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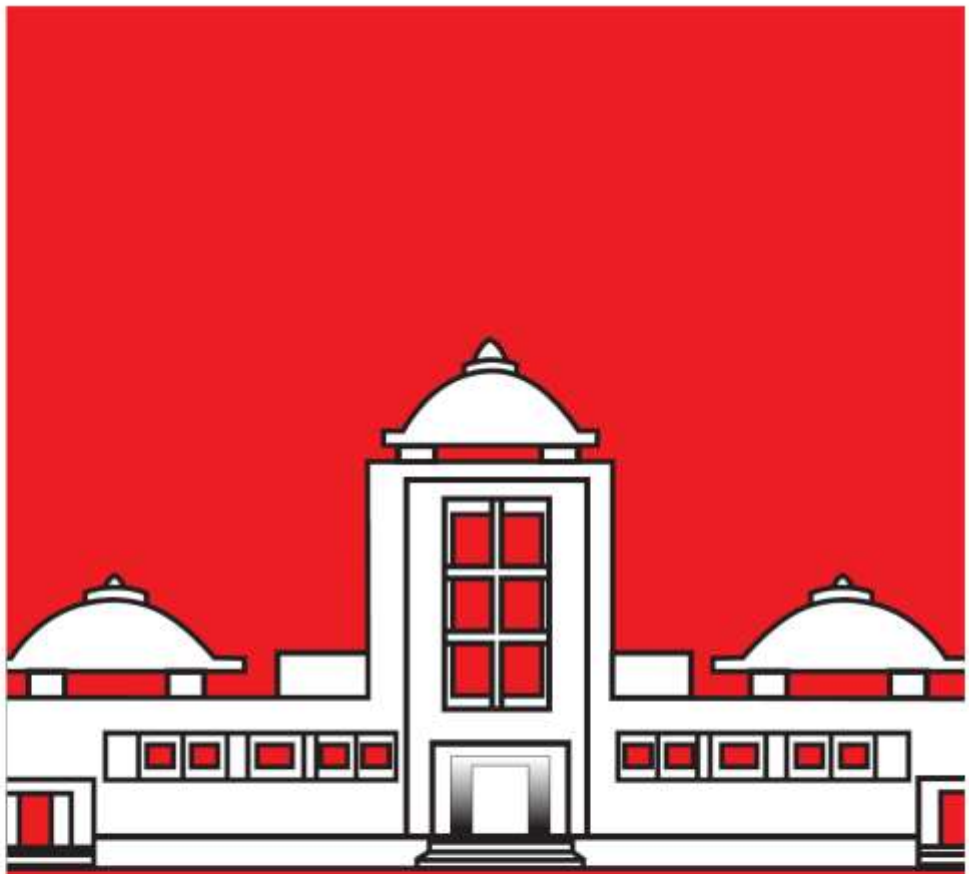

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Contents

A Study of Pharmacological Characteristics and Safety Profile of Tofacitinib

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Abstract

Tofacitinib, which is a novel, selective Janus kinase (JAK) inhibitor, is a contemporary modality of therapy for inflammatory disorders with immunological origin. It's a tiny synthetic molecule that is taken orally and has a high bioavailability and elimination rate, as well as predictable pharmacokinetics and no immunogenicity, all of which are beneficial for its efficacy and safety. It is metabolized mostly by CYP3A4, and drug-drug interactions are a concern. Its use is associated with the rapid decline in C-reactive protein (CRP), as well as dose-dependent reductions in circulating CD16/56+ natural killer cells and dose-dependent elevations in B cells. It is indicated in the management of adults with moderate to severe active rheumatoid arthritis (RA), active psoriatic arthritis, moderate to severe ulcerative colitis, and active polyarticular juvenile idiopathic arthritis in children aged 2 years and older. It's also used to treat COVID-19 sufferers having moderate to severe symptoms. It is also evaluated for the treatment of ankylosing spondylitis, alopecia areata, vitiligo, and atopic dermatitis, as well as prophylactic therapy for renal transplant rejection. Headache, diarrhoea, nausea, nasopharyngitis, and upper respiratory tract infection are some of the most common side effects of tofacitinib. Lymphopenia, neutropenia, anaemia, and an increased risk of cancer and infection have also been reported as more serious immunologic and hematological side effects. This medication has feticidal and teratogenic effects in the animal study when administered during pregnancy. It is not indicated for patients who are allergic to it, have significant hepatic impairment, is pregnant, and breastfeeding. In this study, we have discussed the pharmacological properties of tofacitinib and its safety profile.

Keywords: Tofacitinib, pharmacokinetics, efficacy, safety, pregnancy

Introduction

Tofacitinib is a powerful, oral, selective Janus kinase (JAK) inhibitor that inhibits JAK1 and JAK3 in a preferred manner. Janus kinases are a family of intracellular enzymes that regulate hematopoiesis and immune cell activity through signaling pathways.[1] It is the first of a new class of nonbiologic disease-modifying antirheumatic drugs (DMARDs) that is a targeted, synthetic DMARD that has been designated for the treatment of rheumatoid arthritis (RA) as monotherapy or in combination with methotrexate or another nonbiologic DMARD.[2] It is mainly advised after

unsuccessful treatment with methotrexate, improves joint pain, inflammation, and stiffness by lowering immune system activity through a distinct therapeutic pathway than other DMARDs.[3]

The citrate salt of tofacitinib is used in the formulation of tofacitinib tablets and oral solutions. Tofacitinib citrate is a pyrrolopyrimidine that is pyrrolo[2,3-d] pyrimidine replaced at position 4 by an N-methyl, N-(1-cyanoacetyl-4-methylpiperidin-3-yl)amino group. It is a white to off-white powder with a molecular weight of 312.37 and its chemical formula is $C_{16}H_{20}N_6O$. Figure 1 depicts its chemical structure.[4] This study aims to highlight the pharmacological activities of tofacitinib as well as its safety profile.

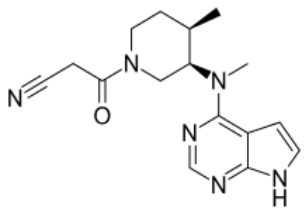

Figure 1. Chemical structure of tofacitinib citrate

History

Dr. John O'Shea, an immunologist at the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH), first recognized the Janus kinases (JAK) enzyme in 1993. Interleukin-2, an important growth factor for T lymphocytes that is responsible for transplanted kidney rejection, was shown to help JAK in controlling the signaling pathway. In 2000, Pfizer working with O'Shea's team to determine the structure and function of JAK3 and its receptors, discovered a JAK inhibitor that was nominated for clinical development. During development, this drug was designated as CP-690,550. At first, its recommended International Nonproprietary Names (rINN) was tasocitinib, but ultimately approved as tofacitinib. It was tested in a rigorous monkey model for kidney transplantation at Stanford University before being used in humans. It was approved by the FDA in November 2012 to treat individuals with moderate to severely active rheumatoid arthritis who have had an unsatisfactory response to methotrexate or who are intolerant of it.[5,6] The FDA only approved its 5 mg twice-daily dose because a larger dose was considered to have an inadequate risk-to-benefit ratio.[7] Before being approved, tofacitinib was extensively researched. By August 2010, phase I trials assessing the bioavailability of oral and intravenous tofacitinib had been completed. Phase II trials were undertaken on Japanese rheumatoid arthritis patients who previously had a poor response to methotrexate. Six Phase III trials were carried on moderate-to-severe Rheumatoid Arthritis patients under the oral rheumatoid arthritis triaLs (ORAL) series to assess its efficacy.[2]

