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Diarrhoea and antidiarrhoeal drugs

J. Fioramonti, C. J. E. Niemegeers and F. Awouters

In man, diarrhoea mainly affects children (500 million annually world-wide) and is the leading cause of death in children under 4 years[26]. In animals, diarrhoea also mainly occurs in the neonatal period. One of the main characteristics of diarrhoea in animals as well as in humans is the diversity of aetiologies within the same species.

AETIOLOGY OF DIARRHOEA IN FARM ANIMALS

Acute diarrhoeal disease remains a major limiting factor in cattle production and 5–10% of calves born each year may be lost due to neonatal enteric infection[34]. This occurs despite important advances in knowledge about the intestinal infections which cause diarrhoea, and about the nutrition and management of the neonatal calf.

The aetiology of diarrhoea in calf remains unclear. *Escherichia coli* infection is the most common disease of young calves and occurs mainly during the first 3 weeks of life. Ten years ago, considerable emphasis was given to the involvement of viruses (rotavirus, coronavirus) as a cause of diarrhoea in the neonatal calf[35]. However, the pathogenesis of acute diarrhoea in calf is complex and also involves environmental and dietary factors associated with the intensity of modern production methods.

Swine dysentery is a major disease affecting pigs in large production units, with an acute form of bloody diarrhoea frequently followed by a subacute or chronic form of mucoid diarrhoea without blood.

Investigations over the last 10 years[57] have revealed that *Treponema hyodysenteriae* is the primary pathogen in the aetiology of swine dysentery but the presence of one or more other anaerobes is a prerequisite for expression of its pathogenicity[56]. Adenovirus has been associated also with mild diarrhoea in pig[21]. Environmental and dietary factors may be also important in the development of the disease.

The most important sign of digestive pathology in the young rabbit (5–15 weeks) is diarrhoea. As in other animals the aetiology is complex with

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non-specific causes. Various kinds of stress are involved (e.g. transport, changes in temperature, noise) and are able to activate the infectious agents. The specific agents mainly include coccidiae but their pathogenic action is very variable since coccidiae are present in the digestive tract of all rabbits[40]. The more pathogenic species are *Eimeria intestinalis* and *Eimeria pellerdyi* while species like *Eimeria perforans* are weakly pathogenic[20].

Chronic diarrhoea is also a disease that affects a wide range of ages and breeds of horse. In this case, it seems that diarrhoea corresponds to an immunologic disorder and not to some chronic infection. The concentration of immunoglobulin A in the serum of horses with diarrhoea was approximately 50% lower than that in the serum of normal horses[49]. Treatment of foals with diarrhoea by intramuscular injection of γ-globulin prepared from serum of normal horses proved successful while antibiotics and anti-diarrhoeal drugs were ineffective[48]. However, the α-adrenergic blocking agent, phenoxybenzamine, has been recently reported to be successful in the treatment of diarrhoea in horses[28] but its mechanism remains unknown; similarities with the efficacy of chlorpromazine in enterotoxic diarrhoea in man and swine[27] can be postulated.

EXPERIMENTAL DIARRHOEA

Many models of experimental diarrhoea have been developed to elucidate aetiology and physiopathological mechanisms and to study potential therapeutic measures.

In calves oral inoculation with enteropathogenic strains of *Escherichia coli* was used to induce diarrhoea and to study the pathogenesis of enteric colibacillosis[39] or the efficacy of some rehydration solutions[16].

A dysentery model in pig was developed using infection with *Treponema hyodysenteriae*[41]. This model was useful for testing the efficacy of various drugs[42], or various dietary supplementations[50] and to study intestinal fluid absorption[2] in swine dysentery. Experimental infections in gnotobiotic pigs also demonstrated the pathogenic synergism between *Treponema hyodysenteriae* and other anaerobes in the aetiology of swine dysentery[56].

Since diarrhoea is the most common sign of coccidiosis in various animal species and since the young rabbit is very sensitive to some coccidiae, experimental coccidiosis was used for determination of hydroelectrolytic[33] or digestive motility disturbances[24]. However, the choice of coccidiae species is difficult because of the high lethality of pathogenic species which does not permit longterm experimental studies; for this reason, *Eimeria magna* has been often chosen.

