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Review Article

Basic Chemistry,Mode Of Action And Clinical Uses Of Co-Trimoxazole

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ABSTRACT

Co-trimoxazole, a combination of sulfamethoxazole and trimethoprim, is a widely used antibiotic with a broad spectrum of activity against various bacterial infections. This abstract provides a concise overview of the basic chemistry, mode of action, and clinical uses of co-trimoxazole. The synergistic action of sulfamethoxazole and trimethoprim targets two consecutive steps in the bacterial folate synthesis pathway. Sulfamethoxazole inhibits dihydropteroate synthetase, a key enzyme in folate synthesis, whereas trimethoprim inhibits dihydrofolate reductase. By disrupting folate synthesis, co-trimoxazole impairs bacterial DNA, RNA, and protein synthesis, leading to bacterial cell death. Co-trimoxazole is employed in the treatment of various bacterial infections, including respiratory tract infections, urinary tract infections, skin and soft tissue infections, and gastrointestinal infections. It is particularly effective against bacteria such as Escherichia coli, Staphylococcus aureus, and Haemophilus influenzae. Additionally, co-trimoxazole is used in the prophylaxis and treatment of Pneumocystis jirovecii pneumonia in immunocompromised individuals, such as those with HIV/AIDS.

INTRODUCTION

In the late 1960s ,the combination of trimethoprim and sulphamethoxazole(co-trimoxazole)was firstly introduced into clinical practices and used to treat many infectious diseases ,like urinary track infections, respiratory track infection, sexually trasmitted diseases(HIV) and many gram-ve bacterial infection and typhoid fever A variety of bacterial, fungal, and protozoal pathogens, such as Nocardia, Listeria monocytogenes, Brucella, Stenotrophomonas maltophilia, Burkholderia, Coxiella burnetii, Tropheryma whipplei, atypical mycobacteria, and Pneumocystis jirovecii, have since been reported to be effectively resistant to co-trimoxazole. Co-trimoxazole has been used to treat susceptible Plasmodium falciparum, Cyclospora, and Isospora infections, among other protozoal illnesses, in addition to toxoplasmosis.

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Co-trimoxazole has shown favorable clinical success in treating invasive methicillin-resistant Staphylococcus aureus infections, according to several retrospective and prospective investigations. Here, we provide a summary of the data that has been gathered over the last three decades about the novel, "unconventional," clinical usage of co-trimoxazole.(1)

Trimethoprim-sulfamethoxazole (co-trimethoxazole) is well established compound that is extensively used for various indication is countries with limited resources, offering An a additional option in the battle against many pathogens, owning to its low cost, acceptable to toxicity profile, availability by both oral and intravenous, routes, and bacteriocidal activity.(2) co-trimoxazole Are the fixed dose combination of two antimicrobial agents Trimethoprim-sulfamethoxazole (TMP-SMX) a diaminopyridine (Timethoprim) and sulfonamide (sulfamethoxazole) purposely chosen to provide sequential and synergistic inhibition of bacterial folate metamolism.(3) Trimethoprim was firstly synthesized during 1950s and gives antimicrobial and antiparasitic activity.it is the prototype of group of nonsulfonamide drugs that gives their action by inhibiting dihydrofolate reductase in bacterial and protozoal cell..(4)

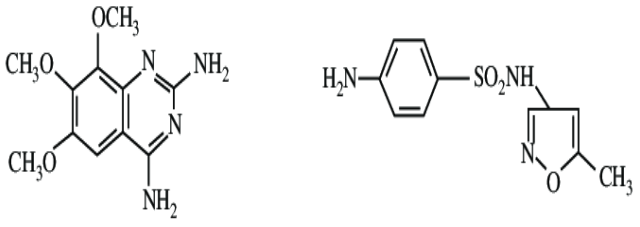


Fig.no.1 Structure of co-trimoxzale

MECHANISM OF ACTION OF CO-TRIMOXAZOLE

These are the fixed dose combination of two drugs trimethoprim and sulfonamide.individualy both are bacteriostatic in nature but in combination gives bacteriocidal action

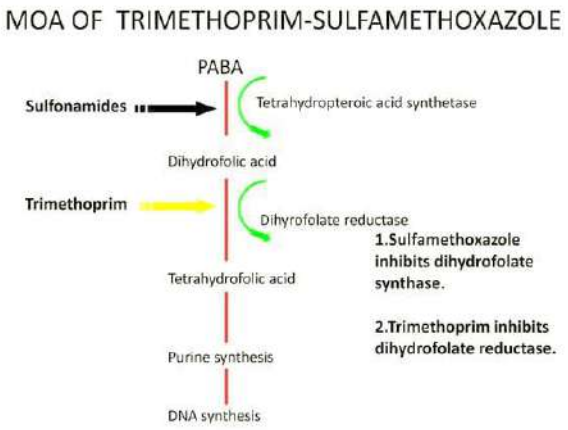


Fig no.2 MOA of Co-Trimoxazole

The mechanism of action of co-trimoxazole(SXT) by inhibiting the synthesis of tetrahydrofolic acid,which is the active form of folic acid is necessary for the synthesis of thymine,purines,and bacterial DNA(Figure).these combination of drug(SXT) exerts its activity upon two key steps on the same metabolic pathway.sulfamethoxazole is the structural analog of para-aminobenzoic acid and by inhibiting the synthesis of its precursor dihydrofolic acid .Trimethoprim(TMP) on other hand ,is an analog of the pteridine moiety in dihydrofolic acid and competes for the dihydrofolate reductase (DfrA) inhibiting the production of tetrahydrofolic acid from dihydrofolic acid.this sequential blokage of 2 enzyme in one pathway result in an effective bacteriocidal action.(5)

