, sulfoxide impurity is found to be having major effect on efficacy of drug. The tolerability of a medicine is linked with number of key factors, which incorporates clinical effectiveness, adverse effects, frequency of drug regimen, ease and route of administration and taste. Study is related to evidence, which gives specificity and safety of drug of licensed dose and a tolerability profile. The most common adverse effects were headache, upper respiratory infection and Neuropsychiatric Events, which were not much different compared to placebo. Montelukast study implies that it is effective and well tolerated in most children. This drug has been associated with Churg-Strauss syndrome in small number of adults, but has not been reported in children. This review will describe the impurities, toxicity studies, adverse effects of drug montelukast. It includes comparative efficacy to other medications and combination therapy for treatment of asthma and allergic rhinitis. Our findings suggest that the toxicity of drug impurities can be monitored by measuring its level.

INTRODUCTION

Montelukast or Montelukast Sodium is a specific cysteinyl leukotriene receptor antagonist, belongs to quinoline series. It is a successful therapeutic agent for the treatment of bronchial asthma and allergic rhinitis (AR). Leukotrienes are critical inflammatory mediators in disease of lower airway, where they play key role in producing inflammation, hyper-responsiveness and bronchoconstriction. An alternative to Inhaled Corticosteroid (ICS) therapy, the addition of second method of use of drug (montelukast) results in improved control of symptoms.

Montelukast was the first antileukotriene to be licensed for use in children aged ≥ 6 years. It has been launched worldwide since October 1997(Finland). The regulatory bodies were satisfied with the overall tolerability profile of the medication.

An Impurity is a component of drug substance which is not a chemical entity or not a form of excipient of drug product. The presence of such impurities may influence the efficacy and safety of pharmaceutical product, even if it is in a small proportion. The efforts focuses on eliminating impurities from drug products, technically it is not possible to remove it all percentage and further elimination increases the cost. Therefore, in order to control impurities, an acceptable risk level concept or Threshold of Toxicological Concern (TTC) approach is useful. Hence, to meet the requirement of impurities present in the drug, their comprehensive studies are done to identify and characterized impurities of montelukast sodium. Although, this drug is well tolerated but several case reports regarding ADRs after use of montelukast has been published. For this reason, it appears desirably to explore, compile and summarize the literature to be a helpful perspective to clinicians, pharmacist and physicians.

ANALYSIS OF IMPURITIES IN DRUG PRODUCTS

Using RP-HPLC

Quantification of 6 impurities in USP is already conducted using RP-HPLC analysis. Impurities indicated were sulfoxide, cis isomer, Michael adducts I and II, methylketone, methylstyrene impurities. These investigated impurities were chosen by considering the clinical importance of the drug, including its target population and usage duration. Many toxicological study models are conducted in order to study its cytotoxicity, like Bacterial Reverse Mutation Test and Genetic Toxicity model. But overall result showed that impurities like sulfoxide were not mutagenic and non-genotoxic. Long-term control medication montelukast is used daily and regularly to achieve and maintain control of asthma. Toxicities of montelukast impurities should be carefully assessed because it is chronically used in patients, particularly in children sometimes for lifetime course. From toxicological perspective, it is important to note that children are more vulnerable than adults to xenobiotics and that they might respond with different health effect. It has also been suggested that cancer risks are generally higher in early-life exposure than from similar exposure durations later in life [1].

Impurity-1: During the basic hydrolysis stage, the cyano group elaborated into carboxylic group and leads to acid viathe transformation of amide intermediate, i.e. impurity-1. If amide intermediate could not be completely hydrolyzed into acid, impurity-1 will be resulted.

Impurity-2: To isolate the montelukast, acetic acid was used in the work up stage. Due to acidic nature, tertiary hydroxyl moiety gets protonated. Since protanatedhydroxy being a good leaving group, it takes away the adjacent methyl group proton and leads to the formation of impurity-2.

Impurity- 3 and 4: Starting material 2 contains saturated and des chloro analogue of 2, these compounds undergo sequential reactions and leads to formation of impurity-3 and impurity-4.

These 4 impurities in montelukast sodium bulk drug were identified, synthesized, isolated and characterised by HPLC techniques [2].

