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The effect of free silica on the mucosal protective and antiflatulent properties of polydimethylsiloxane

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The mucosal protective and antiflatulent properties of polydimethylsiloxane (PMS) alone, or containing free silica have been examined in rats. Both PMS and PMS + 6% silica significantly protected rat gastric mucosa from the irritant effects of aspirin but there was no significant difference between the protective effect of each agent. The antiflatulent property of PMS, as determined by X-ray measurements of foam production in the rat stomach, was significantly enhanced by the addition of free silica.

Polydimethylsiloxane (PMS) is a long chain silicone polymer which is relatively inert chemically, and also pharmacologically inactive when given orally.

The mucosal protective properties of PMS have been demonstrated in many experimental models, particularly in the prevention of experimentally induced gastric ulcers in animals. Such methods have involved the use of prolonged histamine administration in guinea-pigs (Nickerson & Curry, 1953), pyloric ligation according to the Shay technique in rats (Shay, Komarov & others, 1945; Nickerson & Curry, 1953), intermittent electrification in rats (La Barre, 1963) and administration of acetylsalicylic acid and tetracycline in rats (Garcet, Laurre & others, 1962). All report the effectiveness of PMS in protecting the gastric mucosa from damage caused by the various techniques.

The antiflatulent properties of preparations containing PMS have been examined in man by gastroscopists (Rider & Moeller, 1960; Oswald, 1961). The painful distension of the abdomen has also been studied in animals, Quin having examined the effect of silicones in the treatment of bloat in ruminants (Quin, Austin & Ratcliff, 1949). Confusion in terminology, however, has led to an imprecise definition of the term polydimethylsiloxane, no mention being made in some instances of the presence or absence of silica and it should not, therefore, be assumed that the material used is pure PMS.

We report an investigation to examine the effect of silica added to PMS on the mucosal protective and antiflatulent properties which PMS possesses; a novel technique for determining the antifoaming effects of substances in the rat stomach as a model for experimental flatulence is also described.

METHODS

Gastric mucosal protection

Male Wistar rats (100–120 g) were deprived of food, but not water, for 18 h before the experiment, and water was withheld during the experimental period. Each test material was given by gastric intubation 10 min before the administration by the

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same route of 1 ml of a suspension of aspirin (45 mg ml^{-1}) in 1% w/v carboxymethylcellulose (CMC) in water. The rats were killed, by exposure to chloroform, 2 h after receiving the aspirin. Each stomach was removed, opened, gently washed with isotonic saline and examined for lesions in the glandular region using a stereomicroscope. The degree of severity of the lesion was scored on a 0–6 scale by an observer unaware of the doses employed.

A preliminary experiment was performed to determine the dose of PMS that afforded sub-maximal protection against aspirin-induced gastric irritation. Doses of PMS ranging from 0·25 to 2·0 ml were used. Control groups of animals received 1 ml of 1% w/v CMC in distilled water, or 1 ml of aspirin suspension or 2·0 ml of PMS only. There were 10 rats at each dose level and all animals received the same dose, irrespective of body weight.

Subsequently, a comparison was made between the protection afforded by PMS and PMS containing 6% w/v silica. The dose of PMS, selected on the basis of the results of the preliminary experiment, was 0·25 ml, and the same dose of the silica containing preparation was administered to another group of rats; both groups comprised 10 animals. Control groups received aspirin (20 animals), or 1% w/v CMC in water (5 animals) or 0·25 ml of 6% w/v aqueous silica suspension (5 animals) only.

De-foaming activity in vivo

Sprague-Dawley rats (200–250 g) of either sex were deprived of food but not water for 18 h before the experiment.

The following method was developed to allow differentiation between free gas and foam in the stomach of the rat:

Foam was produced by gastric intubation of 0·5 ml of a freshly prepared solution of 0·17M citric acid containing 4% w/v sodium iodide, followed immediately by 0·5 ml of 0·25M sodium carbonate containing 1% w/v saponin. The carbon dioxide evolved, distended the stomach and, in the presence of saponin, produced a layer of foam over the solution in the stomach. Two min later the rat was X-rayed whilst held in a vertical position, and the plates were subsequently examined. Sodium iodide, being a water-soluble, radio-opaque substance was present both in the wall of the bubbles which constituted the foam and in the solution. Thus three distinct layers were visible on the image of the stomach; a lower white layer (solution), an overlying grey area (foam) and a darker upper layer of free gas. The height of the foam layer (in mm) was measured before and 2 min after treatment of each rat with PMS, 6% w/v aqueous silica suspension or PMS containing 6% w/v silica; 5 min was allowed between the first X-ray exposure and the treatment with a test substance. All rats in a group were dosed with the same volume of each substance, irrespective of body weight.