- **Pharmacokinetics**

Trimethoprim-sulfamethoxazole are extremely and nearly completely absorbed from the upper intestinal tract.an oral dose of 160 mg of TMP will give a peak serum level of 2 µg per ml after 2 hour ,the half- life is 13 hours.an oral dose of 1200 mg of SMX will give peak serum level of about 60 µg per ml after 2 hours ,the serum half-life being about 12 hours.Because of their similar pharmacokinetics TMP-SMX are administered together. a single standard dose ratio of TMP-SMX is (1:5) will result in a peak serum

concentration of 1 µg of TMP per ml,and 20 µg of SMX per ml within 2 to 4 hours.(6)

- **Adverse and toxic effect of co- trimoxazole**

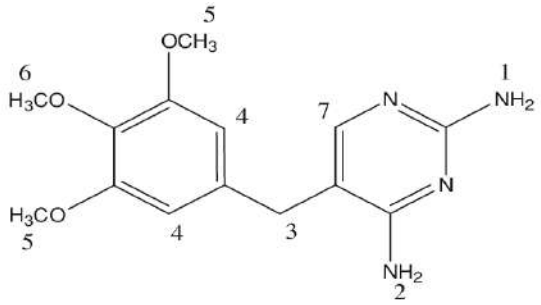
In the surveliance studies describes skin lesions in 3.5 percent and upper GIT symptoms in 3.4 percent of 649 hospitalized patients who receivinng TMP-SMX.all the adverse effect were reversible.more serious,less common reactions of co-trimoxazole occurs megaloblastic bone marroes in alcoholics,pregnant women,patient being treated with phenytoin,and patients with chronic renal diseases.(6)Trimethoprim can cause side effects which can similar to the sulfonamides such as pruritic rashes,gastrointestinal distress,haematologic abnorbilities and fever.People with HIV who take trimethoprim may have a higher chances of experiencing rash and fever.Sulfonamides have the potential to increase patients' susceptibility to photosensitivity. Additionally, they may lead to bone marrow suppression, which can manifest as hemolytic anemia, leukopenia, and thrombocytopenia. It is important to note that individuals with a genetic deficiency in glucose-6-phosphate dehydrogenase (G6PD) are at a heightened risk of experiencing adverse hematologic effects.(7)

CHEMISTRY OF COTRIMOXAZOLE

TRIMETHOPRIM

Trimethoprim,5-(3,4,5-Trimmethoxybenzyl)pyrimidine-2,4,diamine is a synthetic,broad-spectrum anti-microbial agent which act as a inhibitor of bacterial dihydrofolate reductase.this drug is mainly used in combination with sulfonamides for prophylasis and used to treat urinary tract infection and certain types of pneumonia.Trimethoprim is characterized by a very low aqueos solubility.the fact that complicates the preparation of formulation such as those for the intravenous administration.(8) trimethoprim is fairly active against a many gram-positve cocci and gram- negative rods.Estabished the indiactions for the for co-trimoxazole are infections of the sinuses,ears,lungs and urinary tract and infections due to salmonella,nocardia,brucella,stenotrophomonas maltophilia,pneumocystis jrovecii and toxoplasma.(9) Trimethoprim (TMP) is small drug molecule containing 2-aminopyridine scaffold.TMP was initially considered as a antimalarial agent,but now considered as a highly effective against bacterial infection,especially in synergic combination with sulfamethoxazole.TMP is bind to the Dihydrofolate reductase(DHFR) its affinity to binds for bacterial DHFR 3000 times greater than Human DHFR. Dihydrofolate reductase (DHFR,EC1.5.1.3) is a critical enzyme that catalyses reduction of dihydrofolate to tetrahydrofolate.Methotrexate (MTX),Trimethoprim (TMP) and pyrimithamine.having 2-aminopyridine moiety,they are the selective inhibitors of DHFR.The two rings of TMP alllows for structural changes which resulting in different lipophilicity and resistance profile.(10)

- **Chemical structure of trimethoprim**



Trimethoprim is an a aminopyrimidine antibiotic whose structure consist of pyrimidine 2,4 diamine and 1,2,3 trimethoxybenzene moieties linked by a methylene bridge.it has role as an EC 1.5.1.3(dihydrofolate reductase) inhibitor.(fig.)

