Fig. 3a shows differences between differential FT-IR spectrum of the mixture of acetylcysteine and PEG 4000 and the spectrum of pure acetylcysteine.

In the case of acetylcysteine-glycine mixture (trace C, Fig. 2f) an endothermic peak at a temperature of 100–115°C can be seen which is probably the melting endotherm of acetylcysteine. A large shift in melting point signifies that a strong solid-solid interaction has occurred.

At 45°C/70% r.h. the mixture was found to become intensively yellow and hardened. The increase of degradation products was evident by TLC and the amount of acetylcysteine decreased to 32·2%. Fig. 3b shows changes in the FT-IR spectrum of acetylcysteine in the mixture with glycine in comparison with the spectrum of the pure drug. The FT-IR spectrum showed changes over the whole range.

The thermogram of acetylcysteine-adipic acid (trace C, Fig. 2g) shows a downward shift of the acetylcysteine endotherm to a temperature of 100–114°C, which is followed by a broad endotherm (114–140°C), but the adipic acid melting endotherm is absent which can be indicative of an interaction. If characteristic new peaks can be seen in the thermograms of drug-excipient mixtures, it can be inferred that an interaction is occurring between the compounds and is likely to result in a chemical incompatibility (Monkhouse & Van Campen 1984).

No evident interaction in acetylcysteine-adipic acid mixture was indicated by HPLC, TLC or FT-IR spectroscopy after 2 months' storage at 45°C/70% r.h.

Two broad endothermic peaks are found in the case of the acetylcysteine-saccharin sodium mixture (trace C, Fig. 2h) with onsets of transitions at 45 and 85°C. The trace of saccharin sodium (trace B, Fig. 2h) shows two broad overlapping endothermic peaks at 119–130°C, which are absent in the trace of the mixture. The acetylcysteine melting endotherm is also absent. Extra thermal effects in a thermogram before the peak of the lower melting component might be indicative of an incompatibility (Van Dooren 1983).

At 45°C/70% r.h. the mixture became a hard, sticky yellow mass and an increased amount of degradation products was shown by TLC. The amount of acetylcysteine determined by HPLC decreased to 13·7%. From the differential FT-IR spectra it can be concluded that a strong chemical interaction has occurred in this mixture. The differential spectrum shows completely changed signals in the whole spectrum region as shown in Fig. 3c.

No attempt was made during this study to determine the nature of the interactions, be it chemical or physical interaction, eutectic, solid solution or complex formation. The results suggest that acetylcysteine in mixtures with PEG 4000, glycine and saccharin sodium is degraded during storage at humid and elevated temperature conditions. In the case of non-aged mixtures, no changes were observed by FT-IR spectroscopy.

References

Blaug, S. M., Huang, W. T. (1972) Interaction of dextroamphetamine sulfate with spray-dried lactose. J. Pharm. Sci. 61: 1770–1775

Duvall, R. N., Koshy, K. T., Pyles, J. W. (1965) Comparison of reactivity of amphetamine, methamphetamine, and dimethylamphetamine with lactose and related compounds. Ibid. 54: 607–611

Li Wan Po, A., Morso, P. V. (1984) Drug-drug incompatibility in the solid state kinetic interpretation, modeling and prediction. Int. J. Pharm. 18: 287–298

Monkhouse, D. C., Van Campen, L. (1984) Solid state reactions—theoretical and experimental aspects. Drug Dev. Ind. Pharm. 10: 1175–1276

Pharmacopoea Jugoslavica editio quarta (1984) Savezni zavod za zdravstrena zaštitu, Beograd, p. 21.

The United States Pharmacopeia XXII (1990) United States Pharmacopeial Convention, Inc., Rockville, p. 270.

Van Dooren, A. A. (1983) Design for drug-excipient interaction studies. Drug Dev. Ind. Pharm. 9: 43–55

Wells, J. I. (1988) Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances. Ellis Horwood Limited, Chichester, pp 215–219

J. Pharm. Pharmacol. 1992, 44: 518–520
Communicated August 13, 1991

© 1992 J. Pharm. Pharmacol.

