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To cite this version:
R.J. Bywater. DIARRHŒA TREATMENTS-FLUID REPLACEMENT AND ALTERNATIVES. Annales de Recherches Vétérinaires, INRA Editions, 1983, 14 (4), pp.556-560. <hal-00901470>
DIARRHŒA TREATMENTS-
FLUID REPLACEMENT AND ALTERNATIVES

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Abstract

Treatments for diarrhoea in animals include antibiotics, antisecretory drugs, adsorbents and fluid therapy. Of these, antibiotics have a role in bacterial disease, but are probably often used in cases where they contribute little. Other drug approaches (antisecretory, adsorbents, etc.) may in the future be useful, but those so far available do not appear very effective.

Fluid therapy, especially by the oral route, is rational, is effective in both bacterial and viral diarrhoea, and should be the treatment of first choice.

Diarrhoea remains a major problem in calves and pigs probably being the greatest source of loss during the neonatal period. This being so, the treatment of diarrhoea has inevitably become an important part of the veterinarian’s responsibility. The treatments available have been numerous, and have varied in both the degree of rationale for their use, and also the amount of controlled testing to which they have been subjected.

The causes of diarrhoea may be divided into those which are infectious and those which are non-infectious (nutritional), and the resulting diarrhoea may be hypersecretory or malabsorptive. This is shown diagrammatically in figure 1, which also shows the points at which the process of diarrhoea may be approached by drug or other treatments.

Antibiotics

Antibiotics are the most widely used treatment for diarrhoea, despite the evidence for involvement of virus infection, and despite the incidence of resistance among bacteria (especially E. coli and Salmonella).

The antibiotics used to treat diarrhoea are generally those with Gram negative activity, e.g. neomycin, oxytetracycline, ampicillin, amoxycillin, colistin, etc. Of these, some (e.g. neomycin, colistin) are largely unabsorbed, with a local intestinal activity but no systemic effect. Others (e.g. oxytetracycline, ampicillin, amoxycillin) are effective both locally within the intestine and systemically after absorption. There is justification for both the non-absorbed and the partly absorbed antibiotics, since infections with for example enterotoxigenic E. coli (ETEC) may initially be localised within the intestinal lumen, but may later become systemic, when an absorbed antibiotic would be indicated.

There have been relatively few controlled trials of antibiotics as treatment for diarrhoea in calves and pigs. Of these, some have shown certain antibiotics to be effective e.g. apramycin (Pankhurst, 1976), amoxycillin (Palmer et al., 1977) and gentamicin (Jones et al., 1977). However, other trials were unable to show any benefit from antibiotic therapy (e.g. Radostits, 1975). It is of interest that Fisher and de la Fuente (1971) were unable to show any benefit of antibiotics (chloramphenicol and furazolidone) in calves with low immunoglobulin status, and later Buntain and Selman (1980) were also unable to show any benefit of combined
antibiotic and oral fluid therapy but again this was in calves with low immunoglobulin status. The above trials suggest that antibiotic treatment can be of value where susceptible bacteria are involved in the condition, but that any treatment will have a poor prospect of success if the calf has absorbed an insufficient quantity of colostral antibodies.

Treatment with antibiotics in calves would seem to be indicated during the first 4-5 days after birth, or in piglets during the first week of life, i.e. during periods when diarrhoea is especially likely to be due to ETEC. Diarrhoea later in the calf's life is more likely to involve virus infection, where antibiotic therapy could not be expected to directly affect the condition. However, outbreaks of diarrhoea often appear to be associated with mixed infections, (Moon et al., 1978) and when deaths occur (possibly following septicemia) antibiotic treatment may well be appropriate in diarrhoea even though viruses may be the prime cause.

**Antibiotic sensitivity testing**

It is common practice to examine the antibiotic sensitivity pattern of rectal flora using a rectal swab taken from a diarrhoeic calf. This is carried out in an attempt to predict the most efficacious antibiotic to choose for treatment. The rectal swab is, however, a very inefficient means of predicting clinical outcome (Bywater et al., 1978) since the flora within the small intestine may differ markedly from that in the rectum, so invalidating predictions made on the basis of a few organisms taken from the latter site. Of more value is a careful sampling of the small intestine, preferably from a calf killed in the late stage of the disease.

**Antisecretory drugs**

The most widely used drugs with a claim for antisecretory activity are anticholinergic drugs such as atropine or methscopolamine. Unfortunately there is little evidence that these drugs have useful activity against enterotoxin induced secretion, and their inclusion in anti-diarrhoeal preparations is likely to be of little value.