- **IUPAC Name of Trimethoprim**

IUPAC Name 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine

- Molecular weight of Trimethoprim

Molecular weight of trimethoprim is 290.32 g/mol

- Molecular formula of Trimethoprim

Molecular formula of trimethoprim C14H18N4O3

- **Synthesis of Trimethoprim**

Trimethoprim,2,4-diamino 5(3,4,5'trimethoxybenzyl)pyrimidine (33.1.51),can be synthesized in various ways.the first scheme of synthesis is begins from the ethyl ester of 3,4,5-trimethoxydehydrocinnamic acid ,which is formylated with ethyl formate using sodium as a base to make an enol of the semialdehyde 3,4,5'-trimethoxybenzylmalonic ester (33.1.49) which undergoes heterocylisazation reaction with guanidine to make 2-amino 4-hydroxy-(3,4,5-trimethoxybenzyl)pyrimidine(33.1.50).subsequen t replacement of the hydroxyl group in resulting product with chlorine using phosphorous oxychloride and then with an amino group ammonia gives the desired trimethoprim.

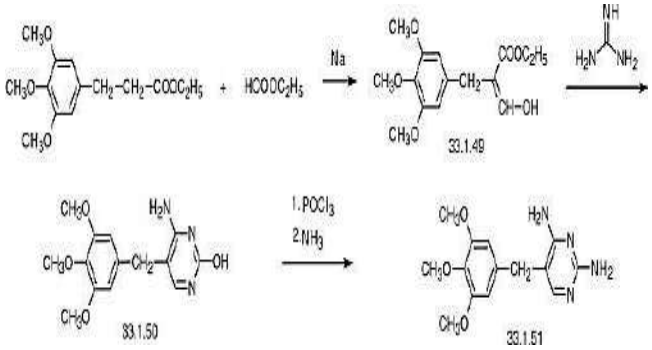


Fig no.2 syntheis of trimethoprim

Trimethoprim also can be synthesized by condensing 3,4,5-trimethoxybenzaldehyde with malonic acid dinirtile in a knoevenagal reaction,which forms the derivative (33.1.53),which partially reduceding to the enamine (33.1.54) by hydrogen using a palladium or carbon catalyst,which upon being reacted with guanidineis transformed into trimethoprim [11]

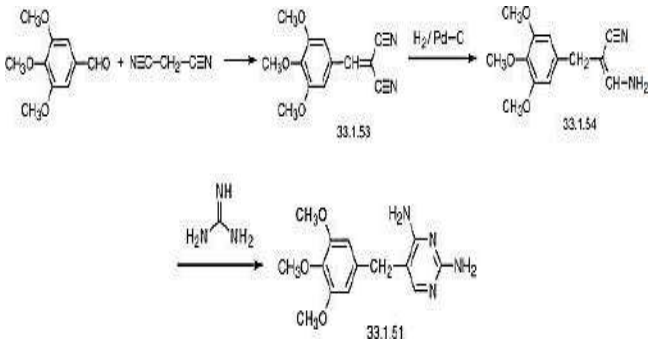


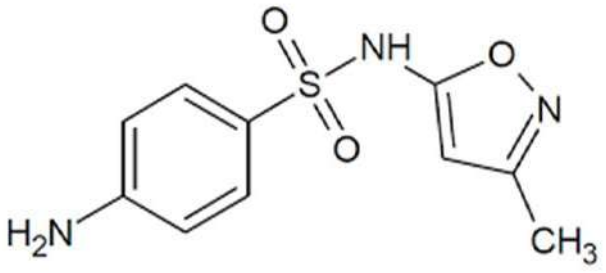
Fig no.3 synthesis trimethoprim

SULFAMETHOXAZOLE

Sulfamethoxazole(SMZ) is an antibiotic used to treat bacterial infection such as prostatitis,bronchitis infection,and Urinary track infection.Additionally it works well against gram negative and gram positive bacteria include Echerichia coli and staphylococcus aureus.Furthermore ,sulfabenzamide as another antibacterial medication is generally consumed in combination with sulfathiazole and sulfaacetamide sold under the brand name of sultrin.an essential functional group of both drug is sulfonamide,so by exchanging different functional group in combination with sulfonamide a wide range of pharmacological drug could be obtained with anticancer,antibacterial,antidiabetics properties.and both the drugs sulfonamide and sulfamethoxazole have donor atom in different locations(N,S,and O).(12) Sulfamethoxazole is a sulfonamide derivative. It has a poor water solubility, rapid elimination through the blood and a number of adverse effects, including skin rashes, fever, hepatotoxicity, haematological disorders, and lymphadenopathy.(13) sulfonamides function as competitive antagonists in microbial cells because they are structural analogs of para-aminobenzoic acid (PABA). PABA is necessary for microbes to produce the precursor of folic acid, dihydrofolic acid. Folic acid is necessary for the production of purines, pyrimidines, and consequently nucleic acids.sulfonamide block the synthesis of folic acid synthesis.Sulfonamides are

more active when combined with trimethoprim or other diaminopyrimidines.Trimethoprim acts on the same metabolic route as sulfonamides by entering bacteria and inhibiting bacterial dihydrofolic acid reductase. As a result, the combination works together effectively. Trimethoprim's binding affinity is substantially higher for the bacterial enzyme than for mammalian enzymes.(14)

- **Chemical structure of sulfamethoxazole**



Sulfamethoxazole is an isoxazole(1,2-oxazole)compound having a methyl substituent at 5-position and a 4-aminobenzenesulfonamido group at the 3-position.it has role as an antibacterial agent,antiinfective agent.

