Special Article

Effect of Antimicrobial Agents on Human Microflora

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Abstract

The most common and significant cause of disturbances in the normal oropharyngeal and gastrointestinal microflora is the administration of antimicrobial agents. The microflora can be influenced by antimicrobial agents because of incomplete absorption of any orally administered antimicrobial agent, secretion of an antimicrobial agent by the salivary glands or in the bile or secretion from the intestinal mucosa. In most cases the influence is not beneficial to the patient because suppression of the indigenous microorganisms often permits potential pathogens to overgrow and cause septic conditions, stomatitis, diarrhoea or colitis. Antimicrobial agents that influence the normal microflora also promote the emergence of antimicrobial-resistant strains. During the recent years, the impact of different antimicrobial agents on the human microflora has been investigated. Thus the effects on the oropharyngeal and intestinal microflora by peroral administration of penicillin, bacampicillin, cefaclor, erythromycin, clindamycin, doxycycline, nitroimidazole, norfloxacin and ciprofloxacin have been studied. The impact on the microflora by parenteral administration of azlocillin, aztreonam, piperacillin, cefoperazone, ceftriaxone, moxalactam, imipenem, nitroimidazole and clindamycin has also been investigated. Pronounced changes were observed in the microflora in patients receiving clindamycin, erythromycin, cefoperazone, ceftriaxone and moxalactam, whereas moderate changes were seen in those patients receiving doxycycline, aztreonam, azlocillin and piperacillin. Penicillin, bacampicillin, cefaclor, imipenem, nitroimidazole, ciprofloxacin and norfloxacin produced only minor changes. In most patients with an altered microflora, colonization with new microorganisms was found.

INTRODUCTION

The normal microflora is a stable ecosystem. Some interpersonal variations exist in the flora composition and in the number of different organisms, but within a given person the microflora remains relatively constant over time. Certain factors are however capable of disrupting this ecosystem.

Irradiation of the head and neck or total extraction of the teeth causes changes in the oropharyngeal microflora and subsequently in the gastrointestinal microflora. Gastric surgery is associated with changes in the microorganisms of the small intestine. Pathologic conditions that affect normal peristalsis can cause a shift in the intestinal microflora. The ingestion of a large bacterial inoculum can overwhelm host defenses.

The most common and significant cause of disturbances in the normal oropharyngeal and gastrointestinal flora is the administration of antimicrobial agents. The importance of antimicrobial agents in the treatment of infectious diseases and in the prophylaxis of infections cannot be minimized. Yet, some of these agents are not without their detrimental effects on the normal microflora, leaving the host susceptible to infection, to superinfection by commensal microorganisms, and to a range of other untoward effects.

Several factors influence the extent to which a given antimicrobial agent will decimate the normal microflora. Predominant among these is the incomplete absorption of orally administered drugs.

Poorly absorbed agents can reach the intestine in active form where they destroy susceptible microorganisms and change the ecologic balance. Parenterally administered antimicrobial agents that are secreted by the salivary glands, in the bile, or from...
the intestinal mucosa also tend to destroy the normal microbial population.

In this article our experience with the effect of different antimicrobial agents on the oropharyngeal and gastrointestinal microflora is reported.

**Effect of Antimicrobial Agents on the Oropharyngeal and Upper Gastrointestinal Microflora**

Antimicrobial agents administered perorally, depending on their pharmacologic properties, may be secreted in saliva or from the mucous membranes in the oropharynx. The main determinant for such secretion is the lipophilicity of the agent. Antimicrobial agents with low lipophilicity tend to give low concentrations in saliva and pharyngeal secretions, whereas antimicrobial agents with a high lipophilicity usually are found in microbiologically active concentrations in the oropharynx. Thus, microorganisms in the oropharynx susceptible to the antimicrobial agent used can be affected, and disturbances of the oropharyngeal and upper gastrointestinal microflora can take place. Changes in the number of different microorganisms may be hard to predict from pharmacokinetic data and susceptibility tests, as *in vitro* susceptibility often differs from *in vivo* susceptibility. Rapid selection or emergence of antimicrobial resistant microorganisms indigenous to the oropharynx and upper gastrointestinal tract may also protect from suppression and subsequent colonization and overgrowth of the normal microflora.

