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Comparative scintigraphic assessment of the intragastric distribution and residence of cholestyramine, Carbopol 934P and sucralfate

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Abstract

It has been demonstrated that orally administered cholestyramine is distributed throughout the stomach and provides prolonged gastric residence via mucoadhesion. Gamma scintigraphy was used to compare the gastric emptying and residence of this resin with two formulations known to exhibit retentive or bioadhesive properties, Carbopol 934P and sucralfate. Fasted normal subjects received a single radiolabelled dose and gastrointestinal transit was monitored for 6 h. The subjects were fed after 4 h to determine the effects of inducing a fed pattern of motility on the retention of the formulations. Initial gastric emptying was similar (Mean $T_{50} \pm$ S.E.M.: cholestyramine = 66.93 ± 9.39 min; Carbopol = 56.57 ± 11.96 min; sucralfate = 48.33 ± 11.07 min; $P = 0.548$: $n = 10$), however, the emptying of cholestyramine slowed beyond 2 h. This resulted in greater residence for cholestyramine (Mean $AUC_{0-6} \pm$ S.E.M. (relative units) = 11516 ± 686 versus 7657 ± 1170 versus 6170 ± 998; cholestyramine versus Carbopol versus sucralfate; $P = 0.004$: $n = 10$), with approximately 25% remaining in the stomach at 6 h compared to 3.84 and 2.65% of Carbopol and sucralfate, respectively. Cholestyramine was also distributed widely throughout the stomach whereas Carbopol and sucralfate were concentrated in the body and antrum. Thus, as cholestyramine had a comparable emptying time to Carbopol and sucralfate but greater gastric residence and wider distribution, it could provide a potential mucoadhesive drug delivery system targeting the gastric mucosa for treatment of conditions such as *Helicobacter pylori* infection.

Keywords: Cholestyramine; Ion exchange resin; Gastric residence; Carbopol 934P; Sucralfate; Gamma scintigraphy

1. Introduction

Previous publications have suggested that the anionic exchange resin, cholestyramine, has the ability to coat the gastric mucosa evenly and provide extended gastric residence (Burton et al., 1995; Thairs et al., 1998). Recent studies by this

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group have suggested that cholestyramine exhibits these properties through its action as a mucoadhesive (Jackson, 1999; Jackson and Perkins, 2000). Although the mechanism is unclear, it is strongly suggested that cholestyramine forms an intimate contact with the gastric mucosa via electrostatic forces. In vitro investigations found that the mucoadherent behaviour was displayed by other anionic exchangers but not cationic exchangers (Jackson and Perkins, 2000), whilst in vivo studies concluded that the gastric retention seen with cholestyramine was not replicated by the cationic exchange resin, Amberlite® IRP-69, and that masking the surface charge of the cholestyramine reduced this gastric retention (Jackson et al., 2000). In vivo investigations have also found that the extended gastric residence of the cholestyramine is independent of resin particle size, administration volume and subsequent feeding (Jackson, 1999).

Drugs may easily be incorporated into ion exchange resins, and released by the influx of competing ions (Borodkin, 1991) providing controlled, sustained or site-specific delivery of drugs (Irwin et al., 1990; Moldenhauer and Nairn, 1990; Mohamed, 1996). As an anionic exchanger, potentially any drug of anionic species, such as theophylline and sodium diclofenac, could be incorporated into cholestyramine. Sodium diclofenac, for example, has been successfully adsorbed onto and released from cholestyramine (Sriwongjanya and Bodmeier, 1998). Other investigations have also used a variety of drugs with cholestyramine (Ko and Royer, 1974; Irwin et al., 1990). With the additional mucoadherent properties, cholestyramine could provide a site-specific drug delivery system targeting the gastric mucosa. This would enhance, for example, the topical delivery of antibiotics, such as tetracycline, to sites of *Helicobacter pylori* colonisation, such as the fundus, that conventional dosage forms fail to reach.