- **IUPAC Name of Sulfametoxazole**

IUPAC name 4-Amino-N-(5-methylisoxazol-3-yl)-benzenesulfonamide

- **Molecular weight of sulfamethoxazole**

Molecular weight of sulfamethoxazole is 253.281

Molecular formula of sulfamethoxazole

Molecular formula of sulfamethoxazole is C10 H11 N3 O3 S

- **CAS Number**-723-46-6
- **Physical Properties**

Sulfamethoxazole is a white to off-white, crystalline powder, practically odorless, and is stable in air. Its melting point is 172o C (15)

- **Synthesis of sulfamethoxazole**

Synthesis of sulfamethoxazole starts with decarboxylation of N-(5-methylisoxazole-3-yl)-carbamic acid to afford 5-methylisoxazole-3-amine, which upon further reaction with para-aminobenzene sulfonamide yields sulfamethoxazole.(16)

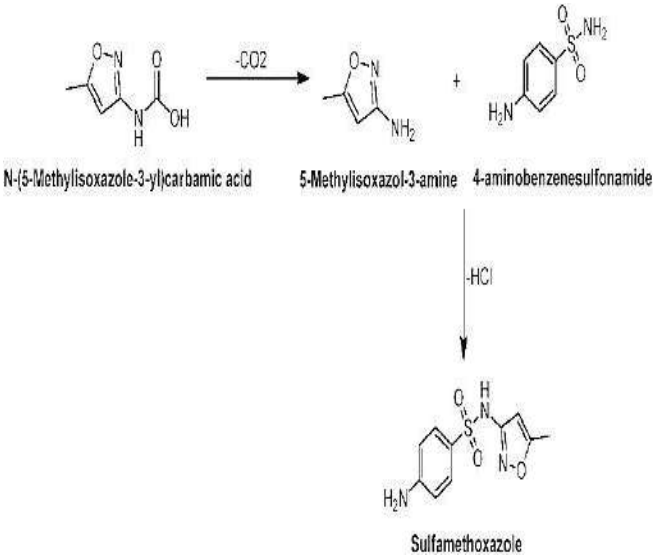


Fig no.4 synthesis of sulfamethoxazole

- **Clinical uses of Co-trimoxazole**

For synergistic benefits, trimethoprim and sulfamethoxazole are almost often taken in tandem.This antimicrobial has antimalarial properties as well.Trimethoprim is bacteriostatic when taken alone, but when coupled with sulfonamides, it becomes bactericidal. Trimethoprim is used in conjunction with sulfonamides to treat Pneumocystis carinii pneumonia, otitis media in infants, prostatic infections, and urinary tract infections. It also helps to eradicate Shigella. Trimethoprim is also utilized for acute conjunctivitis when paired with polymyxin B. Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter species, and coagulasenegative Staphylococcus are the bacteria that can cause simple urinary tract infections. However, because of bacterial resistance, trimethoprim is rarely used alone to treat these infections. There are following clinical uses of co-trimoxazole.(17)

1. Co-trimoxazole in the treatment of Urinary tract infection

Approximately 35% of all hospital-acquired infections are urinary tract infections (UTIs), which are among the most prevalent infectious disorders identified in outpatients and the most common nosocomial infection in many hospitals. In both outpatients and inpatients, Escherichia coli continues to be the primary bacterium responsible for UTIs. The microbiological profile of urinary tract isolates has changed over time due to changes in the antibiotic susceptibility of urinary pathogens, which are impacted by variables such the changing patient population and the widespread use and misuse of antimicrobial drugs. In Turkey, from the early 1980s through the 1990s, co-trimoxazole was often the preferred course of therapy for outpatient infections, including UTIs. The treatment of co-trimoxazole failed due to higher rates of resistance, and as a result, its use was curtailed. Quinolones were consequently the first option for empirical treatment, and their extensive usage has also led to an increase in the rate of resistance to them. The goal of this study was to assess the activity of relevant antibiotics against E. coli strains of urinary tract isolates from outpatients at Refik Saydam National Hygiene Center Laboratory during the period in which co-trimoxazole was replaced by quinolones as the most frequently used antibiotics. (18)

Clinical syndromes in UTI

1. Acute cystitis

Dysuria,urgency, and frequency are linked to acute cystitis. Urine has a discolored appearance, seems unclear, and could be offensive. Haematuria in microscopic form is often seen. Patients with cystitis do not have a fever and should not have an increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) because the condition is not a systemic infection.