Sulfoxide impurity

It is acknowledged that the effective therapy with montelukast taken by a patient is reduced due to generation of sulfoxide as an impurity during manufacturing and storage, as it is considered an inactive compound pharmacologically. The presence of more sulfoxide impurities in drug products for adults may be suggested to occur due to having more ingredients in adult dose formulation compared to pediatric drug and differences in tablet form, it is not possible to

minimize with certainty since many factors play a role in generation of impurities. In previous studies of thermal stress testing study of montelukast, sulfoxide impurity was also observed as main degradation product. Further in another separate research, it was studied that the presence of microcrystalline cellulose in the formulation may induce peroxide oxidation of montelukastwiththepresence of aspartame as a sweetener can cause higher amount of sulfoxide impurity. Sulfoxide is one of the metabolite product of montelukast. In safety testing of drug metabolites, the metabolite is of interest, if it accounts for plasma levels greater than 10 percent of parent drug systemic exposure at steady state. However, sulfoxide metabolite which is identified as a minor metabolite and safety testing is hardly expected to be done. There are many of studies related to identification, quantification and characterization of impurities in drugs. In such study of research, sulfoxide impurity exceeded the threshold value in some drug products, hence it was qualified to study as a major impurity.

In cytotoxic study, even though cytotoxic signs are observed at high doses in some strains, overall results showed that sulfoxide impurity has no mutagenic activity in absence and presence of metabolic activation. In in vitro human lymphocyte chromosomal aberration test, sulfoxide impurity did not show clastogenic activity with and without metabolic activation and no numerical aberrations were observed as well. Some results achieved which showed cytotoxicities at high concentrations, in vivo acute toxicity tests may further be considered to be important for the impurity in the future. In this study, qualification was only needed for the sulfoxide impurity above the limit. Actually, not only investigated impurities but also all unidentified impurities in drugs may affect organism as a mixture. However, risks which may occur in organism just in case of interaction between any sorts of impurities are unknown. Furthermore, there are also combination montelukast products with desloratadine or levocetirizine in market. So, interaction with impurities coming from other active substance might also be studied.

Photolytic degradation of montelukast

Exposure of montelukast to light causes it's isomerization, while a montelukast derivative with geometry (Z) is formed in the location of the double bond [8] The impurity resulted from photo-instability is (Z)-montelukast, chemically which is the sodium salt of l-[[[(lR)-l-[3-[(lZ)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(l-hydroxylmethylethyl)phenyl]propyl]thio]methyl] cyclopropane acetic acid. Another degradation impurity described is montelukast dehydrated, chemically the sodium salt of l-[[[(lR)-l-[3-[(lE)-2-(7-chloro-2-quinolinyl)ethenyl]-phenyl]-3-[2-(l-methylethenyl)phenyl]propyl]thio]methyl]cyclopropane acetic acid. The organic impurities of the target substance have major role in chemical instability of montelukast as well as with instability of the ingredients used for its synthesis orof residues of the used raw materials or solvents. An example of a source of contamination due to instability of intermediate products is the commonly used ingredient montelukastmesylate, 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-methanesulfonyl-oxypropyl)phenyl)-2-propanol. Montelukastmesylate is prepared via a reaction of the relatively stable montelukast alcohol, chemically 2-(2-(3(S)-(3-(2-(7-chloro-2-

quinolinyl)ethenyl)-phenyl)-3-methanesulfonyloxypropyl)-phenyl)-2-propanol, and methane sulfonyl chloride. Thenmontelukast-mesylate is converted by the action of a salt of [l-(mercapto-methyl)cyclopropyl] acetic acid with an alkaline metal (IX) to the target montelukast. In parallel to this reaction the considerably instable montelukastmesylate (VII) is subject to undesired intramolecular conversions, Via an elimination reaction the impurity montelukast eliminate, chemically 2-[2-(3-{3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl}allyl)phenyl]-propan-2-ol, is generated from the intermediate (VII). A cyclization reaction produces another impurity,namelymontelukastcyclizate, chemically 7-chloro-2-{2-[3-(l,l-dimethyl-l,3,4,5-tetrahydrobenzo[c]-oxepin-3-yl)phenyl]vinyl}quinoline, from the intermediate.

Comparative drug studies

Montelukast 4 or 5 mg/day had compared with budesonide inhalation suspension 0.5 mg/day of age 2–8 years with mild asthma or recurrent wheezing for a 12-month, multicenter, randomized study. The frequencies of adverse effects were comparable, most were mild to moderate intensity. In which who took montelukast, there was one case mostly of headache, lower tract infection, and abnormal behavior, which were considered to be related to drug. Few patients stopped taking montelukast due to adverse events, the most typical reasons for withdrawal being asthma or pneumonia, but there have been no deaths. Treatment-related adverse events were more common with montelukast, compared with placebo (8.6%) and levocetirizine (8.3%). Adverse effects that were considered to be drug-related were more common with montelukast (5.8%) than levocetirizine (3.8%) or placebo (2.9%). there have been not a serious treatment-related adverse events. Headache was the foremost typical adverse event with montelukast (3.2%) and placebo (1.9%) but it had been not reported in those taking levocetirizine. The addition of montelukast didn't end during a greater overall rate of adverse events or increased withdrawal rates related to adverse events [3-5].

