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REVIEW ARTICLE

Pharmacological Overview Of Anti-Infective Agents Used In The Treatment Of Intestinal Disorders

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Though structural modifications of drug molecules led to the synthesis of a wide variety of newer therapeutic agents, the conventional drugs of choice maintained their relative importance in many instances, particularly in intestinal infections. Common therapeutic agents used against intestinal infections range from traditional penicllin to modern fluoroquinolones. Therapeutic choices are based on the consideration of their spectrum of activity, selectivity, secondary characteristics, and pharmacokinetic properties. Tetracycline, cephalosporin, ciprofloxacin, and macrolides are the common therapeutic agents effective against intestinal bacterial infections. Addition of fluorine at C6 position increases potency and spectrum whereas a peperazinyl moiety at C7 position of quinolones nucleus increases its tissue penetration capacity. Despite being one of the major causative agents of diarrhea, specific anti-viral drugs are yet to be developed against rota-viruses and other adenoviruses. Intestinal antiprotozoal drugs include imidazole derivatives, hydroxyquinolines, and emetine derivatives. Metronidazole is still the antiprotozoal agent of choice in specific intestinal infections.

Anti-infective agents generally include anti-microbial agents that can kill or suppress the growth of microorganisms and antibiotics that are derived from certain microorganisms and that inhibit the growth of other organisms. In intestinal infections like cholera, dysentery, diarrhea, enteric fever etc. selection of an appropriate anti-infective therapy include some general principles.

- The patient's condition may require empiric therapy before the infecting organism is isolated. In this case "umbrella" therapy is often used with a broad-spectrum anti-microbial agent or a combination that will be effective against the likeliest causative pathogens. Factors that influence the choice of anti-infective agent or its dosage include the patient's age, renal and hepatic function, pregnancy status, site of infection.
- Route of administration of anti-infective agent depends on some corresponding conditions. Oral route is used for mild infection and is especially useful for out patient therapy. Timing or administration by oral route is important if food impairs absorption. On the other hand parenteral route is used for severe infections when high serum concentrations are required, intra-thecal administration is required when the agent does not cross the blood-brain barrier.
- Combination therapy with two or more anti-infective agents has several purposes to provide broader coverage against more than one organisms, for initial (blind) therapy when laboratory results are pending, to provide synergism when organisms are not effectively eradicated with single agent, to prevent the emergence of drug resistance like in tuberculosis. Inappropriate use of combination may result in pharmacological antagonism between the anti-microbial agents, initiate number of adverse reactions and above all the unnecessary treatment expenditure.

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There are different types of infective agents responsible for a wide variety of intestinal infections that include bacterial, viral, mycobacterial, protozoal, helminthic, fungal infections. Bacterial infections are readily treated in most instances by bacteriostatic and/or bacteriocidal agents. Viral infections are difficult enough to treat because of its intracellular location, requiring active participation of a host cell's metabolic processes and very few agents are selective enough to kill a virus without injuring the involved host cell. In protozoal infections, Metronidazole is the agent of choice and is directly trichomonacidal. Helminthiasis may now affect as many as 1 billion people each year and its incidence is increasing with increased travel and agricultural use of land. With the advent of some several new, highly selective anthelmintics, older agents become obsolete.

In 1928, the first anti-microbial agent was discovered named penicillin. The basic structure of the penicillin contains a thiazolidine ring connected to a beta-lactum ring with an attached side chain. The modification or alteration of the side chain determines the antimicrobial and pharmacological actions of the drug. The semi-synthetic penicillins were derived from 6-aminopenicillanic acid that were depleted of side chain precursors. In the process of bacterial cell wall synthesis, penicillins inhibit the peptidoglycan synthesis by conformational similarity to D-alanyl-D-alanine. In addition, almost all bacteria have *penicillin-binding-proteins (PBP)*, related targets for covalent interaction with beta-lactum ring resulting to inhibition of transpeptidase reaction causes spheroplast formation and lysis of the wall. Some evidence also suggests that inhibition of *PBP* by penicillin causes loss of autolysin inhibition lead to cell lysis. Under normal conditions penicillins are rapidly eliminated from the body mainly by the kidney. 60% to 90% of intra-muscular dose in aqueous solution is eliminated in the urine. Wide variety of penicillins like Ampicillin, Amoxicillin and their various derivatives like Bacampicillin, Pivampicillin, Hetacillin are effective against gram-positive organisms including *E. coli, H. influenzae, Salmonella* and *Shigella* and some *Proteus* species.

Clavulanic acid extends the anti-bacterial spectrum of beta-lactum antibiotics by irreversibly binding and thus, inhibiting many bacterial beta-lactamases. The combination of Ticarcillin and Clavulanate is useful in treating strains of *Klebsiella, E. coli, Enterobacter cloacae* and *Citrobacter*. Sulbactam is a penicllanic acid sulfone with limited anti-bacterial activity. Its principal action is to inactivate bacterial enzyme, thereby enhancing the anti-bacterial spectrum of Ampicillin.

Combination of two novel anti-microbial agents Quinupristin / Dalfopristin and Linezolid have recently emerged as approved therapeutic options for vancomycin-resistant-enterococci (VRE) on the basis of *in vitro* susceptibility and multi-center clinical trials[1]. Linezolid, an oxazolidinone compound that acts by inhibiting the bacterial pre-transitional initiation complex formation, has bacteriostatic activity against both vancomycin-resistant *E.faecium* and *E.faecalis*.