Tofacitinib, in a 2014 study was shown to be able to transform white fat tissues into more metabolically active brown fat, suggesting it could be used to treat obesity.[8] In the United States, tofacitinib was approved by the FDA in May 2018 for the treatment of adult patients with moderate to severely active ulcerative colitis.[9] Tofacitinib was approved by the FDA in 2020 for the treatment

of active polyarticular course juvenile idiopathic arthritis (pcJIA) in children and adolescents aged 2 years and older. This medicine has also been researched for the management of other disorders, including psoriatic arthritis, alopecia areata, vitiligo, atopic dermatitis, and ankylosing spondylitis.[10]

Mechanism of Action

Tofacitinib is a tiny molecule but not a biological one. It acts from the inside of the cell, whereas biologics inhibit pro-inflammatory cytokines from the outside.[11]

Tofacitinib is a pan-JAK inhibitor that predominantly suppresses JAK3 and JAK1, as well as JAK2 to a lesser extent. JAKs are intracellular enzymes that regulate hematopoiesis and immune cell activity by transmitting signals derived from cytokine or growth factor-receptor interactions on the cellular membrane. JAKs, within the signaling cascade, phosphorylate and activate Signal Transducers and Activators of Transcription (STATs), which control intracellular activity, including gene expression. The binding of JAK3 to the common IL-2Rγ chain of the type I cytokine receptor family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) is crucial for T-cell activation while JAK1 binds with γ-chain cytokines (IL-6, IL-10, IL-13, IL-22, granulocyte colony-stimulating face, interferons). Downregulation of JAKs results in reduced IL-6 production by synovial fibroblasts, reduced receptor activator of nuclear factor-κB ligand production, decreased pro-inflammatory cytokines signaling via IL-2 and IL-4 inhibition, diminished TNF-stimulated fibroblast-like synoviocytes production, and decreased production of IL-8 by CD14+ monocytes (figure 2). By restricting T cell and other leukocyte recruitment, tofacitinib diminishes synovial inflammation and structural joint damage in RA patients.[2,12]

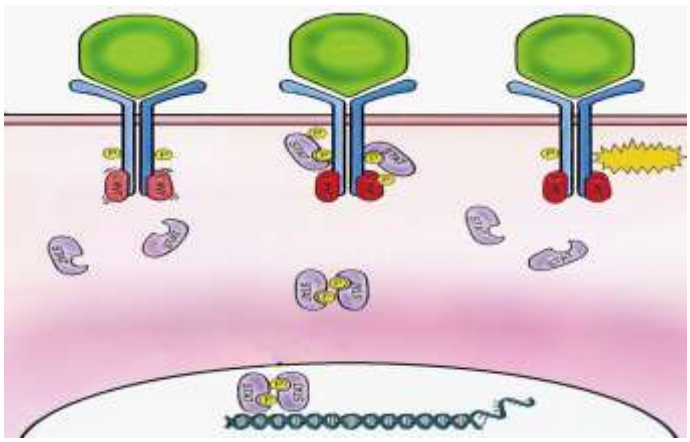

Figure 2. Tofacitinib's mechanism of action

(STAT: Signal transducer and activator of transcription; JAK: Janus kinase)

Pharmacodynamics

Tofacitinib use is attributed to a quick reduction in C-reactive protein (CRP), as well as dose-dependent reductions in circulating CD16/56+ natural killer cells and dose-dependent

increments in B cells. Low level of CRP even after two weeks of tofacitinib cessation, implying that pharmacodynamic efficacy lasts longer than pharmacokinetic half-life. Natural killer cell reduction peaks around 8-10 weeks after treatment begins, and these effects usually fade away within 2-6 weeks after treatment is stopped.[12]

Pharmacokinetics

Following oral dosing, tofacitinib is readily absorbed from the gastrointestinal tract. T_{max} (peak plasma concentration) is reached in around 0.5-1 hour, while the elimination half-life is around 3 hours. After twice-daily dosing, steady-state concentrations are obtained in 24-48 hours with little buildup. Tofacitinib has a 74 percent absolute oral bioavailability. There is a 32% decrease in maximum plasma concentration (C_{max}) when tofacitinib is administered with a high-fat meal with no changes to the area under the plasma concentration-time curve (AUC); consequently, tofacitinib can be administered regardless of meals. The volume of distribution after intravenous administration is 87 L. Tofacitinib binds to about 40% of proteins, with albumin being the most common. It is equally distributed among red blood cells and plasma. It is extensively metabolized in the liver (70%) by CYP3A4 (major) and CYP2C19. Its activity is linked to the parent compound, with eight metabolites maintaining less than 10% of the parent component's potency. 30% of the medication is excreted unaltered in the kidneys.[12,13]

Patients with rheumatoid arthritis, psoriatic arthritis, and UC exhibit similar pharmacokinetic characteristics of tofacitinib, with coefficients of variation (%) in AUC ranging from 22 to 34 percent. Patients with mild hepatic impairment require no dosage modifications; however, patients with moderate hepatic impairment or moderate to severe renal impairment should have their dose reduced. Patients with positive hepatitis B or C virus serology have not been evaluated for its safety or effectiveness.[2,13]

Drug and food interaction

Tofacitinib does not significantly inhibit or induce the activity of the major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), as well as the uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at therapeutic concentration. A human drug interaction study found no alterations in the pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with tofacitinib, confirming these in vitro findings. At the therapeutic level, tofacitinib has a low potential to inhibit transporters including P-glycoprotein, organic anionic, or cationic transporters.[14]

Because tofacitinib is mostly metabolized by CYP3A4, it is likely to interact with medications that inhibit or activate CYP3A4. Tofacitinib's pharmacokinetics are unlikely to be significantly altered by CYP2C19 or P-glycoprotein inhibitors alone. When given with potent CYP3A4 inhibitors (e.g., ketoconazole) or agents expressing both moderate CYP3A4 and potent CYP2C19 inhibition

(e.g., fluconazole), the dose of tofacitinib should be reduced by half. Tofacitinib when combined with potent CYP3A4 inducers (e.g., rifampin) can result in a substantial reduction in AUC and clinical efficacy, requiring dose modification. Tofacitinib should be used with caution when combined with cyclosporine and tacrolimus because there is a risk of serious infection due to increased immunosuppression. Grapefruit juice, a potent CYP3A4 inhibitor, may raise tofacitinib levels and increase the risk of side effects. Because St John's Wort is a CYP3A4 inducer, co-administration may lead to low or absent clinical effects.[2,12]

Dosage

Tofacitinib is taken orally 5 to 10 mg twice daily, or 11 mg once per day. For children, the suggested dose is 2 to 5 mg as tablet form or 1 mg/ml as an oral solution twice daily, depending on their age and weight. It should be consumed whole, whether with or without meals. It should not be chewed, split, or crushed. It is recommended to take it at the same time every day. If a dose is missed, continue with the regular dose the next day, but do not double it.[12,15]

Indication and usage

Tofacitinib is used to treat various kinds of moderate to severely active arthritis in adults (such as rheumatoid arthritis, psoriatic arthritis) having the insufficient effect of or intolerance to methotrexate or other disease-modifying antirheumatic medications (DMARDs). It helps in lowering joint discomfort and inflammation. It can be used alone or in combination with other DMARDs like methotrexate. It is also used to manage adults with moderate to severely active ulcerative colitis who haven't an adequate response to tumor necrosis factor inhibitors. It improves symptoms of ulcerative colitis like diarrhoea, rectal bleeding, and stomach cramps. It is also indicated for the therapy of active polyarticular course juvenile idiopathic arthritis (pcJIA) in children older than two years.[1,12,15]

Tofacitinib has also been studied for the treatment of ankylosing spondylitis, alopecia areata, vitiligo, and atopic dermatitis,[16] as well as prophylactic therapy for kidney transplant rejection[17].