Placebo-controlled studies

The efficacy and safety of montelukast are studied in a world, multicenter, randomized study. The patients were assigned to 12 weeks of treatment with placebo or montelukast 4 mg chewable tablet. There have been no clinically relevant differences between the groups within the general frequencies of adverse effects, individual adverse effects, or the frequency of laboratory adverse effects, especially raised serum transaminase activities. But Asthma was more frequent within the placebo group. The withdrawal frequency was similar compared to the 2 groups. Accidentally, administration of montelukast up to dosages 18 times the recommended daily dose of 4 mg was generally well tolerated.

Many authors concluded that montelukast is well tolerated during this specific group of preschool children. The safety and tolerability of drug montelukast are studied in analysis of pooled data from multicenter, randomized studies and five long-term extension studies. There have been no clinically important differences in individual adverse events between the 2 treatment groups. There have been no dose-related adverse effects of montelukast up to dosages 20 times the recommended daily dose of 10 mg.

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Drug-drug interactions

Theophylline, Prednisone, and Prednisolone - SINGULAIR has been administered with other therapies regularly employed in the prophylaxis and chronic treatment of asthma without apparent increase in adverse reactions. In drug-interaction studies, given clinical dose of montelukast have not showed the clinical important effect on the pharmacokinetics of drugs like theophylline, prednisone, and prednisolone. Montelukast dose of 10 mg for pharmacokinetic steady state, didn't cause clinically significant changes within the kinetics of 1 intravenous dose of theophylline. Montelukast's higher dose daily , didn't cause any major change in plasma profiles of prednisone or prednisolone on following administration of either oral prednisone or intravenous prednisolone [6].

Oral Contraceptives, Terfenadine, Digoxin, and Warfarin - In drug interaction studies, the recommended clinical dose of montelukast not showed clinically important effects on the pharmacokinetics of the drugs, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. Montelukast's higher dose regularly,didn't significantly change the plasma concentrations of either component of a pill containing norethindrone 1 mg/ethinyl estradiol 35 mcg. Montelukast of a dose of 10 mg once daily for pharmacokinetic steady state didn't change the plasma concentration profile of terfenadine or fexofenadine, the carboxylated metabolite; did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin; did not change the pharmacokinetic profile or influence the effect of a single 30 mg oral dose of warfarin on prothrombin time or the International Normalized Ratio (INR). Thyroid Hormones, Sedative Hypnotics, Non-Steroidal Anti-Inflammatory Agents, Benzodiazepines, and Decongestants – These Medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants. Cytochrome P450 (CYP) Enzyme Inducers, Phenobarbital, which induces hepatic metabolism, decreased the realm under the plasma concentration curve. No dosage adjustment for SINGULAIR is recommended. It can be use appropriately for clinical monitoring when potent CYP enzyme inducers, like Phenobarbital or revamping, are co-administered with SINGULAIR. Effect of Montelukast on Cytochrome P450 (CYP) Enzymes is that Montelukastin vitro is a potent inhibitor of CYP2C8.So, the data from a clinical drug-drug interaction study demonstrated that the pharmacokinetics of rosiglitazone not altered when the drugs are co-administered, indicates that montelukast does not inhibit CYP2C8 in vivo. Therefore, montelukast isn't involved to change the metabolism of medicine metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide) [7-8]. Co-administration of montelukast with itraconazole, a powerful CYP3A4 inhibitor, resulted with no significant increase in the systemic exposure of montelukast. Studied Data from a clinical drug-drug interactioninvolving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9) demonstrated that gemfibrozil, at a therapeutic dose, increases the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, gemfibrozil, and montelukast didn't further increases the systemic involvement of montelukast. Based on

available clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil[3].

Other interactions

SINGULAIR contra-indicated to used for the reversal of bronchospasm in acute asthma attacks, including asthma .SINGULAIR shouldn't be abruptly substituted for inhaled or oral corticosteroids.

Aspirin Sensitivity - Patients with diagnosed aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. SINGULAIR is recommended in improving airway function for asthmatics patients with aspirin sensitivity, it isn't been shown to truncate broncho-constrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients [9].