Polyethylene glycol: its adverse gastric effects in rats

C. H. CHO, W. M. HUI*, N. X. LIAO*, X. G. LIU*, S. K. LAM*, C. W. OGLE, *Departments of Pharmacology and *Medicine, Faculty of Medicine, University of Hong Kong, Hong Kong*

Abstract—The effects of polyethylene glycol (PEG) on gastric function and on lesion formation, evoked by topical applications of absolute ethanol to an ex-vivo stomach chamber preparation have been examined. Parenteral injection (i.p. or s.c.) of PEG with different molecular weights (PEG 300, 400 or 4000), dose-dependently reduced the gastric mucosal blood flow and volume of gastric secretion; these effects were greater in rats given PEG by the i.p. route, which also lowered acid output. Topical application of 1·5 mL absolute ethanol produced severe gastric mucosal injury, which was exacerbated by PEG; this lesion-aggravating effect was higher in the i.p.-injected groups. These findings indicate that when PEG is given by injection, it can adversely affect gastric function and increase the damaging action of alcohol. It is suggested that the use of PEG as a vehicle for injection should be re-assessed.

Polyethylene glycol (PEG) is used as a pharmaceutical aid (ointment and suppository base) and it also can be employed as a solvent for some pharmaceutical preparations (Merck Index 1989) because the compound has relatively low toxicity (Smyth et al 1950). However, a preliminary study has shown that PEG of various molecular weights (mol. wt) has a profound adverse effect on the stomach when it is given parenterally (Wong et al 1987). The present study investigates the effects of PEG 300, 400 and 4000 on gastric secretory function and gastric mucosal blood flow (GMBF), using an ex-vivo stomach chamber. The interactions between PEG and ethanol on the stomach are also examined since it is likely that the two compounds would be used in the same preparation; ethanol produces significant gastric damage and has been widely used as an experimental ulcerogen in rodents (Szabo & Cho 1988).

Correspondence: C. H. Cho. Department of Pharmacology, Faculty of Medicine, University of Hong Kong, 5 Sassoon Road, Hong Kong.

Materials and methods

Female Sprague-Dawley rats, 220 ± 10 g, were fed a normal

pellet diet (Ralston, Purina) and housed in a room with controlled temperature (21 ± 1°C) and humidity (65–70%). Solid food was withheld 24 h before starting experiments, but the animals were allowed free access to tap water.

Animals were anaesthetized with pentobarbitone sodium (50 mg kg^{-1}, i.p.) The trachea was cannulated and an ex-vivo gastric chamber prepared by placing a plexiglas ring (2 cm diam., 0·5 cm deep) on the mucosa (Wong et al 1986). The glandular mucosa forming the base of the chamber was first washed with three changes of distilled water. Each experiment consisted of six sequential 15-min periods. The chamber was filled with 1·5 mL distilled water (incubation solution) which was replaced by the same solution at 15-min intervals for the next four 15-min periods. At the fifth period, the chamber solution was changed to 1·5 mL absolute ethanol (BDH, UK). The severity of glandular mucosal damage was determined by measuring the areas of the haemorrhagic lesions 15 min later (Cho et al 1990).

The chamber solution was collected for the measurement of gastric secretory volume at the end of each 15-min interval. A sample of this solution was titrated with 0·01 M NaOH (BDH) to pH 7·4 with an autotitrator (Radiometer, TTT80). The GMBF was measured (Sheppard & Riedel 1982) at the end of each 15-min interval by a laser Doppler flowmeter (Periflux). The zero value was defined by placing the laser probe against a white board and the GMBF was recorded in arbitrary units. Each blood flow measurement was performed with a frequency of 4 kHz and a time constant of 1·5 ms.

Polyethylene glycol 300, 400, or 4000 (Sigma, USA) was either diluted with distilled water to 50% or used without dilution. These preparations were injected either intraperitoneally or subcutaneously at the start of experiments. The data were expressed as means ± s.e.m. and analysed for statistical significance by the paired Student's *t*-test.