Carbopol, a poly(acrylic) acid derivative employed in the pharmaceutical industry as a bioadhesive and gelling agent, has been used in many in vitro investigations into bio/mucoadhesion (Tobyn et al., 1995; Chary et al., 1999; Wong et al., 1999), whilst in vivo studies have explored the potential of Carbopol as a platform for nasal drug delivery (Witschi and Mrsny, 1999), ocular drug delivery (Durrani et al., 1995) and buccal retention (Ali et al., 1998). Carbopol has also been utilised in drug delivery to the gastrointestinal tract (Akiyama et al., 1995; Chary et al., 1999).

Sucralfate is another agent with adherent gastroretentive properties that has been investigated as a potential carrier for drugs (Li et al., 1993; Yokel et al., 1995). Sucralfate is an aluminium salt of sucrose octasulphate and is used as a cytoprotective barrier in cases of gastric lesions and ulceration. The radiolabelling of sucralfate with either technetium-99m diethylenetriaminepentaacetic acid (DTPA) or technetium-99m human serum albumin (HSA) and its use in imaging studies is well-documented (Hardy et al., 1993; Vaira et al., 1993). The technique has also been used to detect and evaluate gastric ulcers and lesions (Puttemans et al., 1987; Ugolotti et al., 1998).

In vitro evaluation of the mucoadhesion of cholestyramine to isolated porcine and human gastric mucosa found that the resin performed well when compared to both Carbopol and sucralfate (Jackson and Perkins, 2000). Cholestyramine produced a good degree of mucoadhesion second only to Carbopol (Jackson and Perkins, 2000). The present in vivo study was undertaken to compare the gastric retentive behaviour of cholestyramine to that of Carbopol and sucralfate, and to determine the intragastric distribution of the formulations. It was hypothesised that cholestyramine would provide comparable retentive properties but exhibit a more dispersed distribution in the stomach.

2. Materials and methods

2.1. Preparation of test materials

Cholestyramine (Duolite® AP-143, Rohm and Haas, France SA, particle size 90–125 μm) was regenerated and made suitable for human ingestion as documented in previous studies (Jackson, 1999; Jackson et al., 2000).

The Carbopol 934P powder (BF Goodrich, UK) was made up according to manufacturer's instructions to a 0.5% w/v ratio. The required volume of water was agitated to create a vortex. The powder was sifted slowly over the vortex and the mixture

agitated constantly for 15 min or until the particles had become hydrated, swollen and formed a clear gel. The speed of the agitation was then reduced to prevent foaming. The Carbopol gel was neutralised to promote thickening. This was done by the drop-wise addition of NaOH. The pH was raised to approximately 4.5. This gave a gel of acceptable viscosity and clarity, which could be easily swallowed.

The sucralfate suspension (Antepsin® suspension, Wyeth Labs., Berks., UK) was used as provided, with no additional preparation.

2.2. Radiolabelling of test materials

All radioisotopes were provided by the Radiopharmacy Unit, Department of Medical Physics, Queen's Medical Centre, Nottingham.

Technetium-99m sodium pertechnetate (^{99m}Tc) was added to the cholestyramine so that each 25 mg dose was radiolabelled with 3 MBq at 21:00 h on the morning of each study day. After 5 min, 20 ml water was added to rinse any unbound activity from the resin, and as much water as possible decanted from the solid. The radiolabelled resin was then dried thoroughly back to a dry weight powder, whilst stirring in a direct flow of warm air using a dryer.

The choice of radiolabel for Carbopol was dependent on the outcome of the in vitro stability studies carried out prior to the in vivo study. Each 5 ml dose was radiolabelled by the addition of either 3 MBq ^{99m}Tc tin colloid, 3 MBq ^{99m}Tc DTPA or 1 MBq ^{111}Indium (^{111}In) DTPA, stirred and left to stand for 10 minutes to associate with the gel. Addition of the radiolabel in some instances caused a loss in the viscosity of the gel. If this occurred, the pH was again raised by the addition of NaOH.

Each 5 ml dose of sucralfate was radiolabelled by the simple addition of 3 MBq ^{99m}Tc DTPA. The radiolabelled dose was then stirred and left for 10 min to allow the radiolabel to associate with the sucralfate.

2.3. Stability testing of test materials

The stability of the radiolabel bound to the test materials was investigated over a 6-h period in acid conditions to simulate the exposure to gastric juice during the in vivo study.