Beyond these infectious models, other types of experimental diarrhoea have been developed to study the colonic motility during diarrhoea, such as castor oil in cats[18] or Ca-sennosides in dogs[25]. Nutritional diarrhoea was also induced for the analysis of the digestive motility disturbances, e.g. grain overload in sheep[10] and cereal food overfeeding in dogs[22].

DISTURBANCES OF DIGESTIVE MOTILITY IN DIARRHOEA

Disturbances of digestive motility associated with diarrhoeal diseases are very variable. In humans, chronic diarrhoea observed in the irritable bowel syndrome has been found to be associated with chronic hypomotility[19, 54]. However, hypermotility or hypomotility are insufficient terms to describe colonic motor disturbances. The colon of all mammalian species investigated is characterized by a duality of contractile activity[23]: tonic contractions of small amplitude, and propulsive phasic contractions. These two kinds of contractions are detected on colonic electromyograms as short and long spike bursts (SSB and LSB) respectively.

Recording of electrical activity of the descending and sigmoid colon in patients with irritable bowel syndrome, manifested by chronic constipation

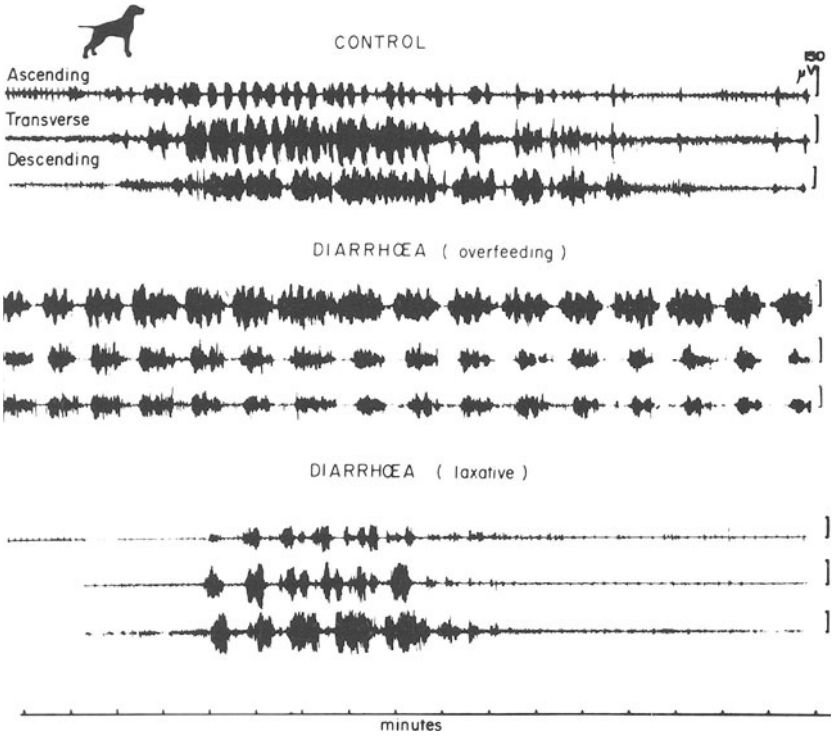

Figure 29.1 Disturbances of colonic motility during diarrhoea in dog. The normal colonic electromyogram consists of bursts of spikes, corresponding to propulsive contractions, grouped in phases lasting about 10 min (upper panel). Feeding large amounts of dry dog food induces production of soft faeces and is associated to propulsive contractions (middle panel). Laxative-induced diarrhoea (senna extracts) corresponds to an hypomotility (lower panel)

or diarrhoea, indicate significant changes in the SSB and LSB activities compared to normal control volunteers[10]. Two major groups of electromyographic changes have been detected. The first, corresponding to an increase in SSB activity was mainly recorded in constipated patients. The second group was characterized by a reduction in both SSB and LSB activity and was often observed in patients with predominantly diarrhoeal symptoms. However, constipation or diarrhoea does not correspond systematically to the afore-mentioned disturbances of colonic motility.

In dogs, the production of abundant and soft faeces induced by feeding a large amount (500 g/day) of dry food is associated with an increase of the propulsive LSB activity and reduction of the SSB tonic activity. In contrast, diarrhoea induced by oral administration of senna extracts corresponds to a strong decrease in both propulsive and tonic contractile activity (Figure 29.1).

