Gastric mucosal damage in sepsis – effects of pretreatment with a synthetic prostaglandin E₁ analogue

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SUMMARY An experimental model was used which includes intragastric instillation of 80 mM HCl and 0.6 ml bile/kg followed by intravenous infusion of live *E coli* in cats for up to three hours. This procedure regularly induces gastric mucosal ulcerations. Mucosal blood flow was measured by microspheres before, early, and late in sepsis. Total gastric blood flow was recorded electromagnetically. Mucosal regeneration capacity as reflected by the RNA/DNA ratio was measured. Misoprostol (a PGE₁ analogue) was infused iv (5 µg/kg×h) or given locally in the stomach (10 µg/kg) before bacteriemia. Misoprostol did not influence the haemodynamic response to bacteria. The gastric mucosal damage was assessed either as an index representative for the entire corpus-fundus region or as the number of areas with intact surface epithelium within the series. Misoprostol iv protected the mucosa from ulceration compared with untreated septic controls while misoprostol intragastrically significantly reduced the number of damaged areas only. Topical misoprostol increased total gastric and mucosal blood flows early in sepsis compared to iv or no pretreatment while no difference was seen during late sepsis. The protective effect of misoprostol was thus not dependent on increased gastric mucosal blood flow. Nor was it mediated through effects on mucosal nucleic acid concentrations or ratio.

Prostaglandins in doses that have no effect on acid production protect the gastric mucosa from damage caused by stress of various kinds. This 'cytoprotective' effect¹ has been well documented in several studies during the last two decades.^{2,3} The mechanism underlying the cytoprotective effect of prostaglandins, however, remains unclear.

Acute gastric mucosal damage (stress ulcer) is a potentially dangerous complication in septicæmia.^{4,5} Cytoprotective agents might be of importance in the prevention of the development of these lesions. Misoprostol, a novel PGE₁ analogue (G D Searle Co Ltd, USA) has been found to have gastric antisecretory and cytoprotective properties.^{6,7}

The aim of this series of experiments was to investigate if intragastrically or intravenously administered misoprostol exhibited protective effects on the gastric mucosa in a standardised feline

septic shock model and to relate this cytoprotective effect, if any, to effects on regional blood flow, mucosal regeneration capacity, and central haemodynamics.

Methods

CATS

The experiments were carried out on 20 cats, weighing 1.9–4.7 kg. They were deprived of food for 24 hours with free access to water. Anaesthesia was induced by approximately 50 mg pentobarbital iv (Pentothal®) and continued with chloralose (50 mg/kg bw).

Operative procedures, determination of gastric mucosal blood flow, histologic examination and biochemical analysis have been previously described in detail.⁸ Briefly, the animals were tracheotomised and ventilated artificially. A thoracotomy was done to allow injection of radioactively labelled microspheres in the left atrium. A Swan-Ganz catheter (5F, Edwards Laboratories, Santa Ana, California, USA) was used for monitoring cardiac output

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(thermodilution; Edwards computer 1520) and pulmonary artery blood pressure (PAP). Systemic arterial blood pressure was recorded and blood samples were drawn from catheters in the femoral arteries. Infusions were given in the brachial veins. After laparotomy and splenectomy the hepatic artery was ligated proximal to the gastroduodenal artery allowing collateral arterial circulation to the liver from the superior mesenteric artery. An electromagnetic flow probe (Cliniflow model 601D, Carolina Medical Electronics Inc, King, North Carolina, USA) was put on the coeliac artery for continuous measurements of approximately total gastric blood flow. An intragastric tube was introduced through a duodenotomy and connected to a reservoir keeping the intragastric pressure constant at 2 cm of water. An iv infusion of glucose containing bicarbonate (10 mmol/100 ml 5.5% glucose; 0.1–9.2 ml/min) was continued throughout the experiment.