Benzylpenicillin, phenoxyethylpenicillin, ampicillin and ceftazidime are found in very low concentrations in saliva and therefore only slightly change the oropharyngeal microflora. However, selection of penicillin resistant viridans streptococci subsequent to prophylaxis with penicillin is well known. The occurrence of penicillin resistant beta-lactamase producing bacterioids and fusobacteria subsequent to penicillin therapy is also observed in increasing frequency. Selection of such strains during penicillin therapy of oropharyngeal infection may aggravate the infection and eventually cause clinical failure of antimicrobial therapy.

Clindamycin and erythromycin are present in saliva and exert pressure on the normal oropharyngeal and upper gastrointestinal microflora. Susceptible microorganisms are often eradicated, and subsequent colonization and overgrowth with resistant aerobic and anaerobic microorganisms are frequently seen. Such colonizing microorganisms can be isolated in blood cultures from severely debilitated patients, such as those treated for acute leukemia and severe aplastic anemia.

Tetracyclines are present in saliva and also concentrate in certain oropharyngeal sites such as the gingival crevices. Emergence of resistant aerobic and anaerobic bacteria rapidly causes overgrowth and therefore maintains the resistance to colonization. The risk of infectious complications with resistant bacteria subsequent to surgery of the oropharynx and esophagus is obvious.

Nitroimidazoles (metronidazole, tinidazole and ornidazole) are distributed in virtually all body fluids in concentrations equal to the serum concentrations. Salivary and tonsillar concentrations follow concentrations of serum, and therefore high levels of nitroimidazoles are achieved in the oropharynx during therapy. The *in vivo* susceptibility of strictly anaerobic bacteria to nitroimidazoles is considerably less than the *in vitro* susceptibility, and relatively large doses of nitroimidazoles have to be administered before suppression of the anaerobic oropharyngeal microflora takes place. The risk of colonization and overgrowth is therefore only moderate. Resistance among strictly anaerobic strains isolated from the oropharynx has still not been reported and the agents can safely be administered both therapeutically and prophylactically without risk of infection by resistant anaerobic bacteria.

The third generation quinolones are only active against aerobic bacteria mainly Gram-negative rods and the influence on the oropharyngeal microflora is therefore minor and only branhamella cocci are affected when ciprofloxacin or norfloxacin has been given.

**Effect of Antimicrobial Agents on the Lower Intestinal Microflora**

Many antimicrobial agents cause changes in the intestinal microflora, the severity of which depends largely on the agent's spectrum and concentration in the luminal contents. Oral antimicrobial agents that are well absorbed in the upper part of the small intestine have little impact on the microflora in the lower intestine. Agents that are poorly or incompletely absorbed can cause considerable changes.

Suppression of the intestinal microflora by antimicrobial agents therefore creates a microbiologic vacuum readily filled by exogenous pathogens or by overgrowth of commensal microorganisms. In certain situations, such as antimicrobial prophylaxis before elective colorectal surgery, and in the treatment of blind loop syndrome, elimination of microorganisms from the intestinal tract is indicated.

Many surgical infections that appear during antimicrobial therapy are caused by Gram-negative aerobic and anaerobic rods that normally inhabit the intestinal tract. Infectious complications due to Gram-negative bacteria are the major cause of morbidity and mortality in surgical patients. The normal gastrointestinal microflora is of great importance in the induction, maintenance, and spread of multiresistant microorganisms in surgical intraabdominal infections.
Phenoxymethylpenicillin and cefaclor cause no change in the intestinal microflora because these agents are hydrolyzed in the intestinal tract and no concentrations are detected in the large intestine. As might be predicted, no new bacterial colonization or increase in resistance is observed. However, phenoxymethylpenicillin has been incriminated in antibiotic associated diarrhea and colitis caused by C. difficile which may indicate other physiological disturbances.

Ampicillin is one of the most widely used semisynthetic penicillins because of its broad antibacterial spectrum. Disadvantages of the agent are its incomplete absorption and rather high incidence of diarrhea during treatment. Certain esters of ampicillin, such as bacampicillin, talampicillin and pivampicillin, are well absorbed when given orally and undergo hydrolysis in the body to yield serum peaks of ampicillin higher than those obtained by ampicillin itself and produce no concentrations in the large intestine. These ampicillin esters cause no changes in the colon microflora and no side effects. Therefore, compared with ampicillin, these esters are ecologically more favorable.

Erythromycin is often used together with neomycin or kanamycin as peroral prophylaxis in elective colorectal surgery. However, when erythromycin is given as treatment for a longer period, undesirable microbial effects due to high intestinal concentrations occur. The aerobic and anaerobic colon microflora is considerably disturbed and new colonization by erythromycin resistant aerobes, anaerobes and yeasts occurs.