In sheep, the spiral colon was characterized by a nearly continuous tonic SSB activity involved in the formation of pellets[46]. In cases of a spontaneous[23]

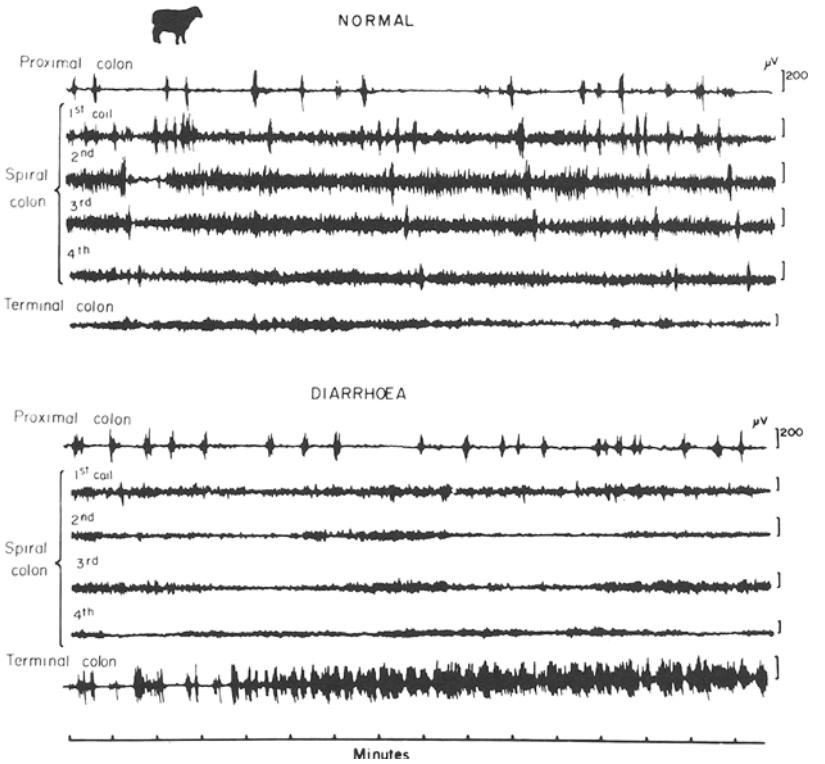

Figure 29.2 Disturbances of colonic motility during diarrhoea in sheep. Colonic electromyograms in same animal during the production of normal faecal pellets (upper panel) or during the production of soft faeces (lower panel). Whatever its aetiology, diarrhoea is associated with an inhibition of the tonic activity of the spiral colon and an increase of the propulsive activity of the terminal colon

or experimental diarrhoea[11] and inhibition of the tonic activity of the spiral colon has always been observed (Figure 29.2).

Thus, inhibition of the tonic activity of the colon is a common finding to the various types of diarrhoea investigated.

Disturbances of the motility of the small intestine have also been described. A general finding is the disorganization of the cyclic motor profile observed in sheep when diarrhoea was induced by intraluminal infusions of hypertonic solutions[45], in rabbits during experimental coccidiosis[24] as well as in a human patient with irritable colon[51].

EFFECTS OF OPIATES AND ANTICHOLINERGIC DRUGS ON DIGESTIVE MOTILITY

The effects of antidiarrhoeal drugs on intestinal motility have been studied largely under *in vitro* conditions. *In vivo* most of the studies concern the digestive transit time but very little information is available on the effects on contractile activity of the digestive tract. Recently, similarities between colonic motor profiles in dogs and humans have been shown[10]. Therefore, colonic motility in the dog was used as a model for studying the effects of some antidiarrhoeal drugs[12, 13].

