Old Herborn University Seminar Monograph 3:
Consequences of antimicrobial therapy for the composition of the microflora of the digestive tract.
Editors: Carl Erik Nord, Peter J. Heidt, Volker Rusch, and Dirk van der Waaij.
Institute for Microbiology and Biochemistry, Herborn-Dill, Germany: 20-24 (1993).

# EFFECT OF ANTIMICROBIAL DRUGS ON THE INTESTINAL MICROFLORA: IMPORTANCE OF PHARMACOKINETIC PROPERTIES OF ANTIBACTERIAL AGENTS

TOM BERGAN

Department of Microbiology, Institute of Pharmacy, and
Department of Microbiology, Aker sykehus, University of Oslo, Oslo, Norway

In order to exert its therapeutic activity, antibacterial agents must reach the site(s) of infection at concentrations that are adequate in order to inhibit the multiplication of the bacteria or - ideally - cause kill of the bacteria in the case of potentially bactericidal agents. At the same time, however, it is desirable that the activity against the microbes in the normal microflora on the skin, mucosal surfaces and, in particular, inside the gastrointestinal canal is left as much as possible undisturbed. The major concern for the intestinal microflora is due to the relatively high number of bacteria there. Thus more than 90% of all the bacteria colonizing the body are found inside the intestines - and 99% of these residing within the colon. Consequently, if we focus on the interaction between an antibacterial drug and the colonic flora, then we know what is happening with nearly all bacteria of any consequence for the well being of the patient. If the colonic flora is left intact, then loose stools and diarrhoea are avoided - and in turn e.g. an occurrence like pseudomembranous diarrhoea due to *Clostridium difficile*.

The importance of pharmacokinetic properties in the context of this conference, i.e. the ability of antibiotics to interfere with the normal microflora (the ecological friendliness of these drugs, as it were) thus boils primarily down to the question of what characteristics are theoretically favourable. In the second event we are concerned with the practical implications, i.e. the ecological favourability of the individual drugs.

It is essential that the concentrations of the antibiotic are below the minimum inhibitory concentrations of the major portion of the normal microflora. This means that the levels should be low in sweat, in saliva and in nasal secretion. The concentrations should also be low inside the intestinal contents; consequently, the antibacterial levels must be low in key secretions like the bile, pancreatic juice and the various secretions of intestinal mucosal glands. These properties can be studied in detail after parenteral administration, although data pertaining to the intestinal glands and pancreatic juice are virtually nil in humans. Biopharmaceutic properties are vital for oral application; this implies that the bioavailability must be high such that one avoids the possibility that most of the dose of a drug is not absorbed and, accordingly, simply transferred to the lower gastrointestinal tract to exert its antibacterial activity there. If a drug is eliminated in high amounts in e.g. the bile, then quantitatively high reabsorption is required in the duodenum and the upper portion of the small intestine in order to achieve low concentrations of the drug in the lower portion of the gastrointestinal tract.

The condition of high bioavailability may, however, not be an important point, since high amounts may be discharged into the faeces. It has, for instance, recently been demonstrated with

ciprofloxacin that this compound, which has a high bioavailability - in the case of ciprofloxacin up to 85% bioavailability has been demonstrated (*Bergan* et al., 1987) - may be eliminated by the mechanism labelled transintestinal elimination (*Rohwedder* et al., 1990). Thereby, the compound is eliminated in significant amounts by passage across the intestinal wall. Transintestinal elimination of ciprofloxacin has been shown to cause very high concentrations of a multiple of up to 100-2000 times the peak serum concentrations inside the colonic contents. In the case of ciprofloxacin, less than 1% of the compound is eliminated in the bile, but 15% by faeces even after intravenous administration (*Rohwedder* et al., 1990).

In cases when large amounts of an antibiotic reach the lower gastrointestinal tract, three mechanisms may explain the lack of a significant interaction with the intestinal microflora. One is binding to intestinal contents. This has been demonstrated to occur for ciprofloxacin (*Edlund* et al., 1988). The second is enzymatic inactivation. This is a possible mechanism explaining why the moderate but potentially sufficient amounts to inhibit portions of the intestinal flora after ampicillin esters like bacampicillin or pivampicillin usually have no deleterious effect on the microflora (*Sjövall* et al., 1986). A third circumstance inhibiting the activity of drugs, which need a high redox potential to act, is anaerobic conditions. Thus the low redox potential of the lower colon will limit the effect of aminoglycosides and fluoroquinolones against aerobic bacteria although they would be inhibited under aerobic conditions.