2. Acute urethritis

Dysuria and urethral discharge are linked to urethritis. 80% of non-gonococcal organisms, such as Chlamydia trachomatis, Mycoplasma genitalium, and Ureaplasma urealyticum, and 20% of Neisseria gonorrhoeae-caused infections are sexually transmitted. The organisms become long-term commensals in the latter infections, which are generally silent nonspecific urethritis.

3. Asymptomatic UTI

Significant bacteriuria, with the exception of pregnant women, newborns, and patients undergoing urological surgery, is frequently asymptomatic and doesn't require therapy.

4. Prostatitis

Acute or long-term bacterial prostatitis is possible Fever, malaise, perineal pain, urgency, frequency, and dysuria are the hallmarks of acute bacterial prostatitis. Prostatic massage should not be given to patients who have an acute infection; the diagnosis is typically established through urine culture.

Men who have persistent prostatitis, especially those with normal intravenous urography results or recurrent epididymitis, are at risk for repeated UTIs.(19)

Patients and Methods

Trimethoprim (TMP) was initially administered as a preventive measure in 1978. All children between the ages of 1 and 12 who comply with taking prophylactic medication for at least 6 months, either co-trimoxazole or TMP (20 mg tablets of TMP were supplied by Burroughs Wellcome Foundation Ltd Dartford), were included in this study, which ran from 1979 to 1986. The clinician chose the medication they believed to be best suitable for the patient. TMP was administered as a single dose at nighttime in conjunction with sulphamethoxazole (5–10 mg/kg) as co-trimoxazole, or at an approximate daily dose of 1-2 rag/kg. Until the illness reappeared, the preventative medication was left

unchanged. If the radiological investigations showed no abnormalities, prophylaxis was continued for six to twelve months. If renal scarring was detected, prophylaxis was administered continuously while VUR was present and until the kidneys were fully developed. Rectal swabs were taken initially and subsequently at 3-month intervals over a year, both during and after prophylaxis, in children presenting with UTI and beginning prophylaxis with TMP in 1979 and 1980. Rectal swabs were also taken from all children who had received at least 6-months of co-trimoxazole prophylaxis in 1980. Rectal swabs from every child presently using preventive co-trimoxazole or TMP treatment and who had been taking it for six months or longer were cultured in 1986.

Table.1 Between 1979 and 1986, a total of 334 children between the ages of 6 months and 12 years received low-dose prophylaxis with co-trimoxazole or trimethoprim (TMP) for six months or longer.

	Co-trimoxazole	TMP
Total children	226	108
Boys	47 (21%)	19 (18%)
Radiology		
VUR – total	130 (58%)	37 (34%)
Severe reflux	29 (13%)	11 (10%)
Renal scars	21 (9%)	6 (6%)
Duration of therapy		
Range: years	0.5 – 7	0.5 – 7
Total: child years	497	176
Recurrences of infection	23	10
Rate 1 per	22 years	18 years
1 per	10 children	10 children

RESULT

A total of 334 kids with typical renal function were included in the study. A minimum of six months of co-trimoxazole prophylaxis was administered to 226 of these children between 1979 and 1986. Of this group, 47 (21%) were boys, 130 (58%) had VUR and 21 children also had renal scarring. Ninety had no visible structural abnormalities. A total of 497 child years of prophylaxis were administered with intervals ranging from six months to seven years. Twenty-two children experienced 23 UTI recurrences during the trial period, translating to a rate of 1 in 22 child years prophylactic, or 1 in 10 children. Twenty of these kids had VUR, and three of them had kidney scars. (20)

2. co-trimoxazole in the treatment of pneumonia

Acute respiratory infections (ARIs) claim the lives of 3.5 million children annually in poor nations. The World Health Organization (WHO) has established a standard case-management strategy that employs straightforward clinical indicators to identify pneumonia and empirical antibiotic treatment for children discovered to have the illness in order to lower the death rate from acute respiratory infections (ARI) in nations with poor diagnostic and laboratory assistance. To reduce ARI mortality, the Pakistani Ministry of Health launched a nationwide case-management program in 1989. Co-trimoxazole, an antibiotic drug approved by the WHO, was suggested for use in outpatient treatment of pneumonia. After a local investigation revealed that 31% of Streptococcus pneumoniae isolates and 43% of Haemophilus influenzae isolates from the blood of children with pneumonia had significant levels of in-vitro resistance to co-trimoxazole, this policy was called into doubt. 3 However, supporters argued in favor of continuing to use co-trimoxazole, citing the lack of evidence linking in-vitro susceptibility to the drug and the clinical outcome for pneumonia, as well as the fact that co-trimoxazole was shown to be effective in a 1993 local study in which outpatients with non-severe pneumonia saw 91% of 95 cases resolved. Changing the national guidelines for treating pneumonia would undoubtedly be challenging and expensive. We conducted a clinical experiment to evaluate the

efficacy of co-trimoxazole versus amoxycillin for both non-severe and severe pneumonia, as well as to investigate the relationship between clinical response and invitro co-trimoxazole susceptibility.