Results

Intraperitoneal injection of PEG 400 or 4000 reduced the GMBF 15 min after its administration. PEG 300 lowered the GMBF 15 min later. This dose-dependent depressive effect of PEG lasted to the end of the experiments, 75 min. PEG 400 produced the biggest reduction of GMBF (Fig. 1). The three compounds of PEG also lowered the gastric secretory volume, which started 15 min later than the action on GMBF (Fig. 1). The higher doses of PEG 300, 400 and 4000 reduced gastric acid secretion 45 min after intraperitoneal injection and this lasted to the end of the experiments (Fig. 1).

Subcutaneous administration of PEG 300, 400 or 4000 also depressed the GMBF and secretory volume, but the responses were less and also delayed for another 15 min when compared with the intraperitoneal route (Figs 1, 2). These compounds,

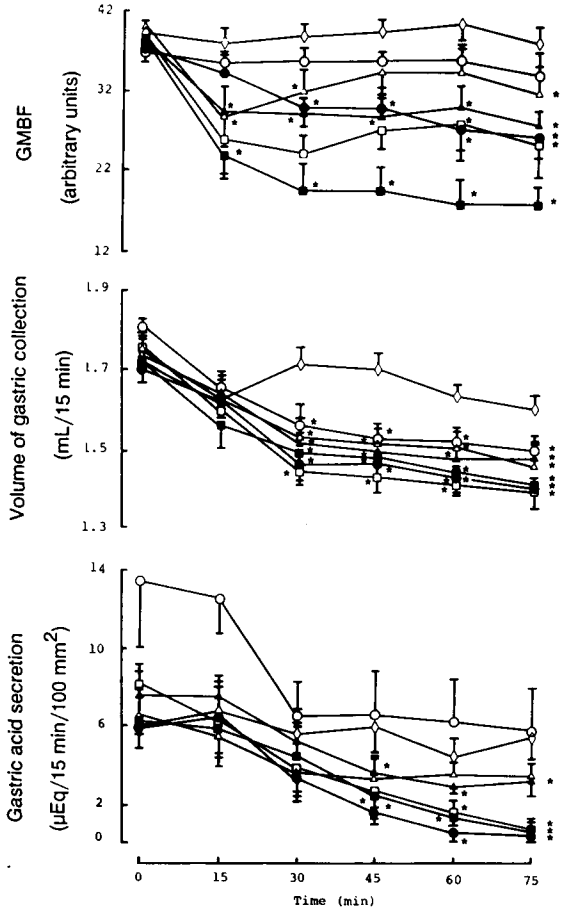

FIG. 1. Effects of PEG 300 (○, 50%; ●, 100%; 2 mL kg^{-1}), PEG 400 (□, 50%; ■, 100%; 2 mL kg^{-1}), PEG 4000 (△, 50%; ▲, 100%; 2 mL kg^{-1}), or distilled water (◇, 2 mL kg^{-1}) given i.p. on gastric mucosal blood flow (GMBF), volume of gastric collection and gastric acid secretion. Values indicate means ± s.e.m. The number of rats used in each group is the same as in Table 1. *$P < 0.05$ when compared with its own value at zero time.