Four groups of 10 rats each received doses of a test substance which increased by a constant logarithmic interval (0·301). A dose-response curve was constructed for each of the three substances under investigation.

Materials

PMS (dimethicone 1000 B.P.C.) (Midland Silicones); Silica (Aerosil 200) (Degussa); PMS containing 6% silica (Rhône Poulenc); citric acid, sodium iodide, sodium carbonate and saponin (BDH).

Table 1. *Protection afforded by polydimethylsiloxane (PMS) against aspirin-induced gastric irritation.*

Treatment (oral)	Severity of gastric irritation in each rat (0–6 scale)	Mean score (± s.e.)	% reduction compared with aspirin-treated goup
1% CMC (1 ml)	0 0 0 0 0 0 0 0 0 0	0	—
Aspirin (45 mg)	5 5 4 3 4 5 4 1 4 2	3·7 ± 0·42	—
Aspirin (45 mg) + PMS (0·25 ml) ..	2 2 3 0 0 4 2 4 3 1	2·1 ± 0·46*	43
Aspirin (45 mg) + PMS (0·5 ml) ..	0 4 2 4 3 2 2 0 4 3	2·3 ± 0·50	37
Aspirin (45 mg) + PMS (1·0 ml) ..	1 2 3 2 0 1 3 2 2 2	1·8 ± 0·29**	51
Aspirin (45 mg) + PMS (2·0 ml) ..	2 0 1 0 2 0 1 2 3 0	1·1 ± 0·35***	70
PMS (2·0 ml)	0 0 0 0 0 0 0 0 0 0	0	—

Significance of difference from groups receiving aspirin only: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

PMS was given 10 min before administration of aspirin; animals were killed 2 h later.

There were 10 rats in each group.

RESULTS

(a) *Gastric mucosal protection*

The results of the preliminary range finding experiment are given in Table 1. Neither PMS nor 1% w/v CMC produced any evidence of mucosal irritation when administered alone. PMS caused a reduction in the severity of the aspirin-induced gastric irritation compared with the unprotected group receiving aspirin alone; protection ranged from 37 to 70%. On the basis of these results 0·25 ml PMS was the dose selected for the main experiment.

Table 2 compares the mucosal protection afforded by PMS and PMS containing 6% w/v silica. Both substances produced a significant reduction ($P < 0.05$) in the severity of the aspirin-induced lesions compared with the unprotected group, but the presence of 6% w/v silica did not enhance the effects of the PMS. Neither 6% w/v aqueous silica suspension nor 1% w/v CMC caused any irritation of the gastric mucosa.

(b) *De-foaming activity* in vivo

The results are based on changes in foam height as measured from X-ray photographs of each rat. The results are presented in Table 3.

Both PMS and silica are relatively weak de-foaming agents when used separately. However, when administered together, the mixture was so effective that difficulty was experienced in accurately administering a dose which would reduce the foam height by less than 50%; a dose-volume of 0·005 ml caused a mean reduction in foam height of 45%.

Table 2. *Protection afforded by polydimethylsiloxane (PMS) and PMS containing 6% silica against aspirin-induced gastric irritation.*

Treatment	Number of rats per group	Severity of gastric irritation in each rat (0–6 scale)	Mean score (± s.e.)	% reduction compared with aspirin treated group
1% CMC (1 ml)	5	0 0 0 0 0	0	—
Aspirin (45 ml)	20	3 3 3 3 4 1 4 3 4 6 4 5 3 2 4 2 2 5 5 3	3·5 ± 0·28	—
Aspirin (45 mg) + PMS (0·25 ml)	10	1 1 3 3 2 3 3 3 1 2	2·2 ± 0·29*	37
Aspirin (45 mg) + PMS containing 6% (w/v) silica (0·25 ml) ..	10	3 2 2 2 2 4 3 3 3 1	2·5 ± 0·27*	28
6% aqueous silica suspension (0·25 ml) ..	5	0 0 0 0 0	0	—

Significance of difference from group receiving aspirin only: *$P < 0.05$.