Samples of the radiolabelled resin (25 mg) were added to 25 ml volumes of water, 0.03 M hydrochloric acid (HCl), or simulated gastric juice (1 l of 0.03 M HCl with the addition of 24 mg pepsin (Sigma, Dorset, UK)). The samples were incubated at 37°C and constantly agitated for 6 h. Samples were taken at 2-h intervals and filtered to obtain resin and solution fractions. The masses of the fractions were calculated and the activity in each sample recorded using the gamma camera. The percentage of radiolabel bound to the resin over 6 h was then deduced.

For the liquid preparations of sucralfate and Carbopol, 5 ml samples of the radiolabelled material were placed in visking tubing bags. These were weighed and assayed to determine 100% activity, then placed in the various dissolution media as above. Again, samples were taken at 2-h intervals from the surrounding media, weighed and the activity counted. The amount of radiolabel bound was then calculated as a percentage of the original material.

2.4. Ethical considerations and subject selection

Approval for the study was obtained from the University of Nottingham Medical School Ethics Committee and the Administration of Radioactive Substances Advisory Committee of the Department of Health.

Ten healthy male and non-pregnant female subjects (two males, eight females; age range 27–56 years, average BMI 24) were recruited from the student and staff population of the University Hospital, Queen's Medical Centre, Nottingham. All subjects were screened by medical questionnaire. Exclusion criteria included excessive tobacco and alcohol consumption, history of gastrointestinal disorders and consumption of medication considered to influence the study outcome. All subjects were given written and verbal information, and written informed consent was obtained prior to the study. All female subjects were pregnancy tested on the morning of each study day.

2.5. Study day procedure

This study was designed as a 3-way randomised crossover study. Crossover days took place 7 days apart to allow for radioactive decay and biological clearance of each formulation.

Subjects were fasted from 21:00 h of the evening prior to the study. A single glass of water was allowed on waking in the morning to prevent dehydration. On the morning of each study day, anatomical markers were prepared from filter paper radiolabelled with 0.05 MBq ^{99m}Tc and sealed in waterproof tape. These were attached, one anterior and one posterior, to the abdomen of each subject, in line with the top of the stomach and were used as points of reference to aid in data analysis. The subjects were then given either 25 mg radiolabelled cholestyramine as a 1 ml suspension in water, 5 ml radiolabelled Carbopol or 5 ml radiolabelled sucralfate. A 1 ml suspension of cholestyramine was chosen on the basis of the increased gastric retention and distribution seen in previous studies (Jackson, 1999; Jackson et al., 2000), similarly with the 5 ml volume of sucralfate (Hardy et al., 1993; Vaira et al., 1993). Five ml of Carbopol was chosen to be of comparable volume to sucralfate.

Immediately after dosing, anterior and posterior static scintigraphic images of 30-s duration were taken every 25 min. This was repeated for a total of 6 h. The images were acquired using a Scintronix Model GRC1 gamma camera, located within the Department of Surgery, with a 48 cm diameter hexagonal field of view and a high-resolution general-purpose collimator. The images were stored on a Sun Sparc 4 workstation running Smart Soft applications (Park Medical, Farnborough, UK).

Subjects were fed a standard test meal of a ham or cheese filled roll, a packet of crisps, a chocolate biscuit and a can of cola, 4 h after the dose was administered. Eating and drinking were restricted at all other times during the study day.

2.6. Data analysis

The anterior and posterior images for each individual subject were analysed by creating a template of regions of interest (ROIs) around the whole stomach, the fundus, the body, the antrum and an area for background radiation. This allowed the comparison of regions between the formulations. The number of counts and pixels within each ROI, displayed by the computer, were transferred to a spreadsheet, via an ethernet link to an Apple Macintosh computer running Microsoft Excel 5.

The counts from each region of interest were corrected for background radiation and radioactive decay. The geometric mean for the anterior and posterior images was then calculated to give the overall activity in the stomach, taking into account the position of the stomach in the body. The data from each individual were then interpolated to produce mean graphs and to calculate the standard errors of the mean. The area under the time-activity curve (AUC_{0-6}) was calculated to represent the total residence time within the whole stomach between 0 and 6 h. The time taken for 50% of the activity to empty (T_{50}) from the whole stomach was also calculated. The AUC_{0-6} for each region was calculated per pixel to take into account ROI size variations and this was used to compare distribution throughout the stomach.