The National Institute of Health COVID-19 guidelines recommend tofacitinib as an alternative to baricitinib or in combination with a corticosteroid or in combination with a corticosteroid and remdesivir, for the treatment of COVID-19 in recently hospitalized (eg, within 3 days of admission) patients on high-flow oxygen or noninvasive ventilation who have rapidly increased oxygen needs and increased markers of inflammation.[18]

Side effects and precautions

Tofacitinib, like any other drug, can cause adverse effects. Nausea, fever, headaches, and diarrhoea are the most prevalent and normally go away quickly. The unwell feeling is usually common with taking tofacitinib, although this passes with time.[19]

Because tofacitinib affects the immune system, it can reduce the body's ability to fight

infections. Infections caused by bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been documented to be serious and occasionally fatal. Pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis are the most common serious infections observed. Tuberculosis and other mycobacterial infections, cryptococcosis, esophageal candidiasis, pneumocystosis, histoplasmosis, listeriosis, CMV infection, BK virus infection, and herpes zoster are among the opportunistic illnesses that have been described. When taking immunomodulating drugs like methotrexate or corticosteroids concomitantly, some patients developed disseminated disease rather than a localized one.[19,20]

During and after therapy with tofacitinib, patients should be monitored regularly for any signs and symptoms of infection. If a patient develops any serious or opportunistic infection or sepsis, tofacitinib should be discontinued immediately. Early and comprehensive diagnostic tests appropriate for an immunocompromised patient should be conducted for a patient who develops a new infection while on treatment; as well as appropriate antimicrobial treatment and close monitoring should be initiated. Patients with a history of chronic lung illness or those who develop interstitial lung disease should take precautions, as they may be more susceptible to infections. With rising degrees of lymphopenia, the risk of infection rises, hence lymphocyte counts should be taken into account while evaluating patients at risk of infection.[12,20]

Before initiating tofacitinib, all patients should be assessed for tuberculosis. Before administering tofacitinib, anti-tuberculosis treatment should be started in patients with an active or past history of tuberculosis for whom an adequate course of treatment cannot be confirmed, as well as patients who are at elevated risk of tuberculosis infection. Patients who tested negative for latent tuberculosis infection before starting tofacitinib should also be regularly monitored for the onset of any signs and symptoms of tuberculosis. Before commencing tofacitinib, the patient should also be evaluated for hepatitis B and C infection, as this medicine may raise the risk of reactivation of these infections.[12,19,20]

Before human trials, animal research with tofacitinib revealed some carcinogenesis, mutagenesis, and reproductive impairment.[20] Patients treated with tofacitinib have developed lymphoma and other solid malignancies. In renal transplant patients treated with tofacitinib and concomitant immunosuppressive medicines, a higher risk of Epstein Barr Virus-associated post-transplant lymphoproliferative disease has been found. So, patients with a higher risk of skin cancer should have their skin examined regularly.[12,19]

In clinical trials, the incidence of gastrointestinal perforation has been observed with the use of tofacitinib. It should be administered cautiously in individuals with a risk of gastrointestinal perforation (e.g., patients taking NSAIDs or with a history of diverticulitis). Patients should be investigated promptly for early recognition of gastrointestinal perforation, presenting with new-onset abdominal symptoms.[12,20]

There is an increased risk of neutropenia, lymphocytopenia, and anemia with tofacitinib therapy. Patients having an absolute lymphocyte count of < 500 cells/mm3, an ANC of < 1,000

cells/mm^3, or hemoglobin of less than 9 g/dL should not take tofacitinib. Each patient should be evaluated for lymphocyte and neutrophil count, and hemoglobin level before starting therapy, after 4-8 weeks of treatment, and every 3 months thereafter.[20,21]

Liver enzymes and cholesterol levels should be checked regularly because some patients on tofacitinib have raised level of it. Start medication immediately if cholesterol level becomes too high.[12] Urgent medical care is required if one develops swelling of the legs or breathlessness because tofacitinib has an increased risk of deep vein thrombosis, pulmonary embolism, and stroke.[22] Tofacitinib can occasionally develop a hypersensitive reaction characterized by rapid swelling, redness, or shortness of breath.[20,21]

Tofacitinib users should also avoid live vaccine immunization (measles, mumps, and rubella (MMR), yellow fever, tuberculosis (BCG), and shingles). It is safe to recommend pneumococcal vaccines which tend to protect against pneumonia, and yearly flu vaccines (excluding nasal flu vaccine). Contact with people who have just received live vaccinations (like nasal flu vaccine) should be avoided. The time between live immunizations and the start of tofacitinib should follow the current immunosuppressive agent vaccination guidelines.[19,20] Tofacitinib may diminish the therapeutic effect of COVID-19 Vaccine (mRNA). Consider holding tofacitinib therapy for 1 week after each vaccine dose, when possible, for patients with stable underlying disease. Additionally, consider administration of the 3rd dose of COVID-19 vaccine in patients on tofacitinib.[12]

Use in specific population

Tofacitinib has been classified as a category D drug as per Australian categories for prescribing medicines in pregnancy.[23] At present, very little is known about the effects of tofacitinib in pregnancy. Animal study shows feticidal and teratogenic effects of this drug when used during pregnancy. So, it is safe to not prescribe tofacitinib in a pregnant lady or planning to become pregnant. Women of reproductive age should use effective contraception while on treatment and for at least four weeks after the final dose. If a patient becomes pregnant, they should be motivated to enroll in the pregnancy exposure registry (toll-free number 1-877-311-8972).[20] It's unclear whether this drug goes into breast milk. Because of its molecular weight and also it is found in animal milk, the possibility of passing into breast milk can’t be ruled out. Breastfeeding is not suggested during therapy and for at least 18 hours after treatment because of the risk of significant adverse effects in the breastfed baby.[19] There has been no formal study on the potential effect of tofacitinib on human fertility. In a rat study, tofacitinib has been found to affect female fertility but not male fertility.[20]

Tofacitinib oral solution's safety and efficacy in children for diseases other than pcJIA have not been demonstrated. Adverse effects seen in younger patients who received an oral solution are similar to those of RA patients. In pcJIA patients under the age of two years, efficacy and safety of even oral solution has not been proved.[20]

Precaution should be taken in treating the geriatric population because they may be more

susceptible to infection while taking this medicine. The use of tofacitinib increases the risk of infections in diabetic patients. So, close monitoring and caution should be exercised when treating patients with diabetes.[20]

Only 5 mg tofacitinib should be used per day by people having moderate to severe renal impairment or moderate liver impairment. In patients with mild renal or hepatic impairment, no dose adjustment is necessary, however, it is not advised in patients with severe hepatic impairment.[20] Tofacitinib should be prescribed cautiously in patients with a history of chronic lung disease or those who develop interstitial lung disease because of the high risk of infection in them.[12] Higher risk of adverse effects (eg, interstitial lung disease, increased transaminases, decreased WBC, herpes zoster, opportunistic infections) have been seen in Asian people taking tofacitinib.[24]

Overdosage

Because there is no specific antidote for tofacitinib overdose, the patient should be carefully monitored for any signs and symptoms of adverse effects.[20]

Contraindications

Hypersensitivity to tofacitinib or any component of the formulation, severe hepatic impairment, pregnancy, and breastfeeding are all contraindications of tofacitinib. Patients with an absolute lymphocyte count < 500 cells/mm3, an ANC < 1,000 cells/mm3, or hemoglobin of less than 9 g/dL should not begin therapy with tofacitinib.[12,25]

Conclusion

Tofacitinib is a non-biologic DMARD (disease-modifying antirheumatic drug) that works by inhibiting the enzyme Janus kinases (JAKs), which affects hematopoiesis and immune cell activity. Tofacitinib monotherapy or in combination with a standard DMARD is successful in lowering disease signs and symptoms and enhancing the health-related quality of life. Adults with moderate to severe active rheumatoid arthritis (RA), active psoriatic arthritis, active ulcerative colitis, and children aged 2 years or older with active polyarticular juvenile idiopathic arthritis have been successfully managed with tofacitinib. It's also used to treat COVID-19 patients having moderate to severe symptoms. It has some side effects, some of which are serious. Hypersensitivity reaction, severe hepatic impairment, pregnancy, and breastfeeding are all contraindications of tofacitinib use. Thus, the risk-to-benefit ratio of tofacitinib therapy should be taken into account before starting treatment in patients.