Of greater interest are drugs which are known to affect mechanisms of enterotoxin-induced secretion. Drugs may therefore be predicted to have activity if they alter cyclic nucleotide concentrations, since changes in cyclic AMP are associated with *E. coli* heat labile toxin (LT) and changes in cyclic GMP are associated with heat stable toxin (ST). A more recently identified intermediary is calmodulin (calcium dependant regulator) which seems to be associated with ST activity (fig. 2).

Nicotinic acid is known to reduce cyclic AMP concentrations, and has (at high doses) some effect in reducing diarrhea caused by ST toxin in piglets (unpublished results).

Salicylates (especially aspirin) have been claimed to have activity against cholera toxin (Farris et al., 1976) possibly by reducing cyclic AMP concentrations through blockade of prostaglandin synthesis. We have been unable to show activity of aspirin against *E. coli* toxin, although a trial in pigs (Johansson et al., 1979) has been reported which showed aspirin to be effective in reducing the incidence of diarrhoea. A report (Jones et al., 1977) on another non-steroid anti-inflammatory agent, flu-nixin meglumine, suggested that this compound reduced the severity of diarrhoea in calves, although the mechanism was unclear.

Chlorpromazine is a drug which is known to affect calmodulin, and there is some evidence that it reduces diarrhea in piglets (Lonroth et al., 1979). The sedative effect is however a complicating factor which probably makes chlorpromazine of limited value as an anti-diarrhoeal drug.

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**Fig. 1.** — Diagrammatic representation of the causes of diarrhoea and the points at which treatment may be directed.

**Fig. 2.** — Possible relationship between *E. coli* S.T. toxin, cyclic GMP and calmodulin (calcium dependant regulator).
The α-2-adrenergic agonists are a group of compounds with demonstrable activity against secretion caused by *E. coli* toxins (Newsome et al., 1981). These drugs mimic the α effects of adrenaline, and include oxymetazoline, clonidine, napthazoline and guanfacine. These compounds, or specifically active related compounds may be of value in treatment of secretory diarrhoeas. While at present antisecretory drugs in general have limited practical application, this is an area where future advances may be predicted.

**Adsorbent drugs**

Kaolin, pectin and attapulgite have been used as “toxin adsorbents”, and there is some evidence that *E. coli* enterotoxins can be adsorbed by attapulgite or charcoal (Drucker et al., 1977; Gyles and Zigler, 1978). However, the ability to absorb enterotoxins in vitro or in ligated intestinal loops may not be reflected in therapeutic efficacy in the disease. Indeed adsorbents (kaolin or kaolin plus pectin) were found ineffective in acute diarrhoea (Portnoy et al., 1976). The anionic adsorbing agent cholestyramine was suggested as being useful in treatment of enteritis in infants (Berant et al., 1976). Nevertheless despite a demonstrable ability to adsorb enterotoxin and so reduce secretory activity in animal models, cholestyramine was not effective in preventing diarrhoea following oral challenge of piglets with enteropathogenic *E. coli* (Mullan et al., 1979).

**Fluid replacement**

The majority of animals which die during an episode of diarrhoea do so as a result of dehydration. It is therefore logical that correction of the dehydration should prevent these deaths. Moreover, the dehydration is similar regardless of the cause of the diarrhoea, therefore rehydration has the attraction of being applicable to diarrhoea whether due to bacteria, virus or other cause.

Rehydration represents treatment of a symptom, albeit a potentially fatal symptom, rather than removal of the cause (bacterial, viral, etc). It could therefore be expected that rehydration would merely delay death rather than prevent it. In practice, however, rehydration does much more than this, since most diarrhoeal infections are transient, and if death due to dehydration is prevented, then a large proportion will recover spontaneously. This appears to be true for virus infections (rotavirus, coronavirus) and even for many bacterial infections (*E. coli*, salmonella) where septicaemia is not involved. Where septicaemia is present, then rehydration may be linked with antibiotic treatment.

**Routes for rehydration**

1. Oral rehydration

The principle of oral rehydration is that of active absorption of glucose and amino-acid within the intestine. This active absorption is linked with absorption of water and sodium, and results in a reversal of the process of net secretion which is the underlying cause of both the diarrhoea and the dehydration (fig. 3). The active absorption is not affected by *E. coli* enterotoxin (Whipp and Moon, 1973). Oral rehydration solutions should therefore contain glucose, amino-acid (usually glycine), sodium, potassium, chloride, and some alkalinising agent (bicarbonate, acetate or citrate). To maximise intestinal absorption of water, the solutions should be isotonic. This has been demonstrated using ligated segments of intestine in calves. A hypertonic solution results in net secretion of water from the blood to the lumen, and so would...
be expected to cause initial aggravation of the dehydration. Isotonic solutions result in net absorption, and so would be expected to be immediately beneficial.

