Probiotics in the prevention and treatment of antibiotic associated diarrhoea

IVOR HIDDING1 AND CATHERINA KONING2
1. Winclove Bio Industries BV - P.O. Box 37239 - 1030 AE Amsterdam
2. Department of Gastroenterology, University Hospital Maastricht - P.O. Box 5800 - 6202 AZ Maastricht

ANTIBIOTIC ASSOCIATED DIARRHOEA (AAD)

The microflora in our intestines is a fragile ecosystem. In a 'healthy' person the approximately 10^{14} bacteria in the intestines live in balance. However, this balance can easily be disturbed by stress factors, like the use of antibiotics. Antibiotics are indispensable for the treatment of several diseases. Since antibiotics can destabilise the natural intestinal flora, the use of antibiotics can result in unwanted side effects such as antibiotic associated diarrhoea (AAD).

Antibiotic associated diarrhoea is defined as "diarrhoea developing a few hours after onset of antibiotic therapy to 6-8 weeks after antibiotic discontinuation". The incidence of antibiotic associated diarrhoea differs from 5-39 percent depending on the type of antibiotic used (broad spectrum antibiotics are most commonly implicated), the definition used for diarrhoea and on host factors. The consequences of AAD in care-taking facilities include a longer stay, a higher cost of care, an increase in the incidence of other nosocomial infections and an increase in morbidity and mortality. To complicate the situation, it should be noted that resistance against antibiotics is an increasing risk factor for which no good pharmaceutical alternative is available.

CAUSES OF AAD

Although the pathophysiology underlying the mechanism of AAD is not fully understood, the cause of AAD may be due to direct toxic effects of antibiotics on the intestine, pharmacological effect on the intestinal motility and direct effects on immune-cell function. However, most cases of AAD are thought to be due to disturbances of the intestinal flora which is associated with loss of colonisation resistance, altered metabolic function and overgrowth of pathogenic bacteria.
Pathogenic micro-organisms associated with AAD are: Clostridium perfringens, Klebsiella oxytoca, Staphylococcus aureus, Candida spp., and Salmonella spp. Moreover, 12-25 percent of AAD is caused by overgrowth of Clostridium difficile which can cause serious complications like pseudomembranous colitis. C. difficile is the most commonly seen pathogen and can be treated well. In 22 percent of cases of diarrhoea related to C. difficile, withdrawal of the inciting agent will lead to resolution of the clinical signs in three days.

In other cases the treatment of C. difficile associated diarrhoea involves oral metronidazole or oral vancomycin for 10 days. Diarrhoea usually resolves in two or three days. However, approximately 20% of patients with C. difficile infection will relapse. Most of them will be treated with another course of metronidazole or vancomycin, but 5 percent will experience more relapses. The management of these chronic cases remains controversial.

The increase in antibiotic resistance of micro-organisms makes alternative treatments more attractive. Living micro-organisms that can mimic the normal functions of the intestinal commensal flora could offer a solution. These micro-organisms are called 'probiotic' bacteria and products containing these beneficial bacteria are called 'probiotics'.

PROBIOTICS

A definition of a probiotic is 'a live microbial food supplement which beneficially affects the host by improving its microbial balance'. A definition generally used at present was proposed by the FAO/WHO in 2002: 'live micro-organisms which, when administered in adequate amount confer a health benefit to the host'.

The characteristics of an effective probiotic have been defined by Saavedra as:
• Resistance to digestion by enteric or pancreatic enzymes, gastric acid and bile.
• Ability to prevent the adherence, establishment and/or replication of pathogens in the gastrointestinal tract.

Probiotics can restore the balance of the microflora amongst others due to their ability to adhere to mucosal cells. This inhibits growth of pathogens by competition for receptors on the epithelial cells. Probiotics can also restore the balance by competition over nutrients.

In addition probiotics strengthen the non-immunological defences of the gastrointestinal tract by:
• Production of antimicrobial substances
• Stimulating mucus secretion
• Reinforcing gut barrier function (maintaining gut integrity)
• Improving gut motility

Finally, it is also suggested that probiotics protect against enteropathogens by immunological defences:
• Stimulating cytokine production
• Enhancing the phagocytic capacity of polymorphonuclear cells and macrophages
• Augmenting natural killer helper (NKH) cell activity
• Enhancing specific antibody responses to pathogenic organisms

TREATMENT OF AAD

Managing antibiotic associated diarrhoea depends on the clinical presentation and the inciting agent used. In mild to moderate diarrhoea conventional methods that are applied include rehydration, discontinuation of the inciting agent or replacement by an antibiotic with a lower risk of inducing diarrhoea. When severe or persistent diarrhoea occurs, the challenge is to identify the cause of this problem. Diarrhoea is usually caused by the loss of important metabolic functions and the loss of the colonisation resistance of the normal flora. However in some cases the severe or persistent diarrhoea is caused by the overgrowth of a pathogen.
PROBIOTICS AND ADVANTAGES IN ANTIBIOTIC ASSOCIATED DIARRHOEA