As the data was normally distributed (determined using Minitab® for Windows Release 10.1 statistical package, Minitab), one way analysis of variance (ANOVA) and 2 sample *T*-tests were carried out to determine any statistical significant difference between the groups.

3. Results

3.1. In vitro validation of the stability of the radiolabel

Over 98% of the ^{99m}Tc pertechnetate label was still bound to the cholestyramine after 6 h, when placed under simulated stomach acid conditions (Table 1). Incubation at pH 1.5 with either HCl or simulated gastric juice resulted in the loss of less than 2% of the radiolabel.

The stability of the ^{99m}Tc DTPA label with sucralfate was slightly lower at just over 90% in simulated gastric juice and over 95% in 0.03 M HCl.

Table 1 also shows the percentage of radiolabel associated with Carbopol. Just under 50% of the ^{111}In DTPA label was lost from the Carbopol under acid conditions after 6 h, whilst more than 60% of the ^{99m}Tc DTPA was lost. Radiolabelling Carbopol with ^{99m}Tc tin colloid, however, demonstrated over 90% stability under these conditions. ^{99m}Tc tin colloid was subsequently used in the radiolabelling of Carbopol for the in vivo studies.

The stability of the chosen radiolabels, over a 6-h period, was therefore considered suitable for the in vivo measurement of gastric emptying in healthy subjects.

3.2. In vivo results

Although some subjects commented on the unpleasant gritty texture of the cholestyramine on swallowing, the radiolabelled formulations were well tolerated and no adverse events were reported. Oesophageal transit was observed during the acquisition of the first image in some subjects, although this was not quantified.

The mean gastric emptying curves for cholestyramine, Carbopol and sucralfate are shown in Fig. 1. Although the cholestyramine was found to empty slightly slower than the sucralfate and Carbopol (Table 2), statistically, there was no significant difference ($P = 0.548$).

The oesophageal transit of the Carbopol and sucralfate suspensions appeared to be rapid, with between 98 and 100% available in the stomach at the start of the 6-h period respectively. Gastric filling, following ingestion of cholestyramine, took place over 30 min with a maximum of only 80% activity being in the stomach at any time.

As is evident in Fig. 1, there was a subsequent rise in the gastric counts with cholestyramine, seen after ingestion of the test meal, from 17.69% at 4 h to 25.64% at 6 h. No rise in gastric counts was observed with either the Carbopol or sucralfate suspensions and only 3.84 and 2.65% respectively was still remaining in the stomach at 6 h. The rise in gastric counts seen with cholestyramine but not Carbopol or sucralfate was thought to be due to the clearance of trapped resin from the mouth and oesophagus. Periodic scans of the oropharynx showed hotspots of activity, indicating trapped resin, which disappeared after eating.

The retention and rise in gastric counts for cholestyramine lead to a significant difference in the overall gastric retention for the three formulations ($P = 0.004$) (Table 2). Cholestyramine was retained significantly longer in the stomach than either Carbopol or sucralfate ($P = 0.021$; $P = 0.0011$, respectively). There was no difference in the gastric retention between Carbopol and sucralfate ($P = 0.39$).

The initial distribution of the formulations throughout the stomach was quite varied (Fig. 2). A significant difference was found between the amounts of the formulations in the fundus ($P = 0.0001$) and body ($P = 0.012$) but not in the antrum ($P = 0.705$). Significantly more cholestyramine was found in the fundus than sucralfate ($P = 0.0001$) or Carbopol ($P = 0.011$) but there was no difference between the amounts of sucralfate and Carbopol found ($P = 0.094$). Again, significantly more cholestyramine was found in the body of the stomach than sucralfate ($P = 0.0018$) but not Carbopol however ($P = 0.24$). No significant difference was found between sucralfate and Carbopol in the body of the stomach ($P = 0.089$). Finally,

Table 1
Percentage of radiolabel bound to test materials after 6 h in various dissolution media

Dissolution media	% Radioisotope bound at 6 h				