

Pharmacological Activity of Propantheline Bromide mixed with Antacids in Guinea-pigs and Human

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The pharmacological effect of propantheline bromide (PB) mixed with dried aluminum hydroxide gel (DAHG) was investigated in guinea-pigs and human. In guinea-pigs, antimuscarinic effect was tested in their isolated ileums, and in human, salivary secretion was measured by Herxheimer. It was found that coadministration of PB together with DAHG resulted in a loss of potency of PB due to degradation, and thus the effects of powdered preparations of PB mixed with DAHG were merely those of antacids alone. But antimuscarinic agents kept away from antacids showed no change in their efficacy.

Keywords—propantheline bromide; dried aluminum hydroxide gel; antimuscarinic agents; antacids; isolated guinea-pig ileum; Magnus method; human saliva; degradation of propantheline bromide; pA_2 values

Coadministration of antimuscarinic agents together with antacids is often put into practice in peptic ulcer therapy. The purpose of this therapy is to neutralize the excessive hydrochloric acid in the gastric juice by antacids and raise the pH to about 4, and to depress the spontaneous gastric secretion by antimuscarinic agents, which in turn result in an inhibition of gastrointestinal motility and a relief of stomach pain and spasm.

Some patients with peptic ulcer have often received an antacid combined with an antimuscarinic agent for many years. The authors have a doubt about the efficacy of such combination of drugs, because Horioka, *et al.* found that an antimuscarinic agent with ester bonds such as propantheline bromide was rapidly degraded when mixed with an antacid.²⁾

This investigation was, therefore, undertaken to examine the effect of propantheline bromide when mixed with dried aluminum hydroxide gel in guinea-pigs and human.

Materials and Methods

Fifty mg of propantheline bromide (PB) and 4950 mg of dried aluminum hydroxide gel (DAHG) were accurately weighed and mixed well in a vibration mill for 2 minutes. This powdered preparation (Compound (I)) was transferred to a petridish and placed in a desiccator with a saturated sodium chloride solution to give 75% relative humidity at 37°. A part of the powders was taken out occasionally at given intervals.

Measurement of Antimuscarinic Effect in Isolated Guinea-pig Ileum—Male Hartly guinea-pigs weighing 250–400 g were killed by cervical dislocation, and the ileum was removed immediately. A ileum strip approx. 1.5 cm long was suspended in oxygenated Tyrode solution (NaCl 8.0 g; KCl 0.2 g; $MgCl_2 \cdot 6H_2O$ 0.21 g; $CaCl_2 \cdot 2H_2O$ 0.26 g; $NaH_2PO_4 \cdot 2H_2O$ 0.06 g; $NaHCO_3$ 1.0 g; Glucose 1.0 g/liter), maintained at 37°. The tone and movements of the isolated ileum were recorded on a smoked drum kymograph with an isotonic lever. All agents were dissolved in Tyrode solution.

Dose-response curves for acetylcholine chloride (ACh) were determined before and after administration of PB, atropine sulfate (Atr) and Compound(I). After control responses to increasing cumulative doses of ACh had been obtained, ACh was washed out by changing the bath fluid and the preparation was given 10 minutes for rest. Then PB, Atr, or Compound(I) was applied into the bath (exposure time 1 minute) and dose-response curves for ACh were again determined. Quantitative evaluation of antagonism against ACh

1) Location: *Maidashi 3-1-1, Higashi-ku, Fukuoka.*

2) a) M. Horioka, T. Aoyama, K. Takata, T. Maeda, and K. Shirahama, *Yakuzaigaku*, **34**, 16 (1974); b) E. Yumioka and S. Ohsako, The 13th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1950.

was performed by determinations of pA_2 values.³⁾ Compound(I) used in isolated ileum was extracted with water and diluted to a suitable concentration with Tyrode solution.

Effects on Salivary Secretion in Human—Ten healthy males and females were joined as subjects. In successive preliminary experiments, each subject took PB tablets in ascending doses until he experienced dryness of the mouth.⁴⁾ The minimum dose needed to produce this effect was used in subsequent experiments, it was 45 mg in five subjects and 60 mg in another five. Each subject received two treatment, (1) PB in capsule and 3 g DAHG + 200 ml water, (2) Compound(II) in the same dose of PB with 3 g DAHG + 200 ml water. The Compound(II) had been placed in the desiccator (75% RH and 37°) for 5 days.

Salivary secretion was measured every 30 minutes. The subject was given three drops of a 5% acetic acid solution on the tongue, and asked to suck saliva by himself for 1 minute without swallowing. The saliva was collected in a graduated tube while sucking continued. At the end of the 1 minute, the acid drops and all saliva were spat out into the funnel. The total volume of saliva was then measured in the graduated tube. The data were analyzed by Students' "t" test.

Results and Discussion

The effect of PB and Atr on cumulative dose-response curves for ACh were shown in Fig. 1. The ACh curves were shifted in parallel after administration of either PB or Atr. In proportion to the dose of PB or Atr, the shift becomes larger.