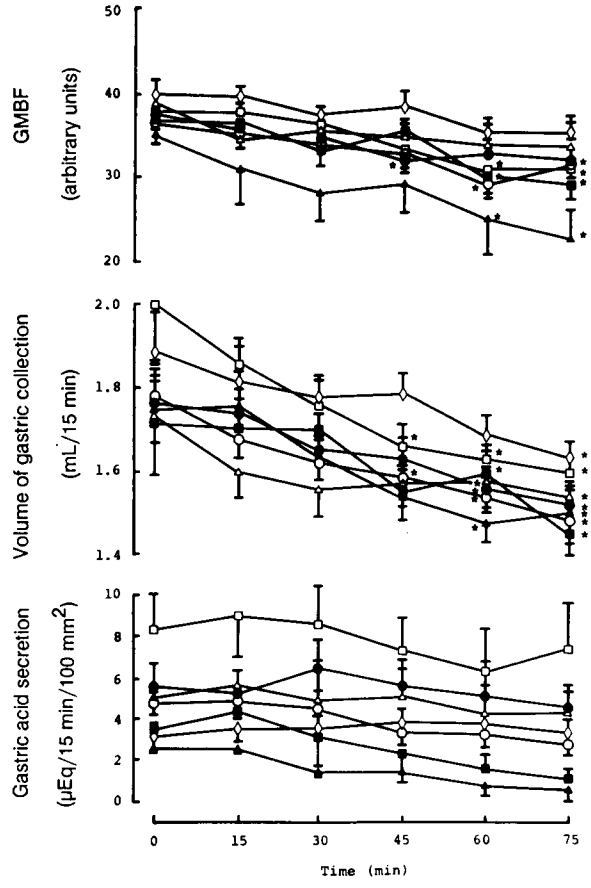

FIG. 2. Effects of PEG 300, PEG 400, PEG 4000, or distilled water given s.c. on gastric mucosal blood flow, volume of gastric collection and gastric acid secretion. The symbols and the number of animals used in each group are the same as in Fig. 1. *$P < 0.05$ when compared with its own value at zero time.

Table 1. Effects of polyethylene glycol (PEG) on ethanol-induced gastric mucosal damage.

Treatment	Number of rats	Gastric lesions (mm^2)
A. PEG given by the i.p. route		
Distilled water	13	28·3 ± 8·0
PEG 300		
50%	6	105·3 ± 29·2*
100%	12	194·0 ± 16·5*
PEG 400		
50%	7	59·4 ± 15·8
100%	7	187·6 ± 28·4*
PEG 4000		
50%	9	79·0 ± 20·8*
100%	9	82·6 ± 17·0*
B. PEG given by the s.c. route		
Distilled water	10	26·4 ± 5·7
PEG 300		
50%	10	68·5 ± 15·5*
100%	10	96·8 ± 17·3*†
PEG 400		
50%	7	63·4 ± 11·4*
100%	6	78·5 ± 21·5*†
PEG 4000		
50%	7	44·6 ± 13·2*
100%	6	97·0 ± 35·5*

All treatments were at 2 mL kg^{-1}. Values indicate means ± s.e.m. *$P < 0.05$ when compared with the corresponding distilled-water treated group. †$P < 0.05$ when compared with the corresponding i.p.-treated group in A.

however, did not affect gastric acid secretion, which was reduced in the intraperitoneally injected-groups (Figs 1, 2).

Ethanol incubation for 15 min produced severe gastric mucosal injury which was located at the glandular portion of the stomach. A preliminary study (unpublished) had already indicated that PEG 300, 400 or 4000 given alone by either route has no ulcerogenic effect on the stomach; however, all these three mol. wt PEGs dose-dependently increased the severity of ethanol-evoked gastric damage. Intraperitoneal administration of the higher doses of PEG 300 and 400 produced a greater potentiating effect when compared with their subcutaneously-treated counterparts (Table 1).

Discussion

PEG is regarded as a relatively non-toxic substance (Smyth et al 1950) and has, therefore, been widely used as a pharmaceutical base or vehicle for various drug preparations. The present study, however, demonstrates the potential adverse effects of PEG of various mol. wts on the rat stomach. The compound not only reduced the GMBF but also decreased the gastric secretory function (Figs 1, 2). PEG also exacerbated gastric damage produced by ethanol and the effect was dose-dependent (Table 1). It has been demonstrated that reduction of gastric secretory volume and GMBF are causative factors for the formation of gastric lesions induced by ethanol (Wong et al 1986; Cho & Ogle 1990); these findings may explain the ability of PEG to aggravate ethanol-induced gastric damage in rats. Experimental evidence indicates that the PEG analogue, Triton WT1339, can enhance carbon tetrachloride hepatotoxicity in rats (de Ferreyra et al 1981) and it is thought that this effect could be due to an increase in lipid peroxidation and a detergent-like action. It has further been reported that topical application of PEG produces acidosis and chelates tissue calcium (Herold et al 1982); both effects have been shown to be involved in stress- and ethanol-induced gastric mucosal damage (Koo et al 1989; Wong et al 1991). PEG could, therefore, also act through these mechanisms to exacerbate ethanol-evoked mucosal damage.