Opiates

The stimulation of colonic motility in dogs by morphine was first demonstrated in 1940 by Adler and Ivy[1]. Studies over long periods[12] show that the typical pattern of colonic motility in the dog is disrupted by intravenous administration of morphine (0.1 mg/kg). A 180–240 min period of significant increase in colonic motility followed the injection. In many cases, this response was biphasic. During the first 25–35 min a sustained increase in the baseline with superimposed phasic contractions was observed. This primary response was followed 2 h later by an additional tonic response accompanied by an increase in the frequency of phasic contractions. These stimulatory effects were abolished by previous administration of naloxone or atropine while methysergide blocked only the second phase of colonic stimulation. Moreover, methysergide blocked the response when injected by the intracerebroventricular route at doses inactive by the intravenous route[13], suggesting that the long-lasting stimulatory effects of morphine on colonic motility are centrally mediated through serotonergic receptors.

Similarly, loperamide (0.5 mg/kg i.v.) significantly increased the colonic motility index in dogs but only during the first 30 min following its administration[32].

However, extrapolation of data obtained on the dog colon would be speculative. For example, morphine also induced a centrally mediated increase in the motility of the small intestine in sheep, but this response was blocked by previous administration of nalorphine[9], while in dogs morphine and nalorphine induced the same stimulatory effects at the colonic level[12].

Moreover, opiates stimulate the motility of the small intestine in dogs[14] and in humans[31] while an inhibition has been found in rats[55]. Similarly, in horses morphine induced a strong inhibition of colonic motility preceding a period of increase in tonic activity (Fioramonti, unpublished results), while in dogs only colonic stimulation has been observed (Figure 29.3).

In summary, the constipating effects of opiates, beyond their action on the movement of water and electrolytes[7], are induced by different modifications of intestinal motility. They are mediated through mechanisms which vary with the animal species and the part of the digestive tract.

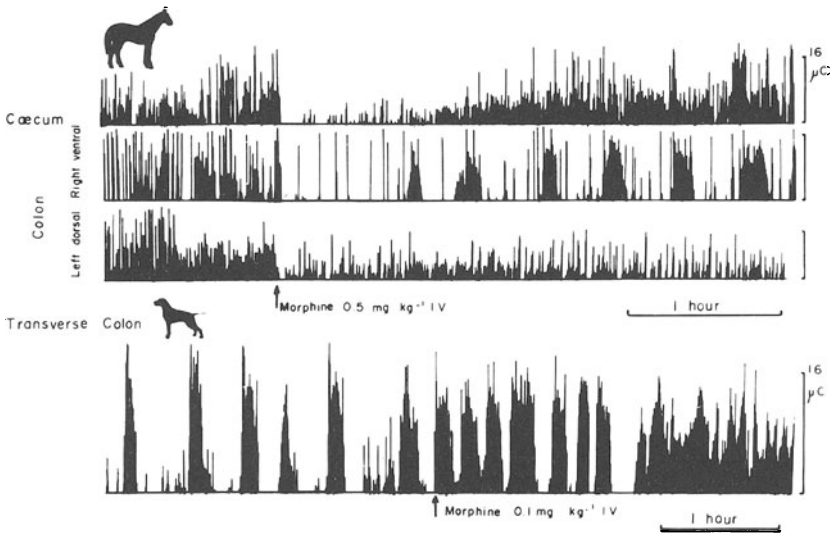

Figure 29.3 Species differences in the response of large bowel motility to morphine. Integrated electromyograms of the caecum, ventral and dorsal colon in horse (upper panel) and of the transverse colon in dog (lower panel). Morphine induces in horse an inhibition of the whole large bowel which shows a localized stimulation of the cyclic activity except for the dorsal colon, while in dog a stimulation of colonic motility is observed

Anticholinergic drugs

Anticholinergic drugs generally have an inhibitory effect on the motility of the digestive tract[6]. These inhibitory effects appear clearly at the colonic level in the dog[32]. A nearly total inhibition was observed during the hour following intravenous administration of atropine sulphate or prifinium bromide (0.5 mg/kg).

However, atropine-resistant contractions of the digestive tract, as evidenced in the taenia of guinea-pig caecum[17], indicate the need for more research on smooth muscle physiology. Recently, an atropine-resistant activity of the descending and sigmoid colon has been found in man[44]. After subcutaneous administration of atropine sulphate (15 μg/kg) tonic contractions

and localized phasic contractions were strongly decreased while the occurrence of aborally propagated contractions remained unchanged.