DETERMINATION OF GASTRIC MUCOSAL BLOOD FLOW

Approximately 900 000 microspheres labelled with ^{141}Ce , ^{103}Ru or ^{46}Sc in 10% dextran containing 0.05% of Tween 80 were injected in random order before, 15 min and 150 min after the start of bacterial infusion. If the arterial blood pressure decreased to a level of 50 mmHg, however, the last injection was made at that time (range 70–150 min). The time for injection is therefore referred to below as 'early' and 'late' sepsis. A reference blood flow sample was withdrawn from the thoracic aorta at a speed of 3.4 ml/min (= reference flow) starting 10 seconds before microsphere injection and continued for 70 seconds. At the end of experiments parts of the fundus, major curvature and antrum were excised, the mucosa dissected free and dissolved in concentrated sulphuric acid. Radioactivity was measured in a gamma scintillation counter (Ultra-gamma®). Blood flow was given by the formula:

$$\text{Tissue blood flow (ml/min} \times 100 \text{ g tissues)} \\ = \frac{\text{tissue radioactivity} \times \text{reference flow}}{\text{reference radioactivity}}$$

HISTOLOGICAL EXAMINATION

After the experiments the stomach was rapidly removed and tissue secured for gamma counting. The remainder was mounted on cork, fixed in 4% buffered formalin, prepared for paraffin embedment, cut at 3–4 μm , mounted and stained with haematoxylin-eosin. The glasses were coded with histological examination. The gastric mucosal lesions were graded as described previously.⁸ Grade 0 = normal mucosa, grade 1 = oedema beneath the

superficial epithelium, grade 2 = disappearance of the surface epithelial cells, grade 3 = damage of the upper half of the glands, grade 4 = disappearance of the glands.

A gastric mucosal damage index was calculated as the sum of the maximal damage in three predetermined corpus areas (anterior wall, posterior wall and major curvature). Thus, a gastric index varying from 0 to 12 was obtained in each animal. In addition, the gastric mucosal damage was assessed by counting the number of areas with intact epithelium (grade 0–1) in the different series.

RNA AND DNA ANALYSIS

A 5×5 mm biopsy was obtained from the mucosa of the anterior gastric body before sepsis induction and analysed for RNA and DNA concentration. At the end of experiments two additional biopsies were also obtained from the posterior wall and major curvature of the corpus. The mean of these two values gave the mucosal RNA and DNA concentration after sepsis. RNA was determined according to the method described by Ceriotti⁹ and DNA according to the method of Burton.¹⁰ Standards were obtained from Sigma Chemical Company, St Louis, USA.

BACTERIAL PREPARATION

An *Escherichia coli* strain (*E. coli* 06K 13H1) from WHO Collaborative Centre for Reference and Research on *Escherichia* (State Serum Institute, Copenhagen, Denmark) was used. The bacteria were cultivated in nutrient broth. Just before the infusion, the bacteria were washed in saline, resuspended in 0.9% NaCl, and infused at a concentration of 10^9 live cells/ml. All cats received 1 ml/kg $\times$ min for two minutes and then 1 ml/kg $\times$ hour for up to three hours.

EXPERIMENTAL PROCEDURES

After preparation the cats were allowed to stabilise for 30 minutes. One minute before the iv infusion of live *E. coli*, 0.6 ml bile/kg (obtained from the cat gall bladder) and HCl at a concentration of 80 mmol (volume adjusted to keep intragastric pressure at 2 cm of water, see above) were instilled into the stomach in all cats. In one group of animals, no pretreatment was given ($n=8$, controls). Six other cats received a continuous iv infusion of 5 $\mu\text{g/kg}$ $\times$ hour of misoprostol dissolved in 2.5 ml phosphate buffer (pH 7.4) starting 10 minutes before the induction of sepsis and continued throughout the experiment. Another six animals were given 10 $\mu\text{g/kg}$ of misoprostol in saline administered intragastrically (ig) 10 minutes before the sepsis induction. Arterial blood was sampled for determination

of platelets and white blood cells, pH, pO₂ and pCO₂ before drugs, at early, and at late sepsis.

STATISTICAL METHODS

Data are expressed as mean±SE if based on five or more observations; otherwise the mean value alone is given. Ordinal scale data are given as median and interquartile range. When testing statistical significance the non-parametric methods (the Wilcoxon's matched-pair signed rank test and the Fischer exact probability test) described by Siegel¹¹ and Wilcoxon's rank test were used. A p level <0.05 was considered as significant.