A series of studies on the interaction between the normal bacterial microflora and antibacterial agents given in therapeutic doses over a period of ca 1 week have shown that some drugs are favourable and some less so to the microbial environment (*Nord*, 1988; *Nord* et al., 1986). Thus three categories of antibacterial agents can be distinguished: Ecologically favourable, ecologically unfavourable, and ecologically uncertain (Table 1)

Characteristic of the Group I substances is that less than 1% of the bacteria of the colonic microflora is modified quantitatively. The explanation is due to a combination of the intrinsic antibacterial activity and the pharmacokinetic properties of the drugs. Thus benzylpenicillin is given parenterally and less than 1% eliminated in the bile and the faecal concentrations are low. This combined with a narrow antibacterial spectrum and enzymatic inactivation due to a high susceptibility to beta-lactamase produced by the *Bacteroides* and other bacteria reduce the concentrations to levels unable to exert any significant influence on the intestinal bacteria.

**Table 1**: Different groups of antimicrobial agents with regard to their interaction with the normal bacterial microflora

| group I<br>ecologically favourable | group II<br>ecologically unfavourable | group III<br>ecologically uncertain |
|---|---|---|
| benzylpenicillin | piperacillin and other ureidopenicillins | trimethoprim-sulphonamide |
| imipenem | cephalosporins (varying degrees) | aminoglycosides |
| fluorinated quinolones | tetracyclines, also doxycycline | |
| ampicillin prodrugs like bacampicillin | clindamycin, lincomycin | |
| metronidazole | erythromycin (and other macrolides) | |

**Table 2**: Relationship between drug excretion in bile and rate of diarrhoeas (*Bergan*, 1986)

| Antibacterial agent | Biliary excretion of dose (%) | Rate of diarrhoeas (%) |
|---|---|---|
| Ampicillin | <1 | 10 |
| Benzylpenicillin | <1 | 5 |
| Cloxacillin | 5 | 15 |
| Carbenicillin | 2 | 8 |
| Cefaclor | 4 | 5 |
| Cefoperazone | 70 | 24 |
| Cefoxitin | <2 | <2 |
| Ceftazidime | <1 | <2 |
| Ceftriaxone | 30 | 28 |
| Cephalothin | 2 | 4 |
| Cephalexin | <5 | 11 |
| Chloramphenicol | <1 | 4 |
| Ciprofloxacin | <5 | <2 |
| Clindamycin | 10 | 21 |
| Co-trimoxazole | <1 | 10 |
| Doxycycline | 4-20 | 12 |
| Erythromycin orally (not microencapsulated) | <5 | 22 |
| Erythromycin estolate | 5 | 17 |
| Gentamicin | <1 | 4 |
| Kanamycin | <1 | 4 |
| Nalidixic acid | - | 7 |
| Nitrofurantoin | - | 12 |
| Norfloxacin | <1 | <2 |
| Ofloxacin | <1 | <2 |
| Phenoxymethylpenicillin | <1 | 5 |
| Rifampicin | 25 | 11 |
| Sulphonamides | <1 | 8 |
| Tetracyclines | >10 | 15 |

Prodrugs of ampicillin like bacampicillin are generally well absorbed. Thus bacampicillin has a bioavailability of 87% (*Bergan*, 1978). Thereby the amount of drug reaching the lower gastrointestinal tract is limited. Biliary concentrations are low and ampicillin is subject to reabsorption. Indeed, the amounts that proceed towards the lower colon would to a considerable extent be enzymatically inactivated. Accordingly, the rate of diarrhoea after bacampicillin is 0.7% compared to 12% after the classic, oral ampicillin (*Bergan*, 1979).

The fluorinated quinolones are reducing the numbers of aerobic Gram-negative rods, but otherwise leave the Gram-positive aerobes virtually unchanged and the anaerobes quantitatively unchanged. This occurs in spite of very considerable faecal quinolone concentrations. However, it appears that the major portion, more than 95% of the ciprofloxacin, is bound to faecal contents and thus not freely available as antibacterially active drug (*Edlund* et al., 1988).

