

TREATMENT OF DIARRHEAL DISEASE IN CALVES

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Abstract

Treatments for diarrhea 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. Those so far available do not appear to be very effective.

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

Introduction

Diarrhea 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 diarrhea 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 the amount of controlled testing to which they have been subjected.

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

Antibiotics

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

The antibiotics used to treat diarrhea 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. For example, infections with enterotoxigenic E. coli (ETEC) may initially be localized within the intestinal lumen, but may later become systemic, when an absorbed antibiotic would be indicated.

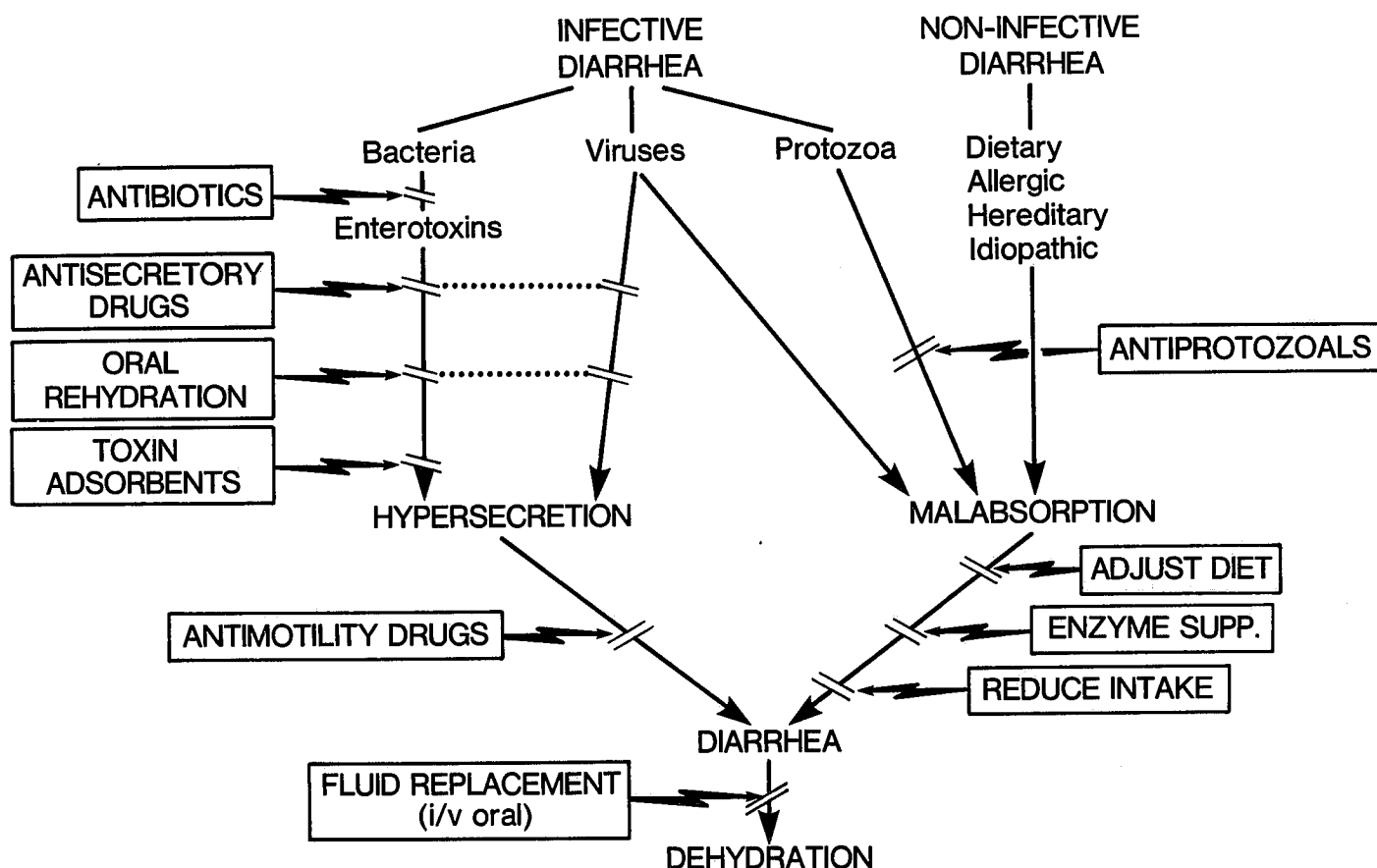


Figure 1. Diagrammatic representation of the causes of diarrheal and the points at which treatment may be directed.