Results

HAEMODYNAMICS

In the pre-septic period arterial blood pressure was 126±9 mmHg in controls; 120±14 and 116±9 for iv and ig misoprostol groups, respectively. Misoprostol administered either iv or ig had no effects on 'resting' blood pressure. At the end of the experimental period six of eight control cats and four of six in both misoprostol groups were hypotensive or not alive (Fig. 1). Pulmonary artery blood pressure increased from 14 to 34 mmHg three minutes after bacteria, normalising at 15 minutes, and was 21 mmHg at late sepsis in control (bacteria only); similar pressure levels were obtained in the iv and ig misoprostol series, respectively.

Cardiac output responded similarly in the three groups. A rapid increase was seen at one minute after the start of bacterial infusion followed by a progressive fall to about 60% of basal value at the end (Fig. 1).

Coeliac artery blood flow increased by more than 100% in animals with local administration of misoprostol into the stomach. This vasodilatory effect lasted for about one hour from the instillation of the drug (Fig. 1). In animals without pretreatment or given iv misoprostol coeliac artery blood flow was unchanged.

GASTRIC LESIONS

All cats without treatment (control) had disrupted superficial epithelium giving lesion index 6 or more (median 8 interquartile 7–8). In iv misoprostol series the mucosal index was 5 or less in four of six cats (median 4 interquartile 3–7; p<0.05 compared with control, Fisher exact probability test). In the ig misoprostol group three animals had an index of 5 or less while three had more pronounced lesions (median 5 interquartile 3–6) and the gastric damage index in this group was not statistically different from control. Table 1 details the grading of the gastric mucosal lesions in the three different areas

Table 1 Grade lesion in anterior, posterior and major curvature

	Grade				
	0	1	2	3	4
Anterior wall	○	● ○○○	●●●●	●● ○○	
Posterior wall	○	● ○○○ xxxxx	●●●	x ●●●	●
Major curvature	○	● ○○ xx	xx ●●●	x ●● ○	x ●●● ○
	x	xxx		x	x

Grade 0 and 1 means intact superficial epithelium. ● = control, ○ = iv misoprostol, and x = intragastric misoprostol.

that were examined. In both ig and iv misoprostol pretreated groups significantly more such areas were found with intact superficial epithelium ((grade (0–1); p<0.002 for both iv and ig misoprostol compared with controls).

GASTRIC MUCOSAL BLOOD FLOW

This was unchanged in controls and iv misoprostol group as measured 'early' or 'late' after sepsis induction (Fig. 2). In contrast, local administration of misoprostol increased mucosal blood flow from 8.4±1.2 to 25.1±9.9 ml/min × 100 mg tissue in corpus/fundus and from 6.7±0.8 to 47.8±9.2 in antrum in early sepsis (Fig. 2).

NUCLEIC ACID CONTENT OR THE RNA/DNA RATIO

These were neither influenced by sepsis nor by misoprostol during the period of three hours of the septic state in any of the three groups (Table 2). One of the control animals was excluded because of technical failure.

BLOOD TESTS

All three groups were acidotic at 'late' sepsis (Table 3). pO₂ was 14.2±0.5, 16.6±1.0 and 14.7±1.5 kP in

Table 2 RNA, DNA (μg/100 mg tissue wet weight) and RNA/DNA ratio in gastric mucosa before and after bacteremia (mean values±SE)

		RNA	DNA	RNA/DNA
Control	Before bacteria	37±16	235±84	0.16±0.02
	After bacteria	31±11	207±71	0.21±0.04
Misoprostol iv	Before bacteria	47±14	441±90	0.10±0.02
	After bacteria	32±7	320±34	0.10±0.02
Misoprostol ig	Before bacteria	40±12	367±51	0.11±0.03
	After bacteria	25±4	229±26	0.12±0.03

Fig. 1 Effects of misoprostol pretreatment on arterial blood pressure, cardiac output and coeliac artery blood flow in septic cats. * Denotes significant difference compared with basal value ($p < 0.05$).

the three groups, respectively, before bacteria and did not change during the experiments. $p\text{CO}_2$ decreased from 3.8 ± 0.1 to 2.9 ± 0.2 kPa at 'late' sepsis in cats without pretreatment and from 3.9 ± 0.2 to 2.7 ± 0.4 kPa in ig misoprostol group. Corresponding values for iv misoprostol were 3.7 ± 0.3 and 3.4 ± 0.2 . Misoprostol did not affect the rapid reduction of circulating arterial white blood cells or platelets (Table 4).