Clindamycin exhibits high concentrations in the large intestine when administered either perorally or parenterally, which leads to pronounced changes in the aerobic and anaerobic microflora. Significant decreases in the number of both anaerobic cocci and rods occur and clindamycin resistant enterococci and enterobacteria proliferate. The relative risk of developing C. difficile diseases associated with the use of clindamycin is well known.

Tetracyclines have extensively been used in the treatment of many different infections. Diarrhea and superinfection are side effects that generally limit the use of tetracyclines. Tetracycline has been found to have a greater effect on the occurrence of resistant enterobacteria than doxycycline. Doxycycline produces minor changes in the number of anaerobic bacteria in the colon microflora, and new colonization of enterobacteria and yeasts is not a common finding because of the rapid emergence of doxycycline resistant anaerobic bacteria. The modest changes in the interrelation of microorganisms in the intestinal microflora may explain the relatively few cases of pseudomembranous colitis caused by C. difficile.

Nitroimidazoles (metronidazole, ornidazole and tinidazole) are selectively active against anaerobic bacteria. They have been used successfully in both the treatment and prophylaxis of anaerobic infections. When nitroimidazole was administered perorally, no significant changes in the aerobic and anaerobic colon flora was noted. This finding is consistent with the observation that no microbiologically active concentration of nitroimidazole is found in the large intestine.

When tinidazole was given intravenously in large doses, marked changes were observed in both the aerobic and the anaerobic colon microflora. Aerobic enterococci and streptococci increased, whereas anaerobic cocci, Gram-positive rods, fusobacteria and bacteroides significantly decreased. Concentration of tinidazole higher than the minimum inhibitory concentrations of most anaerobes were observed in the intestine.

The new quinolones have broad antibacterial activities against Gram-negative bacteria in the intestine, especially against enterobacteria and pseudomonas. The activities against anaerobic bacteria are limited. The quinolones affect therefore mainly the aerobic Gram-negative part of the intestinal microflora and significant suppression of enterobacteria by administration of ciprofloxacin or norfloxacin has been found.

Azlocillin and piperacillin belong to the fourth generation of penicillins and have an antibacterial spectrum covering many intestinal bacteria. Azlocillin and piperacillin are excreted in high concentrations in the bile, and therefore in many patients the impact on the lower intestinal microflora is pronounced. Colonization of resistant microorganisms in the intestine may occur but the incidence of C. difficile diarrhea and colitis is reported to be rather low.

Third generation cephalosporins have good activities against Gram-negative aerobic and anaerobic rods and have been used in the treatment and prophylaxis of intraabdominal infections. The potent antimicrobial activity of some of these cephalosporins — ceftriaxone, cefoperazone and moxalactam — in combination with a high biliary excretion has resulted in considerable changes in the lower intestinal microflora. The alteration of the microflora has led to undesirable consequences such as superinfection and C. difficile intestinal diseases. Infections with cephalosporin resistant microorganisms have also been reported. Hypoprothrombinaemia and haemorrhage due to impaired vitamin K production have been observed in patients treated with cefoperazone and moxalactam.

Among the carbapenems one agent — imipenem — has been used for treatment of serious intraabdominal infections. Imipenem has a broad antimicrobial spectrum and covers both the aerobic and anaerobic
bacteria in the intestinal microflora. However, only minor changes have been noted in the intestinal microflora of patients receiving the agent.23 The minor changes are probably due to the low biliary elimination. The selection of resistant microorganisms in the microflora during treatment is low.23 Aztreonam belonging to the monobactams is used in the treatment of infections due to Gram-negative aerobic bacteria. Aztreonam is highly stable towards beta-lactamases produced by aerobic Gram-negative rods and unlike many other beta-lactam antibiotics, aztreonam does not induce beta-lactamase production. Its spectrum of activity in vitro towards Gram-negative bacteria is comparable to the aminoglycosides and the third generation cephalosporins. Aztreonam has no activity against anaerobic bacteria. Selection of aztreonam resistant microorganisms during therapy is rare. In the intestinal microflora, aztreonam suppresses enterobacteria significantly while an increase in the numbers of staphylococci and enterococci has been observed. The anaerobic microflora is not affected.24 Superinfections caused by Staphylococcus aureus and enterococci during aztreonam treatment have also been reported.25

REFERENCES