The efficacy of oral rehydration in treatment of E. coli diarrhoea has been demonstrated in calves (Braun, 1975; Hamm and Hicks 1975; Bywater, 1977) and in pigs (Bywater and Woode, 1980). The latter paper also showed the efficacy of oral rehydration with a commercially available glucose-glycine-electrolyte solution (Lectade, UK; Biodiet, France; Re-sorb, USA; Beecham Animal Health) in rotavirus infection. This was of interest since rotavirus infection may be expected to be associated with damage to intestinal mucosa, yet oral rehydration remained efficacious.

Pigs represent a particular problem in rehydration, since the intravenous route is impractical, as is subcutaneous administration. Intraperitoneal injection can be used, but the volume which can be infused is limited, and uptake is uncertain. Oral rehydration is therefore particularly appropriate. However, when pigs have collapsed, administration may be by stomach tube (especially in young diarrhoeic piglets) or may be rectal. Rectal administration has been used clinically to treat pigs with streptococcal meningitis (Blackburn, personal communication) where death seems to be associated with dehydration through failure to drink. Absorption of fluid from the colon is rapid in the pig, and this route may prove useful where diarrhoea is not present.

2. Parenteral rehydration.

Until the advent of oral rehydration, it was considered that intravenous rehydration was the route of choice (Watt, 1967). This is still an important route, especially in collapsed calves with more than 9% dehydration (fig. 4). These animals will be unable to make full use of oral (or subcutaneous) fluids, because of impaired circulation. Intravenous fluid replacement may be given initially and be followed by oral fluid replacement.

One practical problem associated with intravenous rehydration lies in the difficulty of placing a needle (or cannula) in the jugular vein of a calf which has severely depressed circulation. This can often be overcome by raising the rear of the animal so that gravity assists the filling of the vein. Incision of the skin over the vein is also helpful in the insertion of a needle or cannula.

Fluids for treatment of dehydration should contain an alkalinising element, either bicarbonate or an indirect source of bicarbonate such as lactate, citrate or acetate. Lactate although widely and successfully included in human intravenous replacement fluids, may be less suitable than the alternatives since diarrhoeic calves appear to suffer from excessive blood lactate concentrations, and so further amounts of lactate may be poorly utilised.

The fluid deficit may be assessed by relating symptoms to the likely degree of dehydration. Thus a calf showing a sunken eye, and tight skin may be expected to have lost approximately 8% of its body weight as faecal water. In a 50 kilo calf, this represents an existing deficit of 4.8 l, which needs to be replaced. Depending on the severity of the condition, up to one third of the deficit may be infused during the first hour, with the rest of the deficit corrected over the next 24 h. This need not be given only by the intravenous route, since 1-2 l can be given subcutaneously by using more than one site. Oral administration can be used as soon as the acute phase of the disease is past.

Conclusions

Of the present treatments available for diarrhoea in calves and pigs, rehydration, especially by the oral route, appears the most soundly based. Antibiotics, although at present probably excessively relied upon, do have a place in the therapy of diarrhoea, preferably in combination with fluid therapy. Antisecretory drugs may in the future be an important new approach to the problem, but so far these, together with adsorbents, are probably of little value in the infection of animals.

EEC seminar on gastro-intestinal diseases in the young pig and calf 1-3 December 1982, INRA CRZV de Theix 63110 Beaumont, France.

References


Question

From Dr. Larvor to Dr. Bywater

I would like to stress the sort of symmetry made in your communication between rehydration and antibiotherapy, placed on the same basis: you have certainly a good antibiotic, but is it for long? In some years, it will be ineffective and then rehydration must remain the basis of therapy. Moreover, antibiotics are active mainly on ETEC, which constitute maybe 20% of the causes of diarrhœa.

Answer

I did not wish to equate antibiotherapy and fluid therapy in what we would recommend, since I believe strongly that fluid therapy should be the first and most important treatment. However, antibiotics do have a role in a secondary treatment, and this should be recognised.

Question

From Dr. Contrepois to Dr. Bywater

I am sceptical about your interpretation of antibiotic resistances in rectal swabs. In the specific case of E. coli diarrhœa, the dominant E. coli in the rectum are also those which are present in the small intestine. If they are resistant in the caecum, they are also in the small intestine. Even if we accept that multiplication of ETEC in the small intestine is associated with the multiplication of other bacterial species, an effect of antibiotics on this associated bacterial overgrowth would be rather a good situation for the proliferation of resistant ETEC.

Answer

I can only interpret the results described as meaning that the conventional sampling of a rectal swabs giving perhaps five colonies out of many millions is a very inaccurate way of sampling even the rectal flora let alone the flora in the small intestine. I believe that many people in practice find rectal swab antibiotic sensitivity a poor predictor of clinical efficacy. The results prevented confirmed this under controlled experimental conditions. The correspondence between flora in the intestine and the rectum may perhaps not always relate as closely as you suggest.