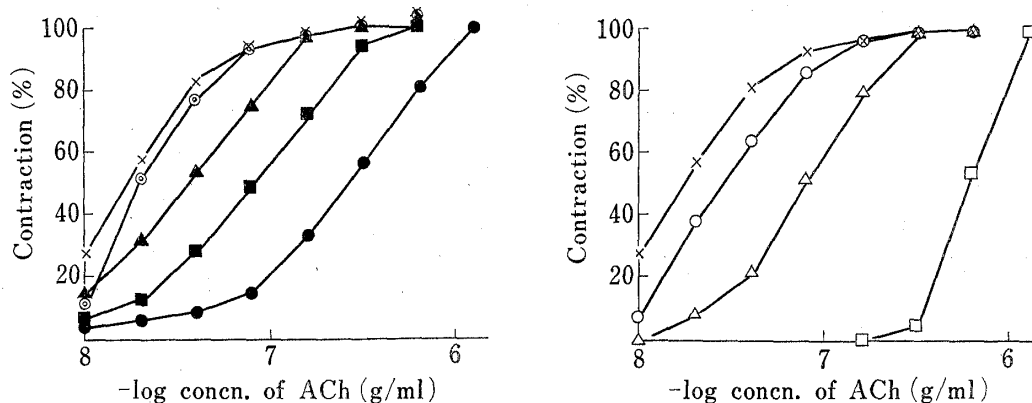


Fig. 1. Effect of Propantheline Bromide (the left) and Atropine Sulfate (the right) on Cumulative Dose-response Curves for Acetylcholine Chloride in Isolated Guinea-pig Ileum

Each mark represents the mean of 6 experiments. Final concentration (g/ml) of propantheline bromide were 0 (—x—), 2.0×10^{-10} (—○—), 7.5×10^{-10} (—▲—), 1.5×10^{-9} (—■—), and 3.0×10^{-9} (—●—). That of atropine sulfate were 2.0×10^{-10} (—○—), 2.0×10^{-9} (—△—), and 2.0×10^{-8} (—□—).

A shift (mm) from the curve for ACh to that of a concentration of the agent, was calculated and there is a direct relationship between the logarithms of the shift and the log concentration of agents, as shown in Fig. 2. Such a parallel shift is an indication of competitive antagonism,⁵⁾ but it was not clear that the direct relationship between the logarithms of the concentration of PB or Atr and that of ACh (Fig. 3).

The pA_2 values of PB and Atr for contraction are 8.57 and 8.63 respectively.⁶⁾ From these values, it was found that the antimuscarinic action of PB was about the same in potency as that of Atr, and PB acts as a competitive antagonist similarly to Atr.

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4) a) D.M. Chaput de Saintonge and A. Herxheimer, *Europ. J. Clin. Pharmacol.*, **4**, 52 (1971); b) A. Herxheimer and L. Haefeli, *Lancet*, **2**, 418 (1966); c) W. Jander, *Z. Anorg. Allgem. Chem.*, **163**, 1 (1927); d) J. Glynn and W. Bastain, *J. Pharm. Pharmacol.*, **25**, 420 (1973); e) G. Graham and M. Rowland, *J. Pharm. Sci.*, **61**, 1219 (1972).

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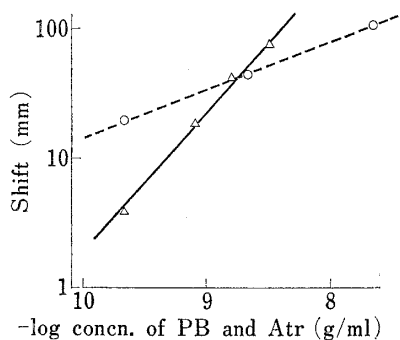


Fig. 2. The Relationship between the Concentration and the Shift

Propantheline bromide was (\triangle) and atropine sulfate (\circ). These indicated the competitive antagonism of both agents.

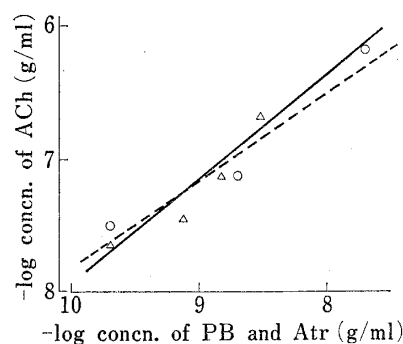


Fig. 3. The Relationship of 50% Concentration of Acetylcholine Chloride to One of Propantheline Bromide (Solid Line) or Atropine Sulfate (Dotted Line)

The doses are plotted on a log scale. The direct relationship was not clear.

The effect of Compound (I) on cumulative dose-response curves for ACh in isolated guinea-pig ileum was shown in Fig. 4. The shift was decreased as the storage time was increased. This indicated that the effect of Compound (I) was reduced with increased storage time.

Changes in pA_2 from each shift (mm) were obtained in Fig. 5. Calculated values of pA_2 were slowly decreased.