Declaration

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Conflict of interest: No conflict of interest among authors

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Use of Quality by Design (QbD) to optimize the ethanol precipitation process in herbal drugs

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Abstract

An analysis of a case study to improve the manufacturing of herbal drug products in economic terms as well as for obtaining higher yields. The example taken in this case is of ethanol precipitation used to obtain APIs as well as saccharides from an herb known as red sage.

Keywords: Herbal Drugs, Extraction, Ethanol, Saccharides, and Red Sage.

Introduction

Ethanol precipitation is a unit operation that is used for the extraction of active ingredients as well as saccharides from an herb known as red sage. The ease of recovery of the active ingredients and removal of the saccharides represent the efficiency of the process of ethanol precipitation. The herbal materials are extracted and concentrated in the first step followed by the process of ethanol extraction produces the supernantant. This supernatant contains concentrated APIs and has minimum concentration of the saccharides. The supernatant is then further concentrated and blended with the excipients and most commonly manufactured as dripping pills by the process of dripping peptidization. There are various factors on which this process depends including:

1. Concentrate: Density, temperature, pH value
2. Ethanol Addition: Ethanol content, ethanol consumption, flow rate, stir rate
3. Environment: Temperature
4. Equipment: Style of addition, position of stir
5. Refrigeration: Setting time, setting temperature.

Out of all the parameters, the critical process parameters considered are:

1. Density of concentrate
2. Ethanol consumption
3. Settling temperature

Quality by design is a systematic approach to development that begins with predefined objectives and focuses on the product and process to control the factors affecting the quality of the final product. This same principle is being used in the process of ethanol extraction to modify the controllable parameters in order to obtain the best results.

Experimentation

Four active pharmaceutical products as well as the removal of saccharides have been studied. Different techniques such as risk priority number (RPN) etc were used to check the effect of the above-mentioned parameters. It was then realized that the retrieval of the API and the separation of the sugars was not possible at the same time. Thus, the ultimate results help us to study the relationship between critical procedure criteria and the efficiency of precipitation of ethanol. This study focuses on innovation in the production of botanical drug products.

The experiments were designed to study the effects of the three critical factors. The ultimate aim of the design was to accomplish an increased understanding of the process and finalize the designing requirements of ethanol precipitation.

The DOE can be demonstrated as these following steps:

1. 100 ml concentrate prepared with different densities
2. 95% ethanol solution (v/v) pumped into it with continuous stirring
3. After desired consumption was reached, the process was stopped
4. Mixtures were sealed and refrigerated for 24 hours.

The process variables chosen were concentrate density, ethanol consumption, and settling temperature. The APIs to be extracted included compounds named Danshensu (DSS), Rosmarinic acid (RA), Salvianolic acid (SAB), and Protocatechuic aldehyde (PA) along with saccharides to be removed.

Table 1. Percebtage Recovery of APIs and removal of Saccharides at different values of crtitical factors

Run No.	DSS	RA	SAB	PA	Saccharides	Concentrate density (g/ml)	Ethanol (ml/ml)	Settling temperature ^{0}C
1	56	81	66	90	56	1.19	2.3	5
2	46	74	54	83	70	1.22	2.3	15
3	47	77	62	90	79	1.22	2.8	25

Danshensu (DSS), Rosmarinic acid (RA), Salvianolic acid (SAB), and Protocatechuic aldehyde (PA)

In the first run, the parameters varied were density and temperature, run two, only temperature, and run three, consumption and temperature. The removal of saccharides is maximum at higher values of the parameters, while the recovery of the APIs drops at these levels.

The above study emphasizes the importance of QbD as a powerful tool to study the relation between the process and critical factors. The conditions that are favorable for the removal of saccharides cause more loss of the bioactive agents. Therefore, a high level of saccharide removal and API recovery cannot be achieved simultaneously. The chemical and physical

properties of the active agents influence the losses of active components. The use of innovative techniques and QbD for the manufacturing of botanical products helps us to optimize and control the process to achieve the most desired outcomes.

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Pharmacotherapeutics in Space

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Abstract

Pharmacotherapeutics in space is the branch of pharmacology that involves the studying of therapeutics and the effects of drugs in space. Since the environment of space is completely different from that of earth, the rules of pharmacology do not seem to work efficiently there. The research done until now is not as effective as on earth and hence scientists depend on the shortcomings from the previous missions. Changes are made and efforts are done with every mission to improve the stay during the entire mission. The study of changes in the human body is an effective criterion to design the formulation and dosage forms for a space mission. Microgravity plays an important role in the changes in pressure, temperature, and radiation in space which affects the human body. The weakened immune system is responsible for the deterioration of the health of the astronaut. The altered conditions of space cause a great decline in health and hence demands better pharmacotherapeutic study in space. Before any mission spacemen go through a series of physical tests and consultation. These tests are required to study the therapeutic needs of each of the crew members. Various studies and research tried categorizing the drugs permitted in space, but they failed due to the inefficiency of proper documentation, anecdotes, and voluntary reporting.

Keywords: Pharmacology, Space, Apollo Missions, Aerospace Pharmacy, Microgravity, Astronaut

Introduction

Pharmacotherapeutics in space is the study of the therapeutic uses and effects of drugs in space. The factors that it takes into consideration are –

(1) Stability of pharmaceutical dosage forms.
(2) Medical practices based on evidence.
(3) Study of pharmacokinetics (PK) and pharmacodynamics (PD).
(4) Systemic evaluation of therapeutic monitoring.
(5) Facilitate technologies for drug treatment.
(6) Monitoring and management of space missions under keen observation and record results accordingly.

Aerospace Pharmacy

The aerospace pharmacy might sound new, but the concept has been around for centuries.

The concept arose simultaneously with aeronautics and the need is ever demanding. Aerospace pharmacy is simply calling attention to the gaps in current understanding of the metabolism of a living being in space towards a drug and the difficulties in translating terrestrial-based drug studies to a meaningful interpretation of drug stability and effectiveness in space.

Space Pharmacology

Space pharmacology is the study of pharmaceutical drugs used during spaceflights. The studying of drugs in such conditions is necessary because the effects of drugs lose their efficiency during the flight and hence the research is an important part of such in-flight missions.

Research Approach

The research around this field is still primitive and is based on experiential learning. After studying and working around it, all the shortcomings in the previous missions seemed plausible to overcome. Therefore, can be put to use in the forthcoming missions. At present, the knowledge of the effects of spaceflight on medication stability continues to be under research, and still a long way to go. Lack of requisites to track the medication use and their response has impeded the collection of effective data. Hence the pharmaceutical effectiveness is difficult to categorize.