Physicians should know the eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy of their patients. An interaction between SINGULAIR and these underlying conditions has not been established.

Nonclinical Toxicology of Carcinogenesis, Mutagenesis, Impairment of Fertility - No evidence of tumorigenicity was seen in carcinogenicity studies. There is no further study regarding mutagenic or clastogenic activity within the subsequent assays; the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chrosomal abnormality assay in Chinese hamster ovary cells, and within the in vivo mouse bone marrow chrosomal abnormality assay. Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg.

Additionally, it is unknown that whether montelukast is excreted into human breast milk, but there is caution regarding the use of such medication.

Neuropsychiatric events

Serious Neuropsychiatric (NP) events have been in reports with use of Montelukast Sodium (SINGULAIR). The post marketing reports included, aggressive behavior, anxiousness, depression, disorientation, disturbance in attention, stuttering, hallucinations, insomnia, irritability, memory loss, obsessive-compulsive symptoms, restlessness, suicidal thoughts and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of such psychiatric disorder. NP events have been reported mostly during SINGULAIR treatment for asthma, but some were also reported after the SINGULAIR discontinuation. Because of the chance of NP events, the advantages of SINGULAIR might not outweigh the risks in some patients, particularly when the symptoms of disease could also be mild and adequately treated with alternative therapies. We can control the use of SINGULAIR for patients with allergic rhinitis having an inadequate response or intolerance to alternative therapies. Pharmacist must discuss the benefits and risks of SINGULAIR use with patients and caregivers when prescribing SINGULAIR and advice patients or caregivers to be alert for changes in behavior or for new NP symptoms when taking SINGULAIR. If changed behavior is observed, or if new NP symptoms were seen, advise patients to discontinue SINGULAIR and get in touch with a healthcare provider immediately. In many of the cases, symptoms were gone after stopping SINGULAIR therapy; but in some cases symptoms persisted even

after discontinuation of SINGULAIR. Therefore, it is meant to continue monitoring and provide a supportive care until symptoms disappers and re-evaluate the benefits and risks of restarting treatment with SINGULAIR if such events occurred. Many studies that have analyzed published case reports or data-bases of adverse drug response reporting systems gave suggestion that montelukast use is associated with neuropsychiatric events such as anxiety, sleep disturbance, depression, and suicidality. However, two of recent systematic reviews on this issue reported that the association between neuropsychiatric events and montelukast use, reported by studies using Pharmacovigilance databases and not by observational or cohort studies [10].

Adverse reactions

The clinical trials conducted under more varying conditions, where adverse reaction rates studied in the clinical trials of a drug are not compared to the rates in the clinical trials of another drug and not to reflect the rates observed in clinical practice. The most common adverse reactions in controlled clinical trials were; upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, influenza, rhino rhea, sinusitis. Adults, 15 Years aged and Older with Asthma SINGULAIR has been evaluated for safety in clinical trials. In placebo-controlled clinical trials, other adverse experiences reported with SINGULAIR seen in greater than or capable 1% of patients and at an incidence more than that in patients treated with placebo.

Neuropsychiatric disorders and sleep disturbances, affects the pediatric population more often and exert a negative impact on patients' quality of life, although most of them had a clinical resolution after montelukast discontinuation. Currently, the pharmacological mechanisms causing neuro-psychiatric alterations unclear. Various pre-clinical experiments, exploring the function of this pathway in the central nervous system, revealed an over-expression in the reparative process occurring during particular pathological conditions. Even though studies on children are lacking, it may be hypothesized that, in susceptible pediatric patients, blocking CysLT1 by its specific antagonists causes neuropsychiatric adverse reactions. Montelukast can cause hepatobiliary and pancreatic dysfunction. Notably, it has been described in a fatal hepatotoxicity; however, in this case it was not possible to describe the mechanism of triggering hepatotoxicity. Interestingly, various experimental models of drug-induced hepatotoxicity in rats has showed a protective effect of montelukast.

Simplicity of the treatment regimen, as well as efficacy and the frequency of adverse effects contribute to the tolerability of a drug. In general, montelukast is well tolerated in pediatric patients, although it re-mains important to continue to monitor patients for adverse effects. Montelukast is, in general, a well-tolerated drug, both in adult and pediatric patients. In the present research, it appears clear that montelukast administration have many ADRs, of which physicians should be aware in their clinical practice, taking into account that the administration of montelukast, along with concomitant therapies, can increase the risk of drug-drug interaction. A better comprehension of the mechanisms causing ADRs related to this anti-leukotriene could help researchers and clinicians to define a therapeutic strategy aimed to reduce montelukast

toxicity. Further, it is desirable to conduct a more accurate epidemiological studies on large populations in order todefinitiediscovery of risk factors favoring montelukast-associated ADRs.