Patient and methods

The WHO (Geneva), the Centers for Disease Control and Prevention (Atlanta), and the Ministry of Health in Pakistan all authorized this study through their institutional review boards. All children aged 2–59 months who came as outpatients to the Children's Hospital (Pakistan Institute of Medical Sciences) or Rawalpindi General Hospital with coughing or breathing difficulties were considered for study enrollment.Researchers identified and divided children with pneumonia into three groups using established WHO ARI methods.

Non-severe pneumonia was defined as cough or dyspnea with tachypnea (respiratory rate >50 breaths per minute for children aged 2–11 months; >40 breaths per minute for children aged 12-59 months) were considered indicators of non-severe pneumonia.

Severe pneumonia was defined as Coughing or breathing difficulties accompanied by lower chest indrawing (with or without the previously described tachypnea) were considered signs of severe pneumonia.

Extremely severe disease was characterized as a cough or dyspnea accompanied by one or more danger indicators, such as seizures, altered awareness, drowsiness, incapacity to consume fluids, severe clinical malnutrition (grade III, Gomez scale), and stridor when at rest.

Children with extremely serious diagnoses, those living more than 12 miles from the hospital, those taking antimicrobial medications for at least 48 hours prior to presentation (in accordance with standard dosage schedules), those admitted to the hospital for any reason within the previous seven days, those who had previously been enrolled in this trial, and those suffering from hypoxaemia—defined as an oxygen saturation of 87% or less on room air were all excluded.

According to standard WHO guidelines, children who have severe pneumonia should be sent to a hospital so that benzylpenicillin can be injected intramuscularly. In reality, oral antibiotics are frequently prescribed for these kids as outpatient care. Children with either severe or non-severe pneumonia were enrolled in this study.

RESULT

595 kids signed up between November 1991 and April 1992. Seven (1·2%) patients who finished the inpatient phase were not accessible for a follow-up examination, while nine (1·5%) children did not complete the inpatient period.

153 children (26·3%) out of the 580 children whose radiographs were available had indications of pneumonia. 146 (24·5%) children had S pneumoniae or H influenzae isolated from their blood; 131 (89·7%) of these isolates—81 H influenzae and 50 S pneumoniae isolates—were successfully transported to and confirmed at the Centers for Disease Control and Prevention. 76% of the H influenzae isolates could not be typed, and 93% of the isolates were non-b serotypes.

Out of 122 children (20·5%), therapy failure was more likely in those who were given co-trimoxazole than in those who were given amoxycillin.Amoxycillin was superior to co-trimoxazole in treating severe pneumonia in children.(21)

3. co-trimoxazole for the prevention of relapses of wegener’s granulomatosis

Wegener's granulomatosis is a condition with necrotizing granulomatous inflammation of the upper and lower respiratory tract and necrotizing vasculitis, which is most likely to affect the kidneys. It is thought to be of autoimmune origin. The one-year mortality rate is 82% in patients who are not receiving treatment, with a mean survival of barely five months. The prognosis of patients with Wegener's granulomatosis is significantly

improved by treatment with cyclophosphamide and prednisolone. But long-term use of prednisolone and cyclophosphamide is linked to serious, sometimes fatal side effects. It is therefore necessary to use additional strategies to avoid relapses. The positive outcomes of co-trimoxazole, a combination of trimethoprim and sulfamethoxazole, in treating patients with refractory Wegener's granulomatosis or Wegener's granulomatosis limited to the respiratory tract, raise the possibility that microorganisms play a role in recurrences of Wegener's granulomatosis. In order to evaluate the effectiveness of co-trimoxazole in avoiding relapses in patients with Wegener's granulomatosis in remission, we planned a double-blind, placebo-controlled, multicenter experiment. We investigated the impact of co-trimoxazole on the number of infections and serum antineutrophil cytoplasmic antibody titers in addition to the drug's potential influence on the frequency of relapses.

Patient and Methods

In order to determine the effectiveness of cotrimoxazole (800 mg of sulfamethoxazole and 160 mg of trimethoprim) given twice daily for 24 months in preventing relapses in patients with Wegener's granulomatosis in remission during or after treatment with cyclophosphamide and prednisolone, we conducted a prospective, randomized, placebo-controlled study. Using predetermined criteria based on clinical, laboratory, and histological results, relapses and infections were evaluated. Patients were assessed for indications of disease activity, adherence to the prescribed course of care, side effects from the medication, and evidence of infections at least once every three months. Serial measurements of serum antineutrophil cytoplasmic antibody titers were made.

RESULT

41 patients were allocated to receive co-trimoxazole, while 40 individuals were given a placebo. Eight patients (20%) out of the 41 in the co-trimoxazole group required medication discontinuation due to adverse effects. A life-table analysis showed that at 24 months, 82% of patients in the co-trimoxazole group were still in remission, compared to 60% of patients in the placebo group (relative risk of relapse, 0.40; 95% confidence interval, 0.17 to 0.98). In comparison to the placebo group, the co-trimoxazole group experienced a lower number of respiratory tract infections (P0.005) and non-respiratory tract infections (P0.05). Antineutrophil cytoplasmic antibody titers were not significantly different at any point in time. Regression analysis using proportional hazards identified co-trimoxazole medication as an independent factor linked to an extended period of disease-free living.