Difficulties in Space from a Pharmaceutical Viewpoint

The environment in space is entirely different from that of the earth. Hence, the researchers have to keep in mind that the degradation of medication is faster in space than on the ground, pharmacokinetics, and pharmacodynamics of the body also change in space. Microgravity or zero gravity comes into play, and this is a major property of the space that changes everything around pharmacotherapeutics. The ultimate ambition of researchers is to study ways to adapt to the environment in space and then the environment of the earth after their return from space.

Microgravity

Study of microgravity; weightlessness or free fall, in other words, zero gravity is responsible for the changes that occur in the body during an in-flight mission. This is due to microgravity which makes it difficult to walk or stand straight in space. While the acceleration due to gravity or simply gravity on earth is $9.8 ms^{-2}$ which does not let us fly around in the environment.

Gravitational force is a natural phenomenon that brings objects possessing mass together. Due to gravity on earth, we have a weight which is the force we exert on earth. But in space due to zero gravity astronauts fly all around and experience weightlessness.

Effects of Microgravity

Extreme variation in temperature, pressure, and radiation levels causes deterioration of health. In lower gravities, the heart does not need to do as much hard work as it does on earth to

pump blood to the upper parts of the body. This results in an increase in the volume of blood in the upper part of the body. Microgravity causes loss of proprioception changes in fluid distribution. The absence of gravity also leads to the expansion of vertebrae which increases the height of an astronaut by 2 inches.

Pharmacology and Microgravity

Pharmacokinetics (PK) is defined as the metabolism of a drug through the body. Whereas pharmacodynamics (PD) is defined as the body's biological response to drugs. The study of both PD and PK is important to provide a better understanding of pharmacotherapeutics. Changes in both PK and PD properties due to fluid shifts in microgravity are the basis for research in this field.

Effects of Microgravity on a Human Body

a) Exposure to microgravity has an altered result on the functioning of the cardiovascular, neurosensory, and Musco-skeletal systems.
b) The decrease in the cardiovascular system decreases the production of red blood cells and can cause cardiac arrhythmia and fluid redistribution.
c) Balance disorder, loss of eyesight, disruption of taste, decreased mental health, orthostatic intolerance.
d) Bone loss, enlargement of bones, muscle loss, spaceflight osteopenia, decompression sickness.
e) Exposure to continued radiation, injure the body which has later implications for the body.
f) Astronauts experience a loss of consciousness and a significant amount of mass as soon as they reach the earth's atmosphere.
g) Barotraumas, sleep disorders, excess flatulence, and immune suppression are the most common disorders recorded in astronauts.
h) Hampering of Metabolism: Impairment of protein Metabolism, lowering of plasma protein, impairment of renal functioning.

Pre-Mission Preparations

For an astronaut signing up for a mission, he/she has to go through several physical tests for study and monitoring purposes. Disease symptoms, illness, and medications are discussed before the mission with a flight surgeon without any requirement for documentation. Whereas OTC (Over the Counter) drugs are taken with proper consultation and documents, required to be submitted before the mission. According to a recent study, 453 medication uses were reported per crew member during a particular mission.

Inflight Drug Stability

When a drug maintains its physical and chemical properties over time, it is called a stable

drug. Any alteration in solubility, excipients, excipient-active ingredient interaction, and potency is capable of lowering the stability of a drug. Hence, it should be kept in mind that the physical and chemical stability of a drug is an important parameter while making a drug.

Similarly, if the concentration of the API (Active Pharmaceutical Ingredient) in the drug fails to meet United States Pharmacopoeia requirements then the drug will be considered unstable, inefficient, and less potent for use in space missions.

SLEP Studies

SLEP study (Shelf-Life Extension Program) is a federal program developed by the U.S Department of Defence in association with the FDA to lower the cost of the drugs used in space.

According to SLEP studies, only those medicines make it to the medication kit in the mission which has at least 2 years of an expiration date. A few drugs listed under the stable category in the SLEP studies are Ciprofloxacin, Phenytoin, Promethazine, and Acetaminophen.

Inefficiency of Drugs in Space

In the year 1999, Putcha et al presented a study, in which he characterized 13 medications into two categories; mildly effective and ineffective, based on their efficiency in treating particular symptoms.

Another similar study published later in 2014 by Banger et al, confirmed the ineffectiveness of a few drugs in space. He reported an anecdotal study about how astronauts have to take two sleep medications due to the ineffective response of the first.

However, the conclusion made by both the studies cannot be considered because it lacks proper documentation, anecdotes, and voluntary reporting. This makes the report uncertain and the result unreliable.

Another point of consideration is the environment, which plays an important role in altering the metabolism of the body. Therefore, the efficiency of a drug can differ with the changes in the environment. A drug that is highly efficient on earth can be completely useless in space if the metabolism of the body is altered.

Drug Metabolism in the Body

The various reasons described in the context above contribute to research taking place all around the world. Data accumulated over the years after various space exploration programs will contribute to the progress in research and help scientists develop better drugs with more efficient drug metabolism.

Changes in the metabolism of the body will change the way the drug acts in the body and hence affects the efficiency of the drug. The following reasons are responsible for the altered drug metabolism in space –

I. Gravitational unloading causes fluid shift which leads to alteration in hepatic blood flow

mechanism and variable enzyme activity.

II. Microgravity delays gastric emptying causing nausea and vomiting.

III. Altered serum albumin levels and altered renal blood flow may further affect drug absorption, distribution, metabolism, and excretion.

IV. The unequal distribution of the drugs due to the lack of gravity also affects the metabolism of a drug.

V. The alteration of gastrointestinal absorption takes place due to the poor pharmacokinetic behavior of a drug. Therefore, leading to its reduced stability.

Permittance of Drugs in Space

Experiences from previous Apollo missions made the replacement of Marezine with a combination of Scopolamine and Dextroamphetamine for space motion sickness after efficiency studies. Similarly, the drugs mentioned below are a few of the drugs that are permitted in space after studying the conclusions made from previous missions –

I. Aspirin for headache and pain

II. Secobarbital for sleeping disturbances

III. Diphenoxylate (lomotil®) as an anti-diarrheic

IV. Actifed which is a combination of antihistaminic, anti-inflammatory, analgesic, and antipyretic

V. After a sudden unfortunate incidence of cardiac arrhythmia that was reported in the Apollo-15 mission, potassium salt made its place in the space mission medical kits.

VI. An incidence of UTI was reported in Apollo -13 mission which was later treated with Colistin (Colimycin®).

VII. Vitamins, ophthalmic antibiotic ointments, and decongestants were added very late to the emergency kits.

Conclusion

The various developments in space medications are due to the changes made after overcoming the drawbacks of the previous missions. After each mission, research was made to improve the stay of the crew members in space. Even after the return of the astronauts back to earth, health monitoring is required to study the changes caused to the body due to the change in environmental conditions. It was until recently, a difficult task to categorize drugs but now with the advancement in pharmaceutical sciences, better and effective therapies are prescribed for space missions. The goal is to provide the best treatment possible cost-effectively and sustainably. The research in PK/PD studies, formulation studies, drug dosage form studies, physiology studies, bioavailability studies, and exploration towards the advancement of pharmacotherapeutics in space will eventually lead to the development of a novel drug delivery system for chronic and acute symptoms of diseases in space. It will also attenuate pharmacotherapeutic risks by

identifying and giving safe and effective tools for diagnosis, pharmaceutical preparation, intervention strategies, and therapeutic procedures to check chemical and pharmaceutical studies in space.

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A spotlight on the regulatory aspects of Quality by Design (QbD) along with its latest expansion

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Abstract

Quality by Design (QbD) is a vital aspect to build up the perfect quality of a pharmaceutical product. To reduce the process variability and increase the process capability it is a very important tool. For the compilation with the harmonized regulatory aspect, the ICH Q8(R2), Q9, Q10, and Q11 guidelines are followed. With this already developed guidelines there is a new approach of analytical procedure development compilation (Q14) with quality by design is developed by the council to minimize the error in the testing of drug products and to increase the process capability of the drug analytical system. Therefore, the complete process of a product lifecycle will be signified by the addition of this newer guideline.

