Silicones in Experimental Peptic Ulceration

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FOLLOWING THE INITIAL STUDIES[1, 2] in which methylpolysiloxane (silicone antifoam)[3] was shown to be highly effective in preventing ulceration in the pylorus-ligated and in the treatment of histamine-induced gastroduodenal ulceration in dogs, a clinical trial was instituted in patients with chronic peptic ulceration.[4] As the trial progressed it became apparent that the experimental preparation which had been so successful in the previous animal studies[1, 2] had no effect in the ulcer patients. This led to repetition of animal studies on the preparation used in the clinical trial and when they failed to show the beneficial effects which the early studies had shown, trials were undertaken with other types of silicones.

MATERIALS AND METHODS

Studies were undertaken both in Indianapolis by Dr. J. B. Hammond at the Eli Lilly and Company and in the Gastroenterology Research Laboratory at the University of Michigan in Ann Arbor. The animal preparations used were as follows:

1. Pylorus-ligated rats were sacrificed at 18 hours (Lilly) and at 24 hours (U. of M.) after operation, in which the various silicone preparations were given by stomach tube. Quantitation of ulcer-preventing action in the latter study was based on presence or absence of macroscopic ulceration in the rumen including perforation of stomach or perforation of esophagus. In the former study the following grading system was used as an ulcer index:

0 = clear

1 = 1 or 2 small ulcers

2 = more than 1 or 2 ulcers but not many

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3 = many small and large ulcers

4 = perforated or markedly ulcerated

The index was derived by adding the score for each animal and dividing by the number of animals receiving the same treatment. Thus the range of score can vary from 0 to 4.0.

2. Mann-Williamson dog preparation of which 8 received silicone and 7 did not.

3. Histamine ulcers in dogs: 15 dogs were given daily subcutaneous injections of histamine-acid phosphate in beeswax (preceded by 20 mg. benadryl subcutaneously) in the dose of 30 mg. histamine base per day for 18 days, followed by 60 mg. per day until death or sacrifice. Silicone therapy, started 7 days after starting histamine injections, was given daily by stomach tube as a 1/10 dilution of the emulsion in the dose of 3 cc. diluted mixture per kg. initial body weight. The dogs were weighed daily.

MATERIALS

All the silicones used in this study were supplied both to Eli Lilly and to the University of Michigan by Dow Corning Company, Midland, Michigan, by the courtesy of and with the active cooperation of Dr. Melvin J. Hunter and Dr. R. R. McGregor. XEC 151 was an antifoam of the type previously effective in rats and dogs[1,2] but as used in this study, was not of the original batch. 240-41 was the code number for the clinical study,[4] and the last number, -86 and -101, etc., denoted placebo and silicone, respectively, the latter belonging to the XEC 151 group. Reference to numbers in brackets (e.g. 240-41-101 #64) refers to lot numbers as supplied by Dr. Hunter.

RESULTS

1. Pylorus-ligated rats:

A. 380 rats were studied in the laboratories of Eli Lilly 18 hours after pylorus ligation (Table 1). The method of quantitating the results is different from that used in subsequent experiments, in that the ulcer index was the measure depended upon. Table 1 shows that Amphojel in full strength was very effective in preventing ulceration; the placebos 240-61-86 containing 20% Amphojel were ineffective by comparison. Of all the silicones tested 240-41-101 (number 64) was the most effective. This was the preparation used in the clinical trial. Of the XEC 151 preparations, there was

TABLE 1. Eighteen-Hour Pylorus-Ligated Rats (Eli Lilly)

Drug			Animals	Stomach		Ulcer Index	Mortality
				Perforation			
Type	Lot Number	Dose		Esophagus	Stomach		Dead 18 hours
None (Controls)			130	?	28	2.4	47
		1 ml.	10	?	?	1.9	?
Saline		0.3 ml.	10	?	?	2.3	?
		10 ml./kg	20	4	11	3.3	14
		1 ml.	10	0	0	0.1	?
Amphojel	RT 323		10	0	1	0.5	1
Silicones							
	a. XEC 334	3%	10	2	5	3.2	9
	b. XEC 267		9	3	5	3.3	9
	c. XEC 151						
(240-41-101)	#64*		80	0	4	1.52	52
	#74		30	0	6	2.47	21
	#72		10	?	?	1.9	?
	#82		10	2	1	2.6	3
	#83		10	1	2	2.4	3
	#85		10	2	2	3.0	5
	#86		10	2	1	2.4	2
	#92		9	3	1	1.7	4

*XEC 151, Lot 240-41-101, #64 was used in the clinical trial.

variation from lot to lot in effectiveness which could not be accounted for by any of the physico-chemical characteristics of the emulsions.