On the small intestine of sheep, the most important effects of anticholinergic drugs consist of a disorganization of the cyclic motor profile associated with an increase in segmental contractions[8]. Compared to the atropine effects, this disorganization was more important for the prifinium bromide while *N*-butyl-hyoscine bromide was less effective.

From these studies it appears that diarrhoea and its treatment depend upon many complex processes: the diversity of the aetiology of diarrhoea, the relationship between digestive motility, transit of chyme and absorption–secretion, the variability of the effects of antidiarrhoeal drugs according to the animal species, the segment of the digestive tract, and the experimental conditions. This would theoretically imply that in the search for new antidiarrhoeals at least several methods and several different animal species should be used.

In practice, great progress may, however, be expected from the use of a single and simple animal model which mimics to a certain extent the basic pathways of the intestinal response to a foreign challenge. Agents effective in such a model and characterized by a safe and sufficiently specific intestinal action may then, later on, be tested for their therapeutic value in the very diverse clinical forms of diarrhoea that are known either in animals or in man and may in a further step help in elucidating the different processes that play a role in diarrhoea.

PHARMACOLOGY OF ANTIDIARRHOEAL AGENTS

The systematic study of the antidiarrhoeal activity of compounds is relatively recent. Up to 20 years ago, relief of diarrhoea and dysentery in man was mainly pursued with opium preparations, which traditional medicine had selected for this purpose from the many drugs that can cause constipation. This selection appeared to be clinically and also pharmacologically acceptable: morphine and codeine show antidiarrhoeal activity at doses below the analgesic dose[37]. At the same time, however, the central effects of opiates, such as drowsiness, analgesia, respiratory depression and addiction, imposed many practical restrictions to their gastrointestinal use.

The pharmacological progress from opiate alkaloids to the synthetic antidiarrhoeal loperamide has been described in detail[3,38]. The development of loperamide resulted from the synthesis of a new chemical series of piperidine derivatives which lacks the pethidine moiety and from the introduction of the castor oil test in rats which measures antidiarrhoeal activity of compounds instead of constipation.

The induction of diarrhoea with castor oil results from the action of ricinoleic acid formed by hydrolysis of the oil (Figure 29.4). Ricinoleic acid produces changes in the transport of water and electrolytes, resulting in a net hypersecretory response. The normal reaction of the intestine to excessive fluid load is increased peristalsis. In addition to hypersecretion, ricinoleic acid sensitizes the intramural neurons of the gut. This effect of ricinoleic acid

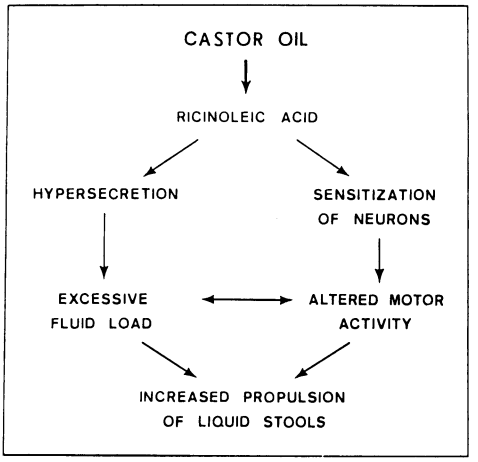

Figure 29.4 Intestinal fate and actions of castor oil

is a general property of hydroxy fatty acids. Ricinoleic acid, therefore, can be considered the prototype of lipids which stimulate the gut, such as the hydroxy fatty acids which are produced by pathogenic bacteria, and the very potent prostaglandins made by the intestine itself. The net result of the neuronal sensitization is to further promote the transport of soft intestinal contents. The described reactions of the gut to ricinoleic acid are the basic mechanisms through which the intestine responds to a wide variety of pathological stimuli. For these reasons castor oil induced diarrhoea was selected for evaluating the effects of antidiarrhoeals.

The standardized castor oil test procedure is as follows. One ml of castor oil applied orally to rats fasted overnight induces profuse diarrhoea within 1 h in all vehicle-treated animals. In rats treated with an antidiarrhoeal, presence or absence of diarrhoea is noted at hourly intervals after the castor oil challenge, and on this basis drug activity is evaluated and expressed in ED_{50}-values which represent doses effective in 50% of the animals.