Keywords: Quality, Product, Tool, Compilation, Harmonized

Introduction

Quality by Design (QbD) can be defined as a systematic approach, deals with a predefined objective and concentrate on the product as well as process understanding through sound sciences and quality risk management[1]**.** Generally, four guidelines are used to develop a product through Quality by Design they are ICH Q8(R2) – Pharmaceutical development, ICH Q9 – Quality risk management, ICH Q10 – Pharmaceutical Quality System, ICH Q11 – Development & manufacture of drug substances. In 2022 ICH released another guidelines to add more strength on QbD approach by including analytical procedure development in the form of Q14.

Elements of Quality by Design[2]

There are several elements based on which the Quality by Design is performed for the pharmaceutical products. Those are –

CQA- Critical Quality Attributes

CMA- Critical Material Attributes

CPP- Critical Process Parameters

QTPP- Quality Target Product Profile

PAT- Process Analytical Tools

Table 1. Goals and advantages of Quality by Design[2]

Goals	Advantages
Achieve the meaningful quality	Proper utilization of resources
Enhance the process capability	More flexible approach
Enhancement in manufacturing capability	Quality can be assured

Regulatory aspects of Quality by Design[3-6]

ICH (International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use) provides the guidelines for Quality by Design in the quality guidelines like:

ICH Q8(R2) – Pharmaceutical development

Pharmaceutical development is based on few elements which define and play a vital role to establish QbD for a pharmaceutical product. Those are flexible regulatory approach, research elements, design space, and control strategy which helps the industry to develop the foundation of the product that can withstand with its quality in any condition throughout its whole lifecycle.[3]

ICH Q9 – Quality Risk Management

Quality risk management is performed based on several steps like – identification, analysis, and evaluation of risk, control of risk, result, and review. It helps to achieve the meaningful quality of a product by measures the minor, major and critical risk factors associated with the products on their development phase which reduces the probability of recalling the product from the market that ultimately leads to the continual business improvement.[4]

ICH Q10 – Pharmaceutical Quality System

The pharmaceutical quality system deals with the management responsibility i.e., the organizational behaviour, product lifecycle (from beginning to end of the operation), and continual improvement which helps to maintain the quality throughout the whole system. Beside this to achieve the smooth work protocol with minor deviation this guideline is also useful[5]**.**

ICH Q11 – Development & manufacture of drug substances

It describes the manufacturing features of a drug. The steps are manufacturing process and control, control strategy, process validation and evaluation, lifecycle management, submission of documents through CTD format, manufacturing process development. The key success area of this guideline is to maintain the documents throughout the whole process.[6]

Latest expansion of Quality by Design guidelines

ICH Q14 - Analytical Procedure Development

It is the newer approach of analytical protocol development by adding the quality by design with analytical procedure development which is released on 2022. It includes analytical target profile (ATP), knowledge and risk management in analytical procedure development and continual improvement, evaluation of robustness and parameter ranges of analytical procedures, analytical procedure parameter ranges, analytical procedure control strategy, established conditions for analytical procedures, lifecycle management and post-approval changes of analytical procedures, development of multivariate analytical procedures, re-calibration and model maintenance, development of analytical procedures for real time release testing: special considerations, submission of analytical procedure related information, documentation. The above parameters are taken into consideration to achieve the overall success in analytical testing.[7-10]

Conclusion

So, to achieve the goals of quality by design and to achieve the good quality of product industries nowadays are following the harmonized regulatory guidelines provided by ICH which results in less product failure and overall business development. Addition of the new guidelines related to analytical development will also create a good impact as the tests will going to be conduct in a specific well-established manner which will create a systematic significance not only in analytical testing but also in overall product development.

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Parkinson's Gut Connection

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Abstract

Along with diabetes and high blood pressure, neurodegenerative disorders are the main cause of morbidity, death, and disability. Parkinson's disease is one of the most common neurodegenerative illnesses, affecting mostly persons in their forties and fifties, aged 60 and more. The actual pathogenesis of the disease starts long back when the person is in his/her 30's or 40's. The classic symptoms of Parkinson's include tremor slowed movements called bradykinesia, rigid muscles, impaired posture and balance, speech and writing difficulty.

Keywords: Parkinson, neurotransmitter, gut, brain, alpha-synuclein

Introduction

The gut, which may be linked in Parkinson's disease, appears to have first appeared in literatures more than 200 years ago, according to the oldest evidence. While most of us recognize Parkinson as the disease of the brain which affects nerve cells deeply present in the brain such as basal ganglia and substantia nigra, primarily involved in the production of an essential neurotransmitter called Dopamine which is responsible for relaying communication between different brain parts crucial for smooth muscle movements and proper nerve functioning. Scientists have found the gut to be linked with the development of Parkinson's disease. Constipation has been identified as one of the most prevalent symptoms of Parkinson's disease, affecting around half of those diagnosed with the disease and typically occurring before the beginning of movement-related deficits.

There is an accumulation of alpha-synuclein called lewy bodies in the brain which over time leads to major loss of neurons in the brain responsible for dopamine production. Lewy bodies, or clumps of alpha-synuclein, were found in both the brain and the gastrointestinal nervous system in post-mortem samples of Parkinson patients, suggesting a link between the gut and the start of Parkinson's disease.

Scientists are still unclear about the exact role of the gut in the pathogenesis of Parkinson but there's a growing body of evidence and hypothesis suggesting the gut's connection with the brain and how changes in the gut can significantly affect brain and nervous system health. Indeed, this research forces us to be more conscious about our gastrointestinal health and pay utmost attention to any changes occurring in GI because it is said that if a person's gut is healthy and if they do not suffer from any significant GI discomforts that will surely eliminate major health

problems occurring later in life. The main question here is, how changes in the intestine drive neurodegeneration in the brain? Some studies propose that aggregates of alpha-synuclein move from intestines to the gut via the vagus nerve, some others suggest that the gut influences brain through inflammation or products of bacterial breakdown stimulates activity along this way.

The Gut-Brain Bridge

The vagus nerve, a bundle of fibres that originates from the brain stem and innervates major abdominal organs such as the stomach, oesophagus, and most of the intestinal tract including the gut, may be affecting the brain. The vagus nerve is the primary route through which pathological triggers of Parkinson's disease travel through the gastrointestinal tract to the brain.

In one study conducted, it was found out that the rodents who were injected alpha-synuclein transversed from the vagus into the brain and gets deposited over there affecting prominent nerve cells responsible for the production of dopamine. Now, one prominent question that arises here is why does the protein accumulate in the gut in the first place?

Certain research suggests that the possibility of alpha-synuclein appearing in the gut could be to help intestines fight off the pathogens, indicating that alpha-synuclein can potentially attract and activate immune cells to elicit an immune response. When we eat, there is a high possibility of harmful microbes entering the body which in turn enter the intestine and are responsible for triggering the buildup of alpha-synuclein in the intestines which is essentially produced as one of the defense mechanisms of the immune system. The misfolded alpha-synuclein begins to accumulate in the enteric nerves' decade before the appearance of neurological symptoms. One misfolded protein triggers misfolding of other immediate proteins which eventually leads to the formation of large chunks of defective and harmful proteins traveling from GI to the brain.

The human microbiome i.e., the totality of good microorganisms presents in the human gut which assists the body in so many processes has been the area of interest among Parkinson's researchers. Some studies suggest that people with Parkinson's harbor a unique composition of gut microbes.