It was noted that intraperitoneal administration of PEG 300 or 400 resulted in a larger potentiating action on mucosal damage by ethanol, when compared with their subcutaneously-injected counterparts. This effect could possibly be due to PEG exerting a faster onset of action and a greater depression on the GMBF and secretory function in the intraperitoneally-injected groups (Figs 1, 2). However, this pattern was not seen in rats given PEG 4000 by the same route. These differential effects are probably due to the much bigger molecules in PEG 4000, which are at least ten times greater than those in PEG 300 and 400; the large molecules in PEG 4000 would, consequently, make it more difficult for the compound to be absorbed from the peritoneal cavity.

A preliminary study has already indicated that parenteral injection of PEG 300 or 400 does not significantly affect the cardiovascular system (unpublished findings), although these two preparations markedly depress GMBF and secretory function of the stomach. The current findings suggest that PEG does indeed have an adverse action on the gastrointestinal tract, although it may be relatively non-toxic to other organs. It is unclear as to why PEG possesses the demonstrated actions. The possibility of such an interaction between PEG and alcohol consumption occurring in man cannot be excluded, although it may be argued that the doses of PEG and of ethanol used in the current experiments are relatively large. However, similar doses of these compounds are used quite frequently in animal studies and this might create potential problems in interpreting experimental results.

References

Cho, C. H., Ogle, C. W. (1990) Modulating action of adenosine on gastric function and ethanol-induced mucosal damage in rats. Dig. Dis. Sci. 35: 1334–1339

Cho, C. H., Chen, B. W., Hui, W. M., Lam, S. K. (1990) The influence of acute or chronic nicotine treatment on ethanol-induced gastric mucosal damage in rats. Ibid. 35: 106–112

de Ferreyra, E. C., de Toranzo, E. G., de Fenos, O. M., Castro, J. A. (1981) Studies on the mechanism of enhancement of CCl_4 hepatoxicity by Triton WR 1339. Br. J. Exp. Pathol. 62: 512–518

Herold, D. A., Rodeheaver, G. T., Bellamy, W. T., Fitton, L. A., Bruns, D. E., Edlich, R. F. (1982) Toxicity of topical polyethylene glycol. Toxicol. Appl. Pharmacol. 65: 329–335

Koo, M. W. L., Cho, C. H., Ogle, C. W. (1989) Does acidosis contribute to stress-induced ulceration in rat stomachs? Pharmacol. Biochem. Behav. 33: 563–566

Merck Index (1989) 11th Edition, Merck & Co., Inc., Rahway, p. 7542

Sheppard, A. P., Riedel, G. L. (1982) Continuous measurement of intestinal mucosal blood flow by laser-Doppler velocimetry. Am. J. Physiol. 242: G668–G672

Smyth, H. F., Carpenter, C. P., Weil, C. S. (1950) Toxicity of polyethylene glycols. J. Am. Pharm. Assoc. Sci. Ed. 39: 349–354

Szabo, S., Cho, C. H. (1988) Animal models for studying the role of eicosanoids in peptic ulcer disease. In: Hillier, K. (ed.) Advances in Eicosanoid Research: Eicosanoids and the Gastrointestinal Tract. MTR Press Limited, Lancaster, pp 75–102

Wong, S. H., Cho, C. H., Ogle, C. W. (1986) Protection by zinc sulphate against ethanol-induced ulceration: preservation of the gastric mucosal barrier. Pharmacology 33: 94–102

Wong, S. H., Cho, C. H., Ogle, C. W. (1987) The influence of omeprazole on the protective effects of secretagogues against ethanol-induced gastric ulceration in rats. Eur. J. Pharmacol. 141: 433–459

Wong, S. H., Cho, C. H., Ogle, C. W. (1991) Calcium and ethanol induced gastric mucosal damage in rats. Pharmacol. Res. 23: 71–79