Discussion

In this experimental model live *E. coli* septicaemia induced pronounced gastric mucosal lesions. Misoprostol administered iv protected the mucosa significantly while the ig administration of misoprostol before sepsis did not result in significant reduction of total gastric lesion index. If comparing numbers of areas in the stomach with intact super-

Fig. 2 Gastric mucosal blood flow in misoprostol pretreated animals and controls. For early and late sepsis see text. Early sepsis flow in intragastric misoprostol group was increased both in antrum ($p<0.01$) and corpus ($p<0.05$) compared with control. * Denotes significant difference compared with basal value ($p<0.05$).

ficial epithelium to those without intact epithelium, however, a significant effect was seen also with the locally administered prostaglandin. The doses given iv or ig were in experiments on conscious dogs shown to be equipotent in so far as the inhibition of gastric secretion is concerned.¹¹ It is very unlikely, however, that the acid secretion inhibitory property of misoprostol is of any importance in the present experimental model in which exogenous acid is instilled into the stomach. Because we do not know whether the doses given are equipotent as concerns 'cytoprotective' effects or not, a strict comparison between iv and ig misoprostol cannot be made. Intragastric misoprostol increased mucosal and total gastric blood flow at early sepsis in contrast with iv misoprostol, which had no such effect. Thus, in the present shock model, topical misoprostol provided limited mucosal protection together with increased

Table 3 Arterial blood pH at early and late sepsis in control ($n=8$), misoprostol iv ($n=6$) and misoprostol ig ($n=6$) animals before and after *E. coli* infusion (mean value $\pm$ SE)

	pH		
	Basal	Early	Late
Control	7.41 $\pm$ 0.03	7.39 $\pm$ 0.04	7.25 $\pm$ 0.06*
Misoprostol iv	7.41 $\pm$ 0.01	7.40 $\pm$ 0.04	7.30 $\pm$ 0.06*
Misoprostol ig	7.43 $\pm$ 0.01	7.40 $\pm$ 0.03	7.20 $\pm$ 0.07*

* Denotes significant difference compared to basal value.

Table 4 Leucocytes (polymorphonuclear and mononuclear; $\times 10^6/l$) and platelets ($\times 10^9/l$) in control ($n=8$), misoprostol iv ($n=6$) and misoprostol ig ($n=6$) before, early and late (see text) after bacterial infusion (mean values $\pm$ SE)

	Basal value	Early sepsis	Late sepsis
Polynuclear leucocytes			
Control	6.6 $\pm$ 1.0	2.1 $\pm$ 0.5*	0.9 $\pm$ 0.2*
Misoprostol iv	9.2 $\pm$ 1.8	3.7 $\pm$ 1.8*	1.3 $\pm$ 0.3*
Misoprostol ig	7.3 $\pm$ 1.0	2.5 $\pm$ 0.6*	1.0 $\pm$ 0.2*
Mononuclear leucocytes			
Control	3.6 $\pm$ 0.5	1.4 $\pm$ 0.3*	2.1 $\pm$ 0.7
Misoprostol iv	1.1 $\pm$ 0.3†	0.5 $\pm$ 0.2*	0.8 $\pm$ 0.2
Misoprostol ig	1.6 $\pm$ 0.3†	0.6 $\pm$ 0.2*	0.7 $\pm$ 0.2*
Platelets			
Control	157.2 $\pm$ 32.6	78.2 $\pm$ 16.5*	119.1 $\pm$ 21.0*
Misoprostol iv	102.9 $\pm$ 19.8	29.9 $\pm$ 6.8*	72.8 $\pm$ 13.0
Misoprostol ig	125.1 $\pm$ 25.9	59.5 $\pm$ 16.3*	84.0 $\pm$ 13.2

* Denotes statistically significant difference ($p<0.05$) compared with basal value and † compared with time-matched control values.

gastric and gastric mucosal blood flow. On the other hand, iv misoprostol had no effect on flow and despite this, the mucosa was significantly protected from ulcerations. This indicates that other mechanisms besides increased mucosal blood flow are important in the protection against gastric mucosal lesions in septic shock. The background to the difference in effect on gastric blood flow between iv and ig misoprostol could possibly be differences in local concentration, but this has not been further investigated.

As discussed previously⁸ gastric ulcerations develop in this septic shock model without signs of gastric or gastric mucosal ischaemia. This is contrary to the currently accepted pathogenesis for stress ulcers as outlined – for example, by Silen *et al.*¹³ The view that mucosal ischaemia is not an important factor in the pathogenesis of acute gastric ulcerations in sepsis is, however, in agreement with other recent data. Genter *et al.*¹⁴ studying the effects of *E. coli* injected iv in piglets, found an increased mucosal blood flow as measured by microspheres. This response failed to appear in animals pretreated with indomethacin, proposing prostaglandins as a mediator of the vascular reactions in the septic gastric mucosa.¹⁵ Rees *et al.*¹⁶ found no difference in gastric venous outflow between ulcerated and non-ulcerated septic dogs, also indicating that gastric blood flow is of less importance. These authors proposed 'functional shunting' in the mucosa, however, resulting in apical gland ischaemia, causing the mucosal damage. The present technique

does not allow studies of blood flow distribution within the mucosa.

The cytoprotective effect of prostaglandins on the gastric mucosa exposed to external injurious agents like indomethacin, acetylsalicylic acid, boiling water etc, is well documented.¹⁻³ Misoprostol gave mucosal protection in aspirin induced gastric damage in dogs^{6,17} and in stress induced gastric ulcer formation in rats.¹⁸ The potentially protective effects of prostaglandins in more 'physiological' forms of stress, such as sepsis or haemorrhagic shock, have not attracted similar attention.

Odonkor *et al*¹⁹ found cytoprotective properties of parenterally given 16,16-dimethyl PGE₂ on mucosal damage in peritonitis induced septicaemia in conscious dogs. Using a canine haemorrhagic shock model including topical aspirin lesion formation was significantly reduced by misoprostol but not by 16,16-dimethyl PGE₂. Misoprostol decreased the shock-induced transmucosal potential difference and increased gastric venous outflow. It was concluded that protective effects of misoprostol were mediated *via* increased blood flow.⁷

Regenerating capacity of gastric mucosal cells has been proposed to be of importance in the development of stress ulcerations in rats and mice.^{21,22} 16,16-dimethyl PGE₂ has been shown to prevent the reduction in RNA and DNA in rat gastric mucosa exposed to 100% ethanol.²² Changes in RNA/DNA ratio reflect increased mucosal regeneration activity.²³ In the present series of experiments, however, no changes were observed in nucleic acid concentration of the gastric mucosa or RNA/DNA ratio in response to the sepsis. Nor did misoprostol, regardless of the route of administration, affect RNA or DNA concentration of the gastric mucosa (Table 2).

Misoprostol delayed systemic hypotension but had otherwise no significant effect on the central haemodynamic or haematological reaction to bacterial infusion. The results of studies using cyclooxygenase (prostaglandin synthetase) inhibitors as well as of those using exogenous prostaglandin supply are contradictory.²⁴ Cyclooxygenase inhibitors have been reported to prevent the pulmonary hypertension²⁵ and the pulmonary platelet trapping²⁶ in septic states. The lack of effect on pulmonary circulation by misoprostol supports the view that other arachidonic acid metabolites, such as thromboxan A₂ and prostacyclin (PGI₂), are of more significance for the pulmonary response to sepsis.

In conclusion, gastric lesions in a feline septic shock model were significantly diminished, but not prevented, by misoprostol. The protective effect was not mediated through increased blood flow or effects on nucleic acids of the mucosa.

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