There have been relatively few controlled trials of antibiotics as treatment for diarrheal 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 & de la Fuente (1971) were unable to show any benefit of antibiotics (chloramphenicol and furazolidone) in calves with low immunoglobulin levels. Later, Buntain & Selman (1980) were unable to show any benefit of combined antibiotic and oral fluid therapy, but again this was in calves with low immunoglobulin levels. 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 immunoglobulins.

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 diarrhea is especially likely to be due to ETEC. Diarrhea later in the calf's life is more likely to involve viral infection, where antibiotic therapy could not be expected to directly affect the condition. However, outbreaks of diarrhea 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 diarrhea even though viral infection may be the primary cause.

Antibiotic Sensitivity Testing

It is common practice to examine the antibiotic sensitivity pattern of rectal flora using a rectal swab taken from a diarrheic 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) perhaps because the flora within the small intestine may differ 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 stages of the disease.

Antisecretory Drugs

The most widely used drugs with a claim for antisecretory activity are anticholinergic drugs such as atropine or methscopolamine. Some evidence has been presented (Ahrens & Zhu, 1982) which suggests that atropine may have some antisecretory effect against enterotoxin-induced secretion. However, clinical data is needed to confirm the relevance of this observation.

Of perhaps 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 dependent regulator) which seems to be associated with ST activity.

Nicotinic acid is known to reduce cyclic AMP concentrations, and has (in 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 diarrhea. A report (Jones et al., 1977) on another nonsteroidal anti-inflammatory agent, flunixin meglumine, suggested that this compound reduced the severity of diarrhea 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 antidiarrheal drug.

The α -2-adrenergic agonists are a group of compounds with demonstrable activity against secretion caused by E. coli toxins (Newsome et al., 1981, 1984). These drugs mimic the α effects of adrenalin, and include oxymetazoline, clonidine, naphazoline and guanfacine. These compounds, or specifically active related compounds, may be of value in treatment of secretory diarrheas. 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 attapulgitte have been used as 'toxin adsorbents,' and there is some evidence that E. coli enterotoxins can be adsorbed by attapulgitte or charcoal (Drucker et al., 1977, Gyles & Zigler, 1978). However, the ability to adsorb 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 diarrhea (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 diarrhea 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 diarrhea 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 diarrhea, therefore rehydration has the attraction of being applicable to diarrhea whether due to bacterial, viral or other causes.

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 diarrheal infections are transient, and if death due to dehydration is prevented, then a large proportion will recover spontaneously. This appears to be true for viral infections (rotavirus, coronavirus) and even for many bacterial infections (E. coli, Salmonella) where septicemia is not involved. Where septicemia is present, rehydration may be linked with antibiotic treatment.

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 diarrhea and the dehydration. The active absorption is not affected by

E. coli enterotoxin (Whipp & Moon, 1973). Oral rehydration solutions should therefore contain glucose, amino acid (usually glycine), sodium, potassium, chloride and some alkalinizing agent (bicarbonate, acetate, or citrate). It is generally accepted that oral rehydration solutions should be isotonic although hypertonic solutions containing increased concentration of glucose have been advocated (Phillips, 1982). However, when hypertonic solutions are placed in the intestinal lumen of anesthetized calves, a net secretion results in movement of water and electrolyte from blood to intestinal lumen. This may be expected to aggravate any existing dehydration.

Moreover, it has been shown (Bywater, 1971) that the healthy calf has a limited tolerance to oral glucose. When more than 300 grams per day (about 5 grams per kilo) of glucose was fed to healthy calves, this resulted in fermentative diarrhea. Some oral rehydration formulations are recommended at a dose rate leading to an intake of 500 g of glucose/day (about 10 g/kilo) in order to increase energy input to around 80% of that provided by milk. As predicted above, such doses of glucose by mouth cause fermentative diarrhea in healthy calves and this diarrhea is associated with a fall in fecal pH, and with concentrations of glucose in feces reaching 80 mM/l (unpublished observations). It may be predicted that calves already diarrheic would be even less tolerant of glucose overload than are healthy calves since malabsorption is likely to be present in diarrhea.

There remains, therefore, scope for discussion regarding the constitution of an ideal rehydration formulation for calves. However, the importance of oral rehydration in treatment of diarrheal disease is now accepted, and will, in one form or another, increasingly become the initial treatment of choice.

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