Imipenem is uniquely active and has a broad antibacterial spectrum. Thus it is difficult to predict why the drug is unusually well tolerated and leaves the intestinal microflora virtually unchanged.

It is notable that the compound is eliminated in less than 1% in the bile. However, the drug is not detected in faeces due to enzymatic hydrolysis.

Among the ecologically unfavourable drugs are macrolides and the like, such as erythromycin and clindamycin. Both of these drugs have a relatively narrow antibacterial spectrum. This applies in particular to erythromycin. However, erythromycin is eliminated in high amounts in the bile and is subject to enterohepatic circulation and appears in very high concentrations in faeces (*Josefsson* et al., 1982). Similar considerations apply to clindamycin, which has a high activity against anaerobic bacteria. Both of these antibiotics are mainly without effect on *Clostridium difficile*, which is, consequently, selected by these drugs. The result is frequent loose stools and - in the case of selective overgrowth of the *Cl. difficile* in some patients - development of pseudomembranous colitis due to the activity of clostridial cytotoxins.

Piperacillin and certain cephalosporins are eliminated in considerable amounts in the bile. There seems to be a rough proportional correlation between the amount of the drugs eliminated in the bile, and their antibacterial activity, and the ability of the drugs to induce changes in the intestinal microflora and consequent loose stools and diarrhoea (Table 2).

Some compounds, such as trimethoprim-sulphonamide and aminoglycosides are classified as ecologically uncertain (group III), because these compounds have not yet been well studied in relation to interaction with the normal microflora. Aminoglycosides rarely cause loose stools or pseudomembranous colitis. This obviously is explained by its lack of activity against the anaerobic bacteria which constitute more than 99% of the colonic flora and the fact that aminoglycosides loose their activity at a low redox potential as applies to the colon. Trimethoprim-sulphonamide combinations are known to cause pseudomembranous colitis and are associated with R-factors, so adverse effects on the balance between the constituents of the faecal microflora can be presumed.

Our experience has shown that studies on the quantitative and qualitative effects of antibacterial agents in particular on the colonic microflora are vital and that knowledge of the pharmacokinetic properties of the drugs contributes to explaining why some compounds interact with the normal microflora and others leave it virtually unchanged.

## LITERATURE


Bergan, T.: Pharmacokinetic comparison of oral bacampicillin and parenteral ampicillin. Antimicrob. Agents Chemother. 14, 801-806 (1978).

Bergan, T.: Aminopenicillins. Concluding remarks. Infection Suppl. 5 (7), S507-S512 (1979).

Bergan, T.: Pharmacokinetic differentiation and consequences for normal microflora. Scand. J. Infect. Dis. Suppl. 49, 91-99 (1986).

Bergan, T., Thorsteinsson, S.B., Solberg, R., Bjørnskau, L., Kolstad, I.M., and Johansen, S.: Pharmacokinetics of ciprofloxacin: intravenous and increasing oral doses. Am. J. Med. 82, 97-102 (1987).

Edlund, C., Lindqvist, L., and Nord, C.E.: Norfloxacin binds to human fecal material. Antimicrob. Agents Chemother. 32, 1869-1874 (1988).

Josefsson, K., Steinbakk, M., Bergan, T., Midtvedt, T., and Magni, L.: Pharmacokinetics of a new, microencapsulated erythromycin base after repeated oral doses. Chemotherapy 28, 176-184 (1982).

Nord, C.E.: Effet des agents antimicrobiens administrés per os sur la flore microbienne de l'oropharynx et du colon chez l'homme. Médicine et Maladies Infectieuses 18 (hors

serie Juillet), 24-28 (1988).
Nord, C.E., Heimdahl, A., and Kager, L.: Antimicrobial induced alterations of the human oropharyngeal and intestinal microflora. Scand. J. Infect. Dis. Suppl. 49, 64-72 (1986).
Rohwedder, R., Bergan, T., Thornsteinsson, S.B., and Scholl, H.: Transintestinal elimination of ciprofloxacin. Chemotherapy 36, 77-84 (1990).
Sjövall, J., Huitfeldt, B., Magni, L., and Nord, C.E.: Effect of beta-lactam prodrugs on human intestinal microflora. Scand. J. Infect. Dis. Suppl. 49, 73-84 (1986).