B. 395 rats were studied at the University of Michigan (Table 2) all by a uniform technique. The animals were allowed food until the night before pylorus ligation and water until the time of ligation. At that time 1 cc. of the test drug was introduced into the stomach and the animals were kept for 24 hours without food or water. A number died during this period, the remainder were sacrificed at 24 hours. In all the animals the volume, pH, and condition of the mucosa of the rumen were noted. They were recorded as good or bad depending on the absence or presence of macroscopic ulceration. In Table 2 the results of treatment with saline, Amphojel, 20 different types of silicone and two organo-metallic catalysts (XEY 5697 A and B) are detailed. Saline alone gave poor results (12 per cent good), Amphojel was a little better (42 per cent good). Among the silicones, a few in full strength gave

TABLE 2. Evaluation of Different Types and Lots of Silicone Compared to Amphojel or Saline Treatment in 24-Hour Pylorus-Ligated Rats*

Drug			Gastric Juice		Survival	Stomach		
Type	Lot #	Dilution[a]	Vol. (ml/ 24 hrs)	pH range[b]	#alive at 24 hours	Good	Bad	Good%
1. SALINE		0.9%			20/73	9	64	12
2. AMPHOJEL		0	19	2-3	17/19	8	11	42
3. SILICONES						12	3	80
A. Antifoam	XEC 5027	0	9.5	4-6	6/15			
	XEC 5507	0	15	4-6	6/15	9	5	64
	XEC 5507	1:10	12.5	5-6	3/10	4	6	40
	XEC 5507	1:100	17.0	1-5	1/8	2	6	25
	XER 5527	0	15.5	3-7	11/15	12	3	80
	XEC 5667	0	22	3-6	10/14	8	6	57
	XEC 5667	1:10	15	5-6	4/6	1	5	20
	XEC 5687	0	?	<3	2/5	0	5	0
	XEC 5517	0	17	2-5	6/8	7	1	88
	XEC 5517	1:10	?	?	3/5	1	4	20
	XEC 5647	0	16	2-5	10/12	9	3	75
		1:10	20	4-5	?	1	3	25
		1:100	21	4-5	?	0	4	0
	XEC 5537	0	23	<3	4/5	1	4	20
B. Fluid	XEO 5577	0	?	?	4/4	0	4	0
	EF 5567	0	19.2	5-7	9/15	11	4	73
	EF 5637	0	17	2-7	3/9	7	2	78
	EF 5547	0	17	4-6	10/15	10	5	67
	XEO 5587	0	20	4-7	7/9	5	4	56
	EF 5557	0	13	<3	3/5	0	5	0
	XEO 5597	0	13	2-6	2/10	8	2	80
	EF 5637	0	19	2-5	3/7	2	5	29
	EF 5637+					10	0	100%
	XEY 5697A	5:1	20	6	10/10			
C. Resin	XER 5607	0	16	<3	2/5	1	4	20
	XER 5617	0	21	4-6	10/14	14	0	100
	XER 5617	1:10	23.4	5-7	10/10	5	5	50
	XER 5617	1:100	17.4	5-6	10/10	2	8	20
	XET 5627	0	19.3	5-7	7/10	7	3	70
4. Organo-Metallic Catalysts	XEY 5697A	0	22.4	6-7	10/10	10	0	100
		1:10	23.2	3-6	14/14	14	0	100
		1:100	30.5	2-6	3/10	10	0	100
	XEY 5697B	1:10	22.6	2-6	5/5	3	6	33
		1:100	22.0	2-6	5/5	0	5	0

[a]All animals were given 1 ml. of the respective fluid by stomach tube at the time of pylorus ligation.