The medications used to treat Wegener's granulomatosis long-term prophylactically need to be well-tolerated and safe. Co-trimoxazole is generally well tolerated for short periods of time, and the prevalence of relatively mild side effects is comparable to that of the majority of other antimicrobial medications.(22)

4. Co-trimoxazole in the Treatment of Rheumatoid Arthritis

An inflammatory joint illness called Rheumatoid Arthritis (RA) typically results in joint damage. Nonsteroidal anti-inflammatory medicines (NSAIDs), corticosteroids, disease-modifying antirheumatic medications (DMARDs), and biological agents are the traditional treatments for rheumatoid arthritis (RA). These treatments are linked to a number of issues.

- DMARDs, including cytotoxic treatments and novel biological medications, have a limited capacity to stop erosive joint degradation.
- Side effects are extremely typical. For example, side effects have been reported in as many as 60% of instances with methotrexate (MTX) and sulfasalazine (SSZ).

- Patients with RA have a higher death rate.The most common cause of death in this population is infection, which is frequently linked to immunosuppression brought on by cytotoxic medicines, corticosteroids, DMARDs, and novel biologic therapies.
- The number of hematologic malignancies that arise in RA patients receiving treatment with MTX, cytotoxic medications, and biological agents is always expanding, and it is still unclear if these medications are safe over the long term.
- Combining multiple DMARDs is frequently necessary to treat a resistant illness, which raises the risk of DMARD side effects.
- Due to toxicity or loss of efficacy, the above-mentioned medicines typically only last a few years before needing to be replaced.

Therefore, a medicine that is both safe and effective is needed. It should also have low immunosuppressive qualities, no risk for cancer, and the ability to function as a broad-spectrum antibiotic with a therapeutic effect that is comparable to that of DMARDs. With its various attributes, cotrimoxazole (CTX), a combination of trimethoprim (TMP) and sulfamethoxazole (SMX), seemed like a perfect fit for this use. Clarifying the potential use of CTX in RA was the goal of the current investigation.

Methods

We searched the literature for CTX using MEDLINE (1966–2000). A critical review was conducted on the pharmacology, mechanism of action, immunomodulatory, anti-inflammatory, and role of CTX and other sulfonamides in the treatment of autoimmune illnesses.

RESULT

CTX Pharmacology and Mechanism of Action

90% to 100% of CTX is absorbed following a single oral dosage. Absorption of TMP is faster than that of SMX. An ideal ratio of TMP to SMX is 2:10, with peak blood concentrations of TMP (2 mg/mL) occurring in humans 2 hours after a 160 mg intake and SMX (40 mg/mL) at 4 hours after an 800 mg ingestion. The same doses administered intravenously (IV) result in serum concentrations of 3.4 and 46 mg/mL, respectively. As a result, TMP concentration rises 1.7 times following IV injection compared to oral administration, whereas SMX concentration remains relatively constant. About 40% of TMP and 65% of SMX have plasma protein binding percentages. TMP is concentrated and dispersed quickly in tissues. The medication enters the synovial fluid, pustum, and cerebrospinal fluid with ease. Over the course of a 24-hour period, up to 50% of SMX and about 60% of TMP that has been injected are eliminated through urine. TMP and SMX have half-lives of 11 and 10 hours, respectively.

CTX inhibits the synthesis of folic acid in 2 ways. SMX competitively suppresses the enzyme dihydropteroate synthase and inhibits the incorporation of para-aminobenzoic acid into dihydropteroic acid, the immediate precursor of pteroylglutamic acid (folic acid). TMP competitively inhibits dihydrofolate reductase and blocks the conversion of folates into folinates. The affinity of SMX (acting as an antibacterial agent) for the bacterial enzyme dihydropteroate synthase is about 10,000 times greater than its affinity for the corresponding mammalian enzyme.(23)

Co-trimoxazole Active Against Bacterial Pathogen

1. Actinomyces

There is literature demonstrating Actinomyces's in vitro susceptibility to co-trimoxazole. There aren't much clinical data available, though. Cotrimoxazole is effective in treating actinomycetoma and skin infections, according to a number of case studies. It is typically used in conjunction with other medications like doxycycline, ampicillin, penicillin, and gentamicin.(24)

2. Aeromonas hydrophila

While there is a wide range of susceptibility, depending on the particular species and geographic area, Aeromonas spp. exhibit good in vitro susceptibility to co-trimoxazole.Though they are based solely on case series and case reports, the limited clinical data demonstrate the effective treatment of co-trimoxazole administered as monotherapy for primarily gastroenteritis and skin and soft tissue infections. (25)