PMS, PMS containing 6% w/v silica or 6% w/v aqueous silica suspension were given 10 min before administration of aspirin; animals were killed 2 h later.

Table 3. *Mean percentage reduction in foam height following oral administration of polydimethylsiloxane (PMS), 6% w/v aqueous silica suspension or PMS containing 6% w/v silica.*

Treatment (by mouth)	Dose volume (ml)	Dose (mg/rat) PMS	Dose (mg/rat) Silica	Mean percentage reduction of foam height (± s.e.)
PMS	0·25	250	—	19 ± 4·0*
	0·50	500	—	29 ± 6·1*
	1·00	1000	—	56 ± 6·2**
	2·00	2000	—	84 ± 3·4**
6% w/v aqueous silica suspension	0·05	—	30	28 ± 4·7
	1·00	—	60	45 ± 5·2**
	2·00	—	120	59 ± 3·6**
	4·00	—	240	75 ± 4·4**
PMS containing 6% w/v silica	0·005	4·7	0·3	45 ± 6·3**
	0·010	9·4	0·6	58 ± 4·7**
	0·020	18·9	1·1	61 ± 4·7**
	0·040	37·7	2·3	87 ± 2·3**

Significance of difference between mean foam height before and after dosing: * $P < 0{\cdot}05$, ** $P < 0{\cdot}001$.

There were 10 rats in each group.

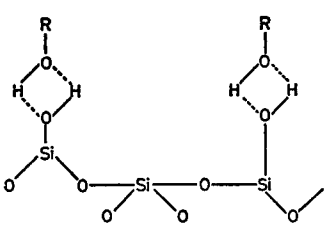
A foam layer was produced in the stomach of each rat by oral administration of 0·5 ml of 0·17M citric acid containing 4% w/v sodium iodide immediately followed by 0·5 ml of 0·25M sodium carbonate containing 1% w/v saponin.

The appropriate ED 50 values for PMS and silica, when given separately, are 750 and 80 mg respectively. To produce the same reduction in foam height with a mixture of the two ingredients, only 4·7 mg of PMS and 0·3 mg silica are required.

DISCUSSION

A technique has been developed whereby the de-foaming properties of PMS and PMS containing 6% w/v silica have been compared in an *in vivo* model of experimental flatulence in the rat; reproducible and dose related effects of these agents were established. The technique should be applicable to the study of other potential antiflatulent agents in other species.

The study has demonstrated that the silica does not modify the protective effect of PMS on the gastric mucosa; however, a substantial enhancement by silica of the *in vivo* anti-foaming activity of PMS has been shown. A possible explanation of this latter effect is suggested by the work of Stober, Bauer & Thomas (1957). They have shown that there are approximately 2000 silanol groups per particle of



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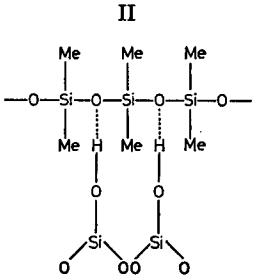

silica and a mechanism for the interaction of the hydroxyl groups at the surface of hydrophilic silica with hydroxylic materials has been proposed (I).

PMS is probably rendered hydrophobic by hydrogen bonding of the molecule to the hydroxyl groups at the silica surface (II).

Spectroscopic measurements by Buist, Burton & Elvidge (1973) show strong evidence for the formation of hydrogen bonds on the silica surface due to the adsorbed PMS. This is demonstrated by enhanced hydrogen bonded hydroxyl absorption at 3450 cm^{-1} and the corresponding fall in free hydroxyl absorption at 3700 cm^{-1} on the silica surface. Hydrophilic silica is water wettable and disperses readily into aqueous media, whereby its effect on the antifoaming properties of the PMS would be lost. The adsorption of the PMS on to the silica renders it hydrophobic and enables the PMS to be more readily dispersed over the whole foam area.

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