[b]Measured by pH Hydrion paper.

reasonable results, but upon dilution the percentage of good results was sharply reduced. The two catalysts, as follows, were very different.

XEY 5697 A is dibutyl tin diacetate

$(C_4H_9)_2$ Si $(OOCH_3)_2$

XEY 5697 B is zinc di (2-ethyl hexoate)
$Zn\ (OOC_8H_{17})_2$

One gave poor results, the other prevented gastric ulceration in 100 per cent of rats of dilutions of up to 1:100 (= .01 cc. of original) without reducing volume or acidity of the contents.

In the latter animals the surface of the mucosa appeared white and coagulated. Acute toxicity studies were performed with XEC 5697 A, in 10 rats given 1 ml./day by gastric intubation and compared to 10 controls given 1 ml. saline per day. Both groups were allowed food.

CUMULATIVE PER CENT OF RATS DEAD

Days	0	1	2	3
XEC 5697 A	0	10%	40%	100%
Saline	0	0	0	0

At autopsy the entire gastrointestinal mucosa was white, coagulated and friable. The other organs appeared grossly normal.

It seemed unprofitable to continue any further ulcer-prevention studies with XEC 5697 A.

2. Dogs:

A. Mann-Williamson preparations: (James B. Hammond, M.D.) Emulsion 240-41-101.

Fifteen dogs were studied, 8 serving as untreated controls. Six developed ulcers and died at 15, 28, 33, 35, 45 and 52 days, respectively, after operation. One sacrificed at 46 days had no ulcer and one at 63 days had numerous erosions of the stomach and jejunum.

Of the remaining 7 animals, 4 were treated with undiluted silicone (50 cc./day) and 3 died with ulcers at 52, 55 and 63 days after operation, respectively; the other sacrificed at 26 days had no ulcers. Three others were treated with diluted silicone (10 cc. in 100 cc. fluid) and died with ulcers at 43, 48 and 66 days, respectively.

B. Histamine induced ulceration:

Ten dogs were injected with 30 mg. histamine base per day for 20 days and then given 60 mg. per day. Four dogs died at 2 (0),* 4 (0), 10 (+), and 11 (+) days respectively. The others were

*Symbols in brackets denote absence or presence of chronic peptic ulceration.

sacrificed 13 days after starting the large dose of histamine. Of these, 4 had gastric or duodenal ulcers, while 2 did not. Thus of the 8 dogs receiving large doses of histamine for 10 days or more, 6 had chronic peptic ulcers.

Of the 6 dogs treated with silicone 5 died, one after 9 days on 30 mg. of histamine daily showing multiple jejunal petechiae. The others died 6 (0), 8 (+), 11 (+), 11 (+) days, respectively, after the larger dose of histamine and one sacrificed at 13 days also had a chronic ulcer. Thus, of 6 dogs, 4 had chronic ulcers, one acute jejunal ulceration and the sixth, no ulcers.

Silicones apparently had no protective action in these dogs, and the results differed appreciably from our earlier experiments with a different silicone preparation in the histamine ulcer in dogs.[2]

DISCUSSION

In the various experiments reported here, some types of silicone gave better protection against experimentally induced ulceration than others, and within each type different factory batches of apparently the same physico-chemical properties gave different results. In none of the batches or types tested here, however, did the effectiveness approach that of the antifoam silicone used in the previously reported experiments. Unfortunately none of the original material could be located, and one is left with the haunting melody of the lost chord. Since there was no way of determining how any of the large numbers of silicones used in these experiments differed critically from the original material, we were at a loss for directions in which to pursue the study and regretfully abandoned further testing with the conclusion that some silicone or silicone-like compound, in which combined spreading, clinging, and water-repelling characteristics may eventually be found suitable for the treatment or prevention of peptic ulceration.

SUMMARY

In the search for a silicone as uniformly successful as the one used earlier, in preventing and treating experimental peptic ulceration in animals, 30 different silicones were used in pylorus-ligated rats, Mann-Williamson dogs and histamine ulcerated dogs. None were found to be uniformly effective and the initial encouraging results reported by us could not be reproduced with subsequent silicone preparations.

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