3. Achromobacter

In vitro, nearly 75% of this newly discovered nosocomial pathogen is susceptible to co-trimoxazole. Clinical data are comprised of case reports and small case series that show a positive clinical outcome for the majority of patients, particularly in the cases of urinary tract infections and bacteremia.(26)

4. Stenotrophomonas maltophilia

Hospitalized individuals are increasingly at risk from this infection, particularly if they have compromised immune systems. For a considerable amount of time, cotrimoxazole susceptibility has been documented.Many case reports, especially those involving endocarditis and meningitis, have provided clinical information. Studies conducted in the past have shown that clinical outcomes are achieved while treating sepsis or bacteremia. Good cure rates were found in a systematic assessment of this pathogen-related skin infection in patients with hematological malignancies. However, co-trimoxazole use in this situation may be restricted due to the development of resistance.(27)

5. Brucella

Since the 1970s, co-trimoxazole has been an effective treatment for this frequent zoonotic pathogen. But because there isn't enough solid data, it's just regarded as a second-line treatment. The information is based on numerous case reports and case series that primarily address brucella endocarditis or CNS infections; these are typically treated with other medications such gentamicin, doxycycline, and rifampicin in combination. Co-trimoxazole has been shown to be effective in treating brucellosis in both retrospective and prospective investigations, including those including children and pregnant women. Co-trimoxazole for the treatment of brucellosis was assessed in two randomized controlled trials (RCTs). But in one trial, co-trimoxazole was part of both therapy groups. Six distinct treatment plans, including co-trimoxazole alone, were examined in the other trial. Except for the streptomycin plus doxycycline treatment arm, all treatment arms were comparable. Given these details, co-trimoxazole may be prescribed as a brucellosis treatment, particularly for pregnant women.(28)

Co-trimoxazole Active Against Protozoa

1. Maleria

In both adults and children, this widespread parasite can lead to serious illnesses. The literature has long included evidence of Plasmodium falciparum susceptibility to co-trimoxazole in vitro. Prophylaxis with co-trimoxazole is known to reduce the incidence of HIV infections in patients. Eight randomized controlled trials evaluated co-trimoxazole's effectiveness in treating malaria; all of the trials involved children, and the majority involved simple P. falciparum infections. In two of these studies, the use of co-trimoxazole in conjunction with isoniazid and rifampin to treat uncomplicated malaria was investigated. When compared to quinine-sulphadoxine-pyrimethamine, mefloquine, or chloroquine, this combination demonstrated to be safe and effective. In two other studies, co-trimoxazole–artesunate was compared to two other drug combinations (chloroquine–artesunate and amodiaquine–artesunate) for the treatment of P. falciparum infections that were not complex. Both groups had excellent outcomes. The information is pertinent to a certain demographic; co-trimoxazole is a great and little-known malaria medication.(29)

2. Acanthamoeba

There are very few effective therapeutic options for the catastrophic CNS illnesses that this parasite can cause. Case studies detailing effective therapy typically include combinations of several medications, such as co-trimoxazole.(30)

3. Isospora belli

This parasite causes gastrointestinal infections and is mostly targeted by immunocompromised people, including HIV patients. Several case reports and two retrospective investigations have shown that co-trimoxazole is an effective treatment for this pathogen, which has been utilized since the 1980s.

In HIV patients with isosporiasis, a short RCT evaluated co-trimoxazole and ciprofloxacin. Co-trimoxazole produced outstanding results

Co-trimoxazole was shown to be effective in preventing isosporiasis in HIV patients beyond their initial episode in another RCT. These findings are included in the CDC guidelines, which suggest co-trimoxazole as the preferred course of treatment for HIV patients with isosporiasis.(31)

4. Cyclospora

This disease, which is thought to be a cause of traveler's diarrhea and diarrhea in immunocompromised hosts, mostly targets adult visitors to endemic locations. A number of case reports as well as a few retrospective and prospective trials demonstrated that co-trimoxazole was effective in treating Cyclospora-induced diarrhea. For the treatment of Cyclospora infections, cotrimoxazole was compared with ciprofloxacin or a placebo in three RCTs. Co-trimoxazole was a successful medication with a low rate of recurrence. Co-trimoxazole is now the recommended first-line treatment for Cyclospora infections due to this knowledge.(32)

Marketed product of co-trimoxazole

- Bactrim
- Septra
- Septrin
- Sulfatrim
- Cotrimoxazole (generic name in some regions)
- Ciplin DS
- Cotrim
- Roubac

CONCLUSION

Co-trimoxazole is a combination of sulphamethoxazole and trimethoprim that has bactericidal properties against a variety of protozoa and Gram-positive and Gram-negative bacteria. Accumulating data suggest that this old antimicrobial medication has significant potential in treating drug-resistant superbug MRSA as well as several other emerging pathogens, even though the majority of evidence on its efficacy comes from case reports and case series.

The above-mentioned indications may remain anecdotal, but one of the most important questions is whether there is a genuine possibility for the strategic use of this "forgotten drug.

Numerous untapped potentials of this agent must be thoroughly investigated through large-scale trials.

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