According to one research, these microorganisms work by producing metabolites such as long-chain fatty acids. It was revealed in one of the animal trials that these chemicals activate microglia cells, which are brain immune cells.

Does Gut Inflammation affect Brain?

Another study conducted on 144,018 individuals showed that gut inflammation, possibly from gut microbes could affect the brain and give rise to Parkinson's. The researchers discovered that those with inflammatory bowel illness had a 28 percent greater risk of Parkinson's disease, whereas those who used anti-inflammatory medications such tumor necrosis factor (TNF) inhibitors had a 78 percent lower risk of the neurodegenerative disease.

Intestinal inflammation and Parkinson:

One of the numerous theories is that a persistently irritated gut raises alpha-synuclein levels locally in the intestine or causes inflammation throughout the body, which changes the permeability of the blood-brain barrier, allowing the toxic protein to readily enter the brain. Or maybe increased levels of circulating cytokines that promote inflammation and simply any change in the gut microbiome can influence gut inflammation which is then transversed to other body organs including the brain.

Research is still in progress to understand the exact role of TNF-inhibitors on both brain and GI, that whether they exert protective effect only to individuals with IBD or they protect the brain by reducing inflammation. Other groups of scientists are also investigating the role of anti-inflammatory drugs used in conditions like rheumatoid arthritis and psoriasis on brain health.

A lot of investigation still needs to be done and going on the gut-brain relation and how treatments catering to the gastrointestinal tract such as constipation affects brain's health, the scientists hope that targeting early gut pathology affects or restores the central nervous system health.

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Role of Ormeloxifene, a Selective Estrogen Receptor Modulator, in the Treatment of Dysfunctional Uterine Bleeding: A Prospective Clinical Study

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Abstract

The most common cause of abnormal uterine bleeding is dysfunctional uterine bleeding (DUB). In women of reproductive age, it causes morbidity, anemia, and needless hysterectomies. This study was carried out to determine the efficacy and safety of ormeloxifene in the management of DUB. This prospective clinical study was done for one year in the Department of Obstetrics and Gynecology at a tertiary care hospital. The study comprised randomly selected 86 women over the age of 18 years who came to the out-patient department with DUB. Following the baseline examination, each patient was given Ormeloxifene 60 mg orally twice a week for the first 12 weeks, then once a week for the remaining 12 weeks. The efficacy of ormeloxifene was determined by comparing pre-and post-treatment pictorial blood loss assessment chart (PBAC) scores, hemoglobin (Hb) concentration, endometrial thickness, the presence of clots in menstrual blood, and dysmenorrhoea. Any side effects that patients had were also recorded. After 24 weeks of treatment, the mean PBAC score was reduced dramatically from 392.54 to 219 ($P < 0.05$). Hb was significantly raised from 8.78 g/dl to 10.46 g/dl ($P < 0.05$). The average endometrial thickness was decreased from 8.72 to 5.35 millimeters ($P < 0.05$). There was considerable improvement, with 68.08 percent of patients ($p < 0.05$) experiencing relief from dysmenorrhoea. Patients in this trial had no serious adverse effects. Because of its outstanding efficacy and safety profile, ormeloxifene is a good candidate for the treatment of DUB.

Keywords: Dysfunctional uterine bleeding (DUB), Selective estrogen receptor modulators (SERM), Ormeloxifene, Pictorial blood loss assessment chart (PBAC), Haemoglobin

Introduction

Dysfunctional uterine bleeding (DUB) is a state of aberrant uterine bleeding without any clinically identifiable organic, systemic, or iatrogenic etiology. It is the most frequent menstrual condition among women of reproductive age which diagnosis is made by excluding all other known causes.[1] It can involve any woman from menarche to menopause and accounts for roughly 20% of gynecology clinic visits. After nutritional anemia, it is an important cause of iron deficiency anemia in females.[1,2] It hurts a woman's physical, mental, social, and material well-being. It has significant economic implications for women in the workplace. It is more common in the

anovulatory than in the ovulatory cycle.[3]

Management of DUB is a challenging task.[4] There are a variety of therapeutic options available, including medicinal therapy and surgical techniques. The RCOG recommends starting with medical therapy before resorting to surgical interventions due to the morbidity involved with surgical procedures.[1] A reliable medicine for the treatment of DUB should meet the following criteria: it should be effective, easy to use, inexpensive, have few side effects, and have a large safety margin. Selective estrogen receptor modulators (SERMs) (also known as Designer estrogens or Fantasy estrogens) bind to estrogen receptors with high affinity and imitate the activity of estrogen in some tissues while acting as estrogen antagonists in others.[3]Ormeloxifene (also known as centchroman) is a SERM that has been found to have an anti-estrogenic action in the uterus, which is the pharmacological basis for its use in DUB.[5]

Ormeloxifene: It has been marketed as a birth control product in India since the early 1990s. Its chemical name is trans-7-methoxy-2,2-dimethyl-3-phenyl-4(4-(2-pyrrolidinoethoxy) phenyl(-chromanhydrochloride). With a molecular weight of 493.5, it is a white to off-white powder. Under standard storage conditions, this medicine is quite stable.[5] This is a non-steroidal, non-hormonal third generation benzopyran SERM that competes with estrogen to block cytosol receptors; antagonizes estrogen's action on uterine and breast tissue, and enhances estrogen's effect on the vaginal, cardiovascular, and central nervous system. It's not only an excellent oral contraceptive, but is also effective for DUB, mastalgia, and advanced breast cancer. It also helps to prevent bone loss, decrease cholesterol, and maintain brain cognitive function. Ormeloxifen has a plasma half-life of roughly one week. It has a high safety profile, with minimal adverse effects such as nausea, headaches, weight gain, and a delayed or prolonged menstrual cycle.[2,6]

Ormeloxifene can be a good alternative to hysterectomy in this era of organ conservation. No such study on ormeloxifene for DUB has been conducted in our institute. So, the purpose of this study was to assess the efficacy and safety of ormeloxifene in the treatment of DUB.

Materials and Method

This prospective clinical work was conducted in the department of Obstetrics & Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India on patients visiting the out-patient department for one year. Before beginning the study, Institutional Ethics Committee approval, as well as signed informed consent from each patient, was taken. Randomly selected 86 women of age more than 18 years presenting with DUB were included in the study. Women with pregnancy, bleeding due to pregnancy complications such as vesicular mole, or abortions, lactating mother, desirous of fertility, IUCD or pill users, acute heavy bleeding necessitating emergency treatment, any pelvic pathology, malignancy of breast or genital tract, postmenopausal bleeding, diabetes, chronic hypertension, blood dyscrasias, thyroid dysfunction, psychological disorders, and liver, renal, and heart disease and hypersensitivity to the drug were excluded from the study. The nature of the study, its objective, regimen, protocol, and follow-up were all discussed in detail with

the patients who met the inclusion criteria.

All patients received a routine clinical examination (general, systemic, breast, and gynecological examination) and laboratory investigations (complete blood count, coagulation profile, blood sugar, thyroid profile, kidney function test, liver function test, pap smear, endometrial histopathology, and transvaginal ultrasonography) after taking thorough history (including presenting complaint, menstrual & obstetric history, and past medical and surgical history).