Figure 6 showed changes of the residue of PB in Compound (I) in relation with the storage time, under the condition of 37° , 75% relative humidity. Quantitative analysis of PB was carried out by Horioka's direct BCG method.⁷⁾ The residue was decreased rapidly to 13% on the next day after being mixed, and was reduced to 10% of initial PB amount on the fifth day. There were no appreciable changes from 4 to 60 days after storage. It was, therefore, suggested that the efficacy of PB was almost abolished in a few days after mixing with DAHG by degradation and/or adsorption.⁸⁾

It was also found that degraded products of PB had no effect in isolated guinea-pig ileum. In addition, it was also confirmed that neither degradation nor decreasing of PB did occur in Tyrode solution (pH 7.61) during the experimental period.

Salivary secretion in man after administration of Compound (II) and PB capsule + DAHG were shown in Fig. 7. At 2 or 3 hours after medication of PB capsule and DAHG simultaneously, obvious decrease of salivary secretion were obtained. The volume of secretion after 2 hours from medication had decreased significantly from the initial volume ($p < 0.01$). Duration time of action of PB (in capsule) was 2.3 ± 0.6 hours, if duration was defined as the time from decreasing of saliva secretion to increasing. But dryness of the mouth persisted to the end of the experiment.

It would take another 2 or 3 hours to recover normal secretion. Efficacy of PB may, therefore, continue for about 4 or 6 hours.

On the contrary, Compound (II) showed no significant decrease in salivary secretion, indicating that Compound (II) had already lost its efficacy by degradation and/or adsorption. It was also seen in Fig. 6.

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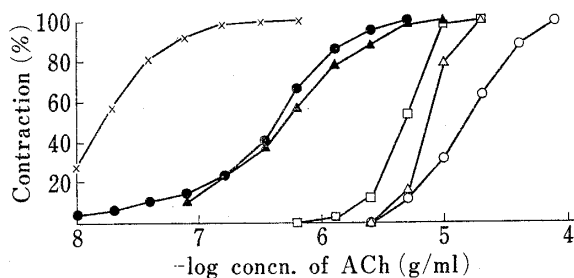


Fig. 4. Effect of Compound (I) on Cumulative Dose-response Curves for Acetylcholine Chloride in Isolated Guinea-pig Ileum

Final concentration of Compound (I) was 3×10^{-7} (g/ml) corresponding to propantheline bromide. The days of storage at 37° in 75% RH was as follows: 4 (—○—), 7 (—△—), 14 (—□—), 18 (—▲—), and 22 (—●—), and ACh was (—×—). Compound (I) was powdered preparation consisting of 50 mg of propantheline bromide and 4950 mg of dried aluminum hydroxide gel.

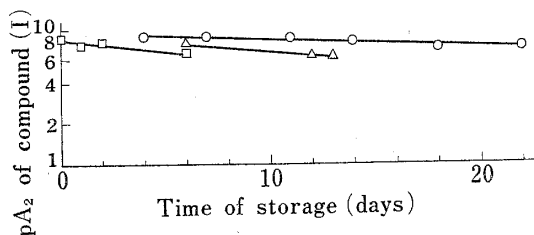


Fig. 5. pA_2 of Compound (I) after Storage at 37° in 75% RH

It seems steadily to decrease. The signs (—□—, —△—, —○—) in figure were the lot symbols. There are a direct relationship on (—□—) and (—○—) between the logarithms of the pA_2 and time of storage ($p < 0.05$).

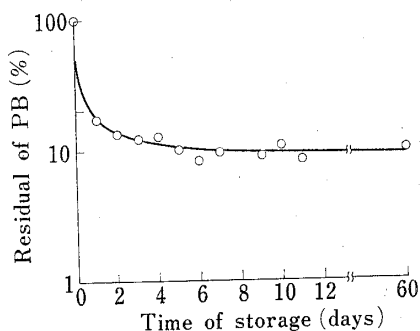


Fig. 6. The Residual of Propantheline Bromide in Compound (I) after Storage at 37° in 75% RH

It was analyzed by the direct BCG method. Residue, plotted on a log scale, was sustained about 10% from the 4th day throughout the experiments.

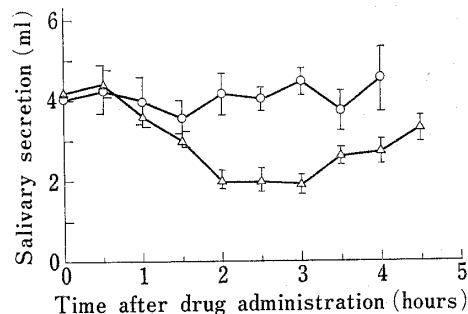


Fig. 7. Salivary Secretion after the Oral Administration of Compound (II) (—○—) and Propantheline Bromide Capsule with Dried Aluminum Hydroxide Gel (—△—) to Volunteers

That shows significant difference from each other ($p < 0.001$). Each mark represents the mean \pm S.E. of 9 to 10 subjects. Compound (II) had been stored for 5 days at 37° in 75% RH before use.

A significant decrease ($p < 0.01$) in saliva secretion was found at the period from 2 to 3 hours after administration of drugs in the PB capsule group as compared with that in the Compound (II) group.

This indicates that the potential of PB in Compound (II) had been decreased completely. But, when PB was kept away from DAHG, PB showed its potency. So, antimuscarinic agents kept away from antacids or preparations consisting of separate granules should have their efficacy.