In 1948, crude filtrates from the cultures of *Cephalosporium acremonium* were found to inhibit the growth of *S. aurius* and led to development of Cephalosporins. These are derivatives of 7-aminocephalosporanic acid and are closely related in structure to penicillin as they have a six-membered sulfer-containing ring adjoining a beta-lactum ring and inhibits bacterial cell wall synthesis by *penicillin-binding-proteins*. Though cephalosporins are ineffective against enterococci but the fourth generation cephalosporin Imipenem has the broadest anti-microbial spectrum. It is derived from a compound produced by *Streptomyces Cattleya* as stable N-formimidoyl derivative. It is active against both gram-positive and gram-negative cocci including Enterobacteriaceae.

Tetracyclines are close congeners of polycyclic naphthacene carboxamide. It is produced semi-synthetically from

chlortetracycline. Absorption of tetracycline is impaired by the concurrent ingestion of dairy products, aluminium hydroxide gels, calcium, magnesium and iron or zinc salts. Primarily bacteriostatic affecting both eukaryotic and prokaryotic cells but apparently penetrates microbial membranes more readily due to presence of active transport systems in microbes. The use of tetracyclines has declined for the treatment of intestinal infections because of increasing bacterial resistance and the development of newer drugs against cholera, brucellosis, tularemia, some *Shigella* and *Salmonella* infections. *Staphylococcal* and *Streptococcal* infections may respond to tetracyclines. However, the drugs are third-line agent of choice.

Norfloxacin and Ciprofloxacin are the fluorinated 4-quinolones, structurally related to the older quinolone Nalidixic acid, with greater tissue-penetrating capacity. The compounds contain a carboxylic acid moiety in the 3 position of the basic ring structure and fluoroquinolones contain a fluorine substitute at position 6 with a piperazine moiety at position 7. They are bactericidal by acting on the enzyme DNA-gyrase. In order to DNA replication or transcription, two strands of double helical DNA must be separated. To prevent over-winding or supercoiling of the DNA, the bacterial enzyme DNA-gyrase maintains negative supercoiling into DNA to be cut off as a released segment. The drugs inhibit the enzyme at subunit-A that carries out the strand-cutting function. Ciprofloxacin is highly active against bacteria that causes enteritis and against *staphylococci,* including strains resistant to Methicillin. But they have poor activity against anarobes. In a recent preliminary study, Arnold *et al* (2002) suggested that ciprofloxacin may be an effective agent when added with other antibiotics in the treatment of Crohn's disease. Recently broad spectrum antibiotics have been reported to be as effective as oral corticosteroids in the treatment of Crohn's disease because, a number of specific infectious causes have been considered particularly *M. avium paratuberculosis.* Evidence suggested that this agent plays a role includes isolation of organism from patients, clustering, and identification by PCR of the organism's DNA in tissue[2].

Gemifloxacin and other fluoroquinolones were found very active against all common entero-pathogenic bacteria except for *C. jejuni.* In a recent study by Fernandez *et al,* the in vitro activity of Gemifloxacin was reported to be superior compared to fourteen other antimicrobial agents against 288 recent isolates of enteropathogenic bacteria[3]. Fluoroquinolones are inhibitors of gamma-aminobutyric acid (GABA) and may cause seizures. They have also been reported to cause pseudo-membranous colitis.

Recently, Nifuroxazide is available in France as over-the-counter drug for the treatment of acute diarrhea in adults. Anti-microbial activities of short-chain fatty acids (acetate, propionate and butyrate) in improvement of experimental *Shigellosis* has also been demonstrated in rabbit model[4]. Dose-dependent bactericidal affects of SCFA on *S. flexneri 2a* has been reported after 96 hours of treatment. Selby and his collegues have reported that *C. jejuni* resistant to fluoroquinolones were inhibited by Erythromycin at the dose of 0.5 mg/L[5].

The earliest step in microbial infection is adherence by specific microbial adhesion to the mucosa and therefore, a synthetic peptide adhesion epitope is under active consideration as a new, novel anti-microbial strategy, applying competitive peptide inhibitors of adhesion against various microorganisms to prevent recolonization[6].

Anti-inflammatory agents mainly regulate the chemical mediators of inflammation by acting on cyclooxygenase and lipooxygenase enzyme systems. In chronic ulcerative collitis and Crohn's disease salicylate is used for its local effect. Glucocorticoids are most useful when conservative management with

aminopenicillinic acid derivatives (salfasalazine) are ineffective. Among the limited anti-inflammatory agents, steroids are still considered as the mainstay to treat inflammatory conditions of intestine. Changes in chemical structure at different rings with hydroxyl (OH) and keto (CO) group bring about changes in specificity, potency, kinetics and intrinsic activities of steroids as the preferred anti-inflammatory agents. Recently, several studies has demonstrated effectiveness of Infliximab in Crohn disease.

Anti-secretory agents to reduce intestinal secretion in diarrhea due to toxigenic bacteria seem to be important therapeutic agents. But clinically safe and useful agents have not yet been developed. Inhibitors of cyclic AMP and adenylate cyclase including chlorpromazine, nicotinic acid, and the plant alkaloid berberine showed some promise in initial studies but their usages are limited because of associated unpleasant effects. Antioxidants have been recently tested and found to modify intestinal secretion and absorption. L-Histidine, not D-Histidine has been shown to reduce intestinal secretion in cholera in animals and man, the drug also reduces colonic inflammation due to Shigellosis in animals. Plant polyphenols are important antioxidants that also reduce intestinal secretion due to toxigenic pathogens. The mechanism of actions of L-Histidine is due to its formation of a Michael adduct between C11 of 11-deoxy-Δ^{11} PGE_2 and [^{15}N] in the imidazole ring of L-Histidine which possesses both antisecretory and antiinflammatory properties. Short-chain fatty acids (acetate, propionate, butyrate) or their dietary precursors can also reduce intestinal fluid loss because of their proabsorptive actions in the colon. Inhibition of nitric oxide production in the intestine has been shown to modify fluid and electrolyte secretion, but no useful agents have yet been developed for therapeutic application.

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