Castor oil induced diarrhoea in rats has been used for more than 10 years. The test provides reproducible results in control and treated animals, it allows evaluation of the potency of a compound, the onset, and duration of the antidiarrhoeal effect. We further know that the castor oil challenge combines hypersecretion and increased propulsion, and that it gives a reliable prediction of the clinical efficacy of antidiarrhoeal compounds[37].

INTESTINAL ACTION OF LOPERAMIDE: SPECIFICITY AND NATURE

When studied in the castor oil test, loperamide was much more potent than morphine[36]. Protection from diarrhoea up to 2 h was obtained in 50% of the rats with 0.29 mg/kg of orally administered loperamide and with 5.21 mg/kg

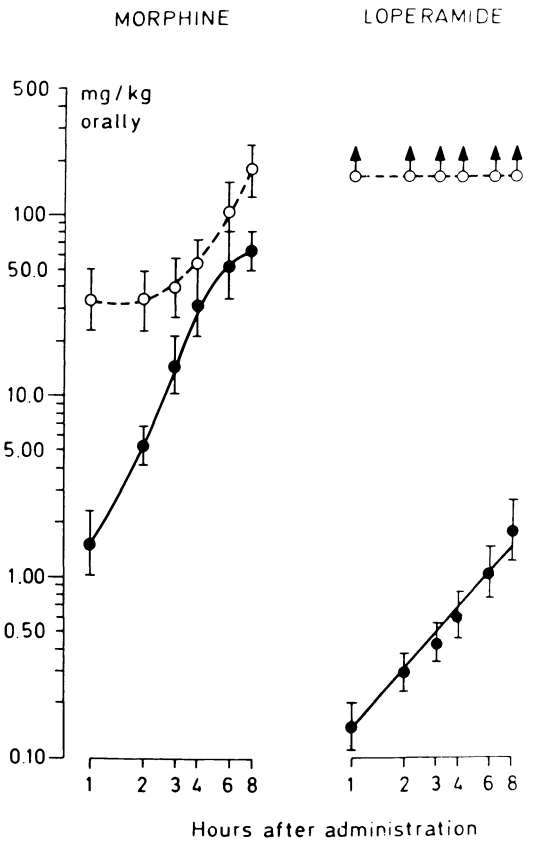

Figure 29.5 Oral ED_{50}-values (with confidence limits) of morphine and loperamide in two tests in rats. Protection from castor oil diarrhoea for 1 up to 8 h (●---●) and inhibition of the tail withdrawal reaction (reaction time >10 s) (○---○) at 1 up to 8 h interval between treatment and test

of morphine (Figure 29.5). This figure also indicates that six times the antidiarrhoeal dose of morphine induced surgical analgesia (tail withdrawal reaction times of more than 10 s), whereas more than 500 times (160 mg/kg) the antidiarrhoeal dose of loperamide did not.

It was found that orally administered loperamide is well absorbed but practically confined to the enterohepatic circulation[15]. Tissues outside the digestive system are therefore, for the most part, excluded from its action. Even when loperamide is deliberately introduced into the general circulation by intravenous injection, central actions were only observed at high, nearly toxic doses[38] and the compound again tended to concentrate in the gastrointestinal tract[58].

Increasing doses of loperamide induce a progressively longer diarrhoea-free period in rats challenged with castor oil. At the same time fluid loss becomes progressively smaller[5]. In contrast to loperamide, aspirin-like drugs

Table 29.1 Some effects of loperamide on intestinal motor function and hypersecretion

Species or preparation	*Process*	*Effect of loperamide*	*Reference*
Guinea-pig ileum (*in vitro*)	Peristaltic reflex	Inhibition	52
Dog colon	Motility	Significant increase during first 30 min	32
Man	Anal sphincter pressure	Significant increase	43
Rat intestine	Cholera toxin or PGE_2-induced fluid accumulation	Antagonism except for increase in cAMP levels	47
Rabbit ileum mucosa (*in vitro*)	Theophylline stimulation of Cl^--secretion	Inhibition	30
Guinea-pig colon	Permeability increase induced by laxative	Dose-dependent reversal	53

produce only a delay in diarrhoea[4]. Although they increase the time available for intestinal absorption, the faecal excretion remains at least as copious as in control animals. Many studies have now established that loperamide changes motor function to a less propulsive pattern, and prevents intestinal fluid accumulation in response to a great variety of secretory agents. Table 29.1 represents a partial list of such studies.