Studies performed with probiotic bacteria have studied the beneficial effects of probiotics in preventing and treating antibiotic associated diarrhoea. D’Souza et al.12 have reported a meta-analysis of nine randomised double-blind trials comparing probiotics with placebo in the prevention of antibiotic associated diarrhoea. They found a combined odds ratio of 0.37 (p<0.001). Their results suggested that probiotics are useful in the prevention of diarrhoea. Cremonini et al.13 also conducted a meta-analysis which included seven studies. The combined relative risk found was 0.40 (p<0.05). This also suggested that there is a strong benefit of probiotic administration on antibiotic associated diarrhoea. None of the probiotic formulations included in the meta-analysis however were specifically developed for antibiotic associated diarrhoea and so the questions remains which is the most suitable probiotic formulation. One should look at the specific characteristics that probiotic bacteria need to have to be effective in the respective application. One selection criterion could for example be the inhibition of Clostridium (in vitro). Besides that, different formulations have been used (monostrain/multispecies) and there are indications that a multispecies probiotic can have several advantages over a monospecies or monospecies probiotic14.

The clinical trials with probiotics that have been performed in the past are numerous but there are a number of drawbacks that should be taken into account:
• partly paediatric patients
• in most cases only clinical outcome was investigated, with limited bacteriology (only culture)
• difference in dose and duration between trial
• difference in used antibiotics
• difference in used probiotics (monostrain/multispecies)

Recently, a study with healthy volunteers was conducted at the University Hospital Maastricht with a specific multispecies probiotic formulation (Ecologic® AAD from Winckove Bio Industries BV). The product contains 10 different probiotic strains (Lactobacillus acidophilus (2x), Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus salivarius, Enterococcus faecium, Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum), which have been specifically selected for this application. The selection criteria were: ability to survive the GI tract (in vitro), pathogen inhibition (a.o. Clostridium), lack to confer possible antibiotic resistance and compatibility with the other strains used in the product. In this study the effect of a specific multispecies probiotic on bacteriological, immunological and clinical parameters was studied both during as well as after antibiotic treatment. Besides diarrhoea incidence, other parameters like the alteration of the intestinal flora (both the composition and metabolic activity) and immunological changes were investigated.

Forty healthy volunteers were treated with 500 mg amoxycillin twice daily from day 1-7 and five gram of the specific probiotic formulation (109 CFU/gr) was given twice daily from day 1-14. The first results of this study showed that bowel movements with a frequency ≥3 for at least 2 days and/or a consistency ≥5 for at least 2 days were reported less frequently in the probiotic group. The significant reduction in diarrhoea during and after antibiotic intake due to the intake of the specific probiotic formulation (to be published). The mechanisms behind these results are still under investigation, but it is thought to be caused by a faster recovery of the natural intestinal flora and immunological changes. This study will be followed by a clinical trial, which will start this year, with COPD- and asthma patients. Expectations for this study are very hopeful, especially after the good results that were found in the first trial, with the healthy volunteers.

The significant reduction in antibiotic-associated diarrhoea in the verum group indicates that this specific probiotic formulation can theoretically offer the following advantages for the patient:
• Faster recovery from diarrhoea
• Less complications
• Less secondary infections
• Lower morbidity and mortality
• Increased comfort/quality of live

Of course the advantages for care-taking facilities should be taken into account as well:
• Reduced duration of hospital stay
• Reduced workload on nursing staff
• Reduction in prescription of antibiotics
• Reduced antibiotic-resistance related problems
• Fewer ward closures for disinfection
• Less bed-days lost because of infection control requirements

In today’s hospital the nursing staff is overworked and it should not be underestimated how important it is to have a large reduction of AAD patients to look after.

CONCLUSIONS

Many different probiotic formulations have been tested in several studies, which were all conducted with a different setup. Moreover, some studies were not double-blind and placebo-controlled. The meta-analyses of D’Souza et al. and Cremonini et al.12,13 suggest that probiotics are useful in the prevention of AAD. However, in the studies included into the meta-analysis, different probiotics were used. None of these formulations were specifically developed for this specific problem (antibiotic-associated diarrhoea) and therefore there is no clear indication of which formulation acts best.

For the development of a probiotic formulation with an optimal beneficial effect, one should look at the specific characteristics that probiotic bacteria need to have to be effective in the respective application. Besides, there are indications that a multispecies probiotic can have advantage over monospecies or monospecies formulations14. The specific multispecies probiotic formulation that was developed and tested in the University Hospital Maastricht has been selected on different criteria and has already proved to be an effective formulation for the risk reduction of antibiotic associated diarrhoea. If the planned patient study shows similar results, this product will be able to offer great advantages for both patients as well as care-taking facilities.

A very recent study also indicates that there might be possible interesting effects of probiotics during and after antibiotic treatment on the total numbers of antibiotic-resistant strains during re-growth of the intestinal flora15. In this trial, with 162 patients, the number of patients harbouring antibiotic-resistant enterococi at day 35 post therapy increased significantly (p<0.05) in the placebo group. There was no change in the incidence rate of antibiotic resistance among patients in the probiotic group. Research in this field is gaining more attention and this may hold a very interesting application of probiotics during- and after antibiotic treatment for the near future.
REFERENCES