Each patient who participated in this trial was followed for a total of 24 weeks. Patients were given ormeloxifene 60 mg orally twice a week for the first 12 weeks, then once a week for the remaining 12 weeks.[6] Therapy was continued regardless of menstrual periods, and patients were asked to return for monthly check-ups. A full menstrual history was collected, and a physical examination was performed at each appointment. The menstrual blood loss (MBL) was measured using a pictorial blood loss assessment chart (PBAC)[7] score (Table 1). Women were instructed to use sanitary napkins with identical absorbency capacity.[3] They were asked to keep a record of how many napkins they used each day and how much soiled each pad was. The number and amount of clots that were passed were also recorded. Different scores were assigned to varying degrees of soiling of sanitary napkins as well as the number and size of clots passed. Menorrhagia was diagnosed when the PBAC score was more than or equal to 100. MBL, clot passage, hemoglobin (Hb), dysmenorrhoea, and endometrial thickness (ET) in the proliferative phase by TVS were the key outcome measures. Any side effects experienced by patients were also noted.

Collected data were expressed as mean ± standard deviation (SD) and range, and the paired t-test and Fisher's exact test were used to evaluate data. All statistical analysis was carried out using SPSS software version 20 (SPSS, Chicago, IL, USA), and differences were considered significant when the p-value was less than 0.05.

Results and Discussion

A total of 86 DUB patients were included in the study. The patient's mean age was 37.71 years, with a range of 18 to 50 years. The mean parity was three, and the average symptom duration was 9.4 months (5-22 months) (Table 2).

Table 1. Pictorial blood loss assessment chart score

	Level of soiling	Score
Pads	Light	1
	Moderate	5
	Saturated	20
Clots	Size of a rupee coin or smaller	1
	Larger than a rupee coin	5

Table 2. Clinical profile of patients

Clinical parameter	Mean (range)
Age (year)	37.71 (18-50)
Parity	3 (1-6)
Duration of symptoms (months)	9.4 (5-22)

Table 3. depicts the various outcome measures. The mean baseline PBAC score before therapy was 392.54, with a range of 120 to 708. The mean PBAC score after treatment was 219, with a range of 0 to 469. The mean reduction in post-treatment PBAC score of 173.54 was statistically significant ($p < 0.05$). Our findings were similar to those of Biswas et al. (2004)[8], Kriplani et al. (2009)[9], and Hadalagi and Rashmi (2018)[2] study. After 3 months of ormeloxifen treatment, Shravage et al. (2011) study reported an 85.7 percent reduction in menstrual blood loss (mean PBAC score decreased from 262 to 73).[10] Another study by Agarwal et al. (2013) found that menstrual blood loss was reduced by 61.1 percent (mean PBAC score reduced from 216 to 84).[11] Because ormeloxifene has an antiproliferative activity on the uterus (endometrium) and produces endometrial atrophy, which may be the cause of reduced menstrual blood loss and hence PBAC score.

In this trial, the mean baseline Hb was 8.78 gm/dl, with a range of 6.82 to 11.47. The mean Hb after therapy was 10.46 gm/dl, with a range of 8.45 to 12.41. The increase in Hb level of 1.68 gm/dl was statistically significant ($p < 0.05$). After 3 months of ormeloxifene treatment, Dhananjay and Nanda (2013) observed a statistically significant rise in hemoglobin level (8.26 to 10.59 g/dl, $P < 0.001$).[12] In the studies conducted by Rani et al. (2016)[13], and Bhattacharya and Banerji (2010)[14], the mean increase in hemoglobin level was 1.23 and 2.54 gm/dl, respectively. This increase in hemoglobin level was most likely caused by the control of excessive menstrual bleeding.

Our study found pre-treatment endometrial thickness of 8.72 mm and post-treatment endometrial thickness was 5.35 mm, with a significant decrease of 3.37 mm ($P < 0.05$). This finding was similar to that of Gandotra et al. (2017)[1], Karmakar and Deshpande (2016)[4], and Dhananjay and Nanda (2013)[12] study.

The presence of clots is a strong indicator of abnormally high menstrual blood flow.[15] In this study, the frequency of clots was shown to be lower (6.97%) after treatment than before treatment (72.09%), and the difference was found significant ($p < 0.05$). Several researches demonstrate similar results to ours. Women in the Sawarkar et al. (2018) trial showed a significant reduction of clot passage from 78.9 to 7.07 percent.[16] Gaur et al. (2018) study showed improvement by the absence of clots in 96 % of patients.[6]

Dysmenorrhoea is a common problem that is reported by the majority of patients. The prevalence of dysmenorrhea in our study was lower (17.44%) after treatment than before

treatment (54.65%), and the difference was statically significant ($p < 0.05$). In this trial, 68.08 percent of patients improved their dysmenorrhoea, compared to 81.8 percent and 83.33 percent in Laxmi (2003)[17] and Komaram et al. (2013)[3] studies, respectively. In the Grover et al. (2013) trial, dysmenorrhoea improved in 62.5 percent of the cases.[5]

Table 3. Outcome measurements

Parameter		Pre-treatment	Post-treatment	p value
PBAC score	Range	120-708	0-469	< 0.05
	Mean SD	329.54-184.05	219±116.26	
Hemoglobin level (gm/dL)	Range	6.82-11.47	8.45-12.41	< 0.05
	Mean SD	8.78±1.36	10.46±1.10	
Endometrial thickness (mm)	Range	4.23-13.17	1-10.34	< 0.05
	Mean SD	8.72±2.61	5.35±2.74	
Presence of clots	No. (proportion of subjects)	62 (72.09)	6 (6.97)	< 0.05
Dysmennorhea	No. (proportion of subjects)	47 (54.65)	15 (17.44)	< 0.05

As shown by table 4, the majority of patients (26.74 %) had amenorrhea followed by 13.95 % who had hypomenorrhea and 9.30 % had complained of spotting. 6.97 % of patients had some form of gastrointestinal symptoms like nausea, pain abdomen, dyspepsia, etc, 3.48 % had headache and 2.32 % had weight gain. Although considered as a side effect, amenorrhea/hypomenorrhea really acted as a favorable consequence.[4] In the study done by Rani et al. (2016), amenorrhoea was noted in 22 % of patients.[13] Most frequent side effects in Gaur et al. (2018) study was prolonged cycle beyond 35 days (50%) followed by mild abdominal pain (37.55 %) and weight gain in 6.25 % patients.[6] Bhattacharyya and Banerji (2010) study had side effects like amenorrhea (63.63 %), stress urinary incontinence and genital prolapse (each 27.27 %), spotting and hypomenorrhea (each 9.1 %).[14] In our analysis, no cases of ovarian enlargement were detected, however in the Kriplani et al. (2009)[9] study, 7.1 percent of patients reported ovarian enlargement after therapy with ormeloxifene. Hence, there appears to be sufficient evidence to recommend ormeloxifene as an ideal drug for the treatment of DUB.

Table 4. Side effects of ormeloxifene

Side effects	Number	Percentage (%)
GI symptoms	6	6.97
Amenorrhea	23	26.74

Side effects	Number	Percentage (%)
Hypomenorrhoea	12	13.95
Spotting	8	9.30
Headache	3	3.48
Weight gain	2	2.32

Conclusion

Ormeloxifene has a substantial effect on reducing endometrial thickness, reducing menstrual blood loss, and improving dysmenorrhea, all of which improve the patient's overall condition and quality of life, as seen by the significant improvement in hemoglobin level. Although described as a complication, amenorrhea or hypomenorrhea was a favorable result in DUB. Ormeloxifene is undoubtedly a better alternative to hysterectomy for women who want to avoid surgery and maintain their reproductive functions. Thus, ormeloxifene has a great prospect in the treatment of dysfunctional uterine bleeding due to its efficacy, patient acceptability, compliance, low cost, and nominal side effects.

The **limitations** of this research work include 1) the small size of the study group. There is a need for a larger research group. 2) There was no hysteroscopy performed. 3) The study group was not followed up for a long time.

Declaration

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