Safety profile

The most common reports of clinical adverse events of montelukast drug treatment were fever, upper respiratory infection, and asthma exacerbation. Although montelukast is considered a safe drug because it's reported incidence of adverse drug reactions (ADRs) was similar to that of the control group. Main concern related to montelukast-associated ADRs included the occurrence of Churg-Strauss Syndrome (CSS) and the possible association between LTRA and suicidality. A case- crossover study of some patients with CSS reported that the use of montelukast was associated with a 4.5-fold increased risk of CSS of within 3 months. CSS, also known as eosinophilic granulomatosis with polyangiitis, is a rare autoimmune disorder that causes vasculitis in patients of history with asthma or allergic rhinitis. Treatment for CSS includes glucocorticoids (such as prednisolone) and some other immunosuppressive drugs. Therefore, montelukast is simply a confounding factor, and the withdrawal of steroid use can be associated with the development of CSS symptoms.

The United States Food and Drug Administration issued a warning in 2008 regarding the possible association between montelukast use and suicidality; and in 2020, it announced that the drug requires a warning about mental health side effects because of prescribed many other anti-allergy medicine and many health care professionals and patients/caregivers are not aware of the risk of mental health side effects. One study investigated the association between montelukast and antidepressant use and reported that montelukast initiation was also associated with antidepressant prescription. However, the study concluded that antidepressant use, not montelukast use, may be related with asthma severity. These findings do not concluded the safety of montelukast; therefore, clinicians should consider the benefits and risks of montelukast before prescriptions. The efficacy of montelukast for pediatric asthma is lessor to that of ICSs. Nonetheless, montelukast has several advantages [11].

First, the patients using ICS must use the correct inhalation technique, whereas no other special skills are required to administer montelukast.

Second, both patients and prescribing physicians shall use a drug that is administered only once a day.

Third, there is no impact on growth, unlikeof ICSs, which can potentially impair a child's growth.

Montelukast maintenance therapy is primarily recommended for asthmatic children having symptoms more than once a month but less than once a week and is recommended as an alternative method for children with asthma. Serum EDN can be used as a biomarker to monitor the effectiveness of pediatric asthma treatment. We recommend to starting maintenance therapy with montelukast when the EDN level is ≥ 53 ng/mL and stopping when the EDN level decreases to <45 ng/mL. However, additional studies are needed to determine the validity of these recommendations [12].

Affect of obesity on drug

A new study suggests that the severity of people's asthma was found to be greater among those in the overweight and obese groups. In addition, the inhaled steroid was found to be better than Singulair at increasing the quantity of Asthma Control Days (ACD) among people within the traditional weight category. An ACD is defined as each day with no quite two puffs of an inhaler, no night-time awakenings and no asthma attacks. On the opposite hand, the inhaled steroid resulted during a reduced effect within the percentage of ACDs among obese people within the study -- that's , the advantage of the inhaled steroid declined with increasing body mass index. In contrast, the positive impact of Singulair did not decrease in obese and overweight people when compared to its impact on people of normal weight. The research also suggests that the upper an individual's body mass index, the greater his or her response to Singulair compared to a placebo, a pill with no medicinal benefit [12].

Montelukast and cardiovascular events

Cysteinyl leukotriene namely LTC4, LTD4 and LTE4 are pro-inflammatory mediators of the 5-lipooxygenase pathway, which has a role in asthma as well as genetic and preclinical evidence of a contribution to Cardiovascular (CV) diseases. From the study, it was observed that 4.6% of asthmatic patients suffered a major CV event during observation period. The result showed a potential role of LTRAs, montelukast in targeting inflammation and reducing ischemic events in asthmatic patients.

CONCLUSION

All these impurities were isolated by liquid chromatography and specific spectroscopic techniques. The sulfoxide impurity was concluded to be an ordinary nonmutagenic impurity in studies conducted by reviewed research. This result is positive for regular consumers, children and adults. Studies also have included other toxicity effects of Montelukast. Compliance is further build by level of support and supervision provided by parents and caregivers. Simplicity of treatment, efficacy, and tolerability of drug contribute to monitor patients for adverse effects and effects due to toxicity of drug impurity. These findings can help to characterize the parameters affecting the stability of drug and provide useful insight into way of analysis of drug study.

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