In some of these studies, such as the inhibition of the peristaltic reflex in the guinea-pig ileum[52] loperamide was much more potent than morphine and both drugs could also be qualitatively distinguished.

In the motility studies on the dog[32], loperamide (0.5 mg/kg i.v.) was less active than morphine (0.1 mg/kg i.v.) and had a short duration of action, i.e. there was no second phase of centrally mediated stimulation.

Loperamide and morphine-like drugs have a direct local action on intestinal opiate receptors, which appears to be essential for their antidiarrhoeal activity. However, in binding studies loperamide also shows high affinity binding of large capacity to other receptors. One of these has been identified as the calmodulin binding site, which is considered important in calcium-dependent hypersecretion in the intestine[29] and to which loperamide, in contrast to morphine-like drugs, binds at low concentration[59].

SYMPTOMATIC TREATMENT OF DIARRHOEA AT PRESENT AND IN THE FUTURE

Loperamide acts on the common pathways the intestine follows in response to a variety of diarrhoeal stimuli. Symptomatic treatment of acute and chronic diarrhoea in man with loperamide has found wide acceptance. The medication is, in general, rapidly effective and no side-effects occur, undoubtedly because of the exceptional intestinal specificity of loperamide.

When treatment is considered with other available drugs the pharmacological results of Table 29.2 are of great interest. Eight drugs with known

Table 29.2 Pharmacological results of eight drugs with 'antimotility' and/or 'antisecretory' activity

Compound	*ED_{50} castor oil test* (mg/kg)	*ED_{50} second test* (mg/kg)	*Antidiarrhoeal specificity*
Acetylsalicylic acid	95.3	38.0*	0.40
Atropine	9.3	0.39†	0.042
Clonidine	0.028	0.085‡	3.0
Codeine	10.8	56.6**	5.2
Indomethacin	8.7	6.2*	0.71
Isopropamide	74.6	12.4†	0.29
Lidamidine	1.7	24.9‡	14.9
Loperamide	0.29	>160**	>552

*Nystatin paw oedema test (anti-inflammatory activity)
†Mydriasis (anticholinergic activity)
‡Automatic side-effects (exophthalmos, piloerection and hypotonia)
**Tail withdrawal reaction test (narcotic analgesis activity)

'antimotility' or 'antisecretory' effects were tested in the castor oil test to obtain the dose protecting from diarrhoea for 2 h. The same drugs were studied in another test, which measures the possible primary effect expected from compounds belonging to a particular pharmacological class.

Compounds with very different mechanisms of action, including blockade of intestinal muscarinic receptors, inhibition of prostaglandin synthesis and clonidine-like (adrenergic) action showed antidiarrhoeal activity, but generally at high doses when compared to their primary activity. The first restriction to their clinical use appears to be the lack of intestinal specificity. As in the case of the progress from codeine to loperamide, more specific drugs may be found in the future.

CONCLUSIONS

The incidence and severity of diarrhoea in the neonatal period remains a serious health problem in farm animals as well as in man. A wide range of infectious agents, environmental factors, motility patterns and responses to drugs that act on intestinal smooth muscle have been detected by studying diarrhoea and motility in different species.

As a result a large number of experimental models are now available, which more closely mimic particular types of diarrhoea and which allow a more detailed evaluation of the field of application of the available drugs. The development of a new drug is for practical reasons, such as, for example, a systematic study of structure activity relationships, only possible by using carefully selected animal models. Castor oil diarrhoea in rats is clearly an appropriate model, which has been of great value in the development of synthetic antidiarrhoeal drugs and in the discovery of loperamide. Antagonism of intestinal propulsion as well as of fluid accumulation can be obtained with loperamide in the absence of undesirable systemic effects. The same high degree of intestinal specificity should be pursued in new compounds that

have a different mechanism of action. Such new drugs may be excellent tools to further clarify the pathogenesis of the multiple forms of diarrhoea and may perhaps become the treatment of choice for a particular type of diarrhoea.

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