Short Communication

THE COMPARATIVE PROTECTIVE EFFECTS OF DEGRADED CARRAGEENIN AND ALUMINIUM HYDROXIDE ON EXPERIMENTALLY PRODUCED PEPTIC ULCERATION

BY W. ANDERSON AND J. WATT

From the Evans Medical Research Laboratories, Speke, Liverpool, and the Department of Pathology, University of Liverpool

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ACUTE peptic ulceration of the duodenum can be produced experimentally in guinea pigs within 24 hours of the administration of a large dose of histamine in beeswax-oil provided a covering dose of an antihistamine is given to protect the animals from acute shock.

Degraded carrageenin, a sulphated polysaccharide (Ebimar) has been shown to react with mucus lining the gastric mucosa and in low concentrations to interfere with peptic digestion. It provides complete protection against duodenal ulceration produced by the above method[1,2]. In the present experiments we have compared its effects on ulcerogenesis with those of aluminium hydroxide.

Methods. Male guinea pigs (300–400 g.) were prepared for experiment by depriving them of food from 5 p.m. on the day before the experiment. The next day at 4.30 p.m. the animals were injected intraperitoneally with promethazine 7·5 mg., followed within half an hour by an intra-muscular injection of histamine acid phosphate 30 mg./kg. in a 10 per cent (w/v) beeswax : arachis oil vehicle. The suspension was made by triturating 1·5 g. histamine acid phosphate (200 mesh) with the vehicle and adjusting the volume to 50 ml.

The animals were studied in groups of five, and the drugs were administered in 2 ml. doses intra-oesophageally at 3 hour intervals from 6 hours before to 21 hours after the histamine injection. Ebimar was given in aqueous solutions containing 20, 10, 5, 1, or 0·2 per cent w/v. Aluminium hydroxide was administered as liquid gel containing the equivalent of 4, 2, or 1 per cent Al_2O_3 w/w. The control group were given 2 ml. of water at the same intervals.

The animals were killed 24 hours after the histamine injection. The stomach and duodenum were removed, fixed in formol saline, and the degree of damage was assessed numerically according to the scheme, Table I.

Results. The degree of damage in the stomach and duodenum in each group of five animals is recorded in Table I. The maximum score if all five animals were severely damaged would be 15 for the stomach, 15 for the duodenum, giving a total score of 30.

It is seen in the control group which received water only that the maximum score was reached in the duodenum. Considerable protection from ulceration in the duodenum was apparent in the groups treated with

10 per cent and 20 per cent sulphated polysaccharide, and in those treated with 2 per cent and 4 per cent aluminium hydroxide.

Less protection was provided with the lower concentrations of each of these drugs. In contrast, however, the sulphated polysaccharide afforded greater protection against stomach ulcers than aluminium hydroxide.

It was observed that considerable caking of aluminium hydroxide had occurred in the stomachs of the groups receiving 4 per cent and 2 per cent gel, but this was not evident in the group receiving 1 per cent gel.

TABLE I

NUMERICAL ASSESSMENT OF THE DEGREE OF GASTRIC AND DUODENAL DAMAGE IN SULPHATED POLYSACCHARIDE AND ALUMINIUM HYDROXIDE-TREATED ANIMALS. CONTROL GROUP RECEIVED ONLY WATER

	Sulphated polysaccharide per cent					Aluminium hydroxide gel per cent as Al_2O_3			Water
	20	10	5	1	0·2	4	2	1	
Stomach ..	3–4	2–3	2–3	3	0–1	4–6	8–9	10	9–10
Duodenum	0	3	8	14–15P	12–13P	0	0	6–7	14–15P
Totals ..	3–4	5–6	10–11	17–18P	13–14P	4–6	8–9	16–17	23–25P

Key: 0 No damage,
1 very slight damage, for example, one or two small lesions revealed on careful examination,
2 immediately obvious but not extensive damage,
3 immediately obvious and widespread damage; perforation is indicated by P.

In the sulphated polysacharide treated groups, particularly those receiving the higher concentrations, a fine gelatinous film was observed over the mucosa, especially in the lower third of the stomach and in the duodenum.

Discussion. The method of producing acute peptic ulceration in the above experiments allows the slow release of histamine over a prolonged period. In the guinea pig, histamine stimulates the secretion of a large volume of highly acid gastric juice[3], and it is believed that this factor is primarily responsible for the mucosal damage[4,5]. The results in the aluminium hydroxide series may be said to be in fair agreement with this theory.

From the results of experiments as yet unpublished, we have evidence that in the histamine stimulated guinea pig 2 ml. of 4 per cent aluminium hydroxide gel greatly reduces the acidity of the gastric juice for 2 to 3 hours; 2 per cent gel causes some reduction, but with 1 per cent gel the free acid is only very slightly reduced. It may, therefore, be assumed that over the 27 hour period during which aluminium hydroxide was administered in the present experiments little, if any, free acid is likely to have been present in the stomach or duodenum in the group receiving the 4 per cent gel. This assumption was confirmed by the fact that at post-mortem examination no free acid was detected in the gastric juice in the group receiving 4 per cent gel, but free acid was present in the stomachs of the groups receiving the 2 per cent and 1 per cent gels. As already indicated (Table I), duodenal lesions occurred only in the group given 1 per cent gel. It is noteworthy that despite the accumulation of substantial

amounts of aluminium hydroxide in the stomachs of the group receiving 2 per cent gel, a distinct reaction for free acid (Topfer's reagent) was obtained in the post-mortem juices.

On the basis of the aluminium hydroxide experiments, where increasing damage appears concurrently with increase in free acid, it is not possible to assess the relative importance of the acid and pepsin in the pathogenesis of the ulcerative lesions described. Although these experiments might suggest that the protective action of aluminium hydroxide gel was because of its antacid properties, it must also be appreciated that the anti-peptic activity of this compound may play an important role. Nevertheless, the use of antacids in peptic ulcer therapy is well established and the demonstration of a protective action by the antacid in these experiments perhaps not too surprising. It is interesting to observe on the other hand, that degraded carrageenin which possesses no antacid activity should afford protection to the extent reported.

The evidence we have already obtained about the properties of degraded carrageenin suggests that it has at least two main actions[1,2], and we consider that these actions may be intimately concerned in the protective effects of the sulphated polysaccharide used in these experiments. Degraded carrageenin reacts with mucoprotein in a manner to be expected of polyanionic substances in acid environment. We tentatively conclude that the complex formed between mucoprotein in the mucus lining the stomach and degraded carrageenin serves to enhance the physical protection afforded by mucin. In addition, the degraded carrageenin confers anti-peptic properties on this complex.

REFERENCES

1. Anderson and Watt, *J. Physiol.*, 1959, In the press.
2. Anderson and Watt, *J. Pharm. Pharmacol.*, 1959, **11**, 318.
3. Watt, *Quart. J. exp. Physiol.*, 1955, **40**, 364.
4. Code, *Surg. Clin. N. America*, 1943, **23**, 1091.
5. Watt, M.D. Thesis, University of Aberdeen, 1956.

After Dr. Anderson presented the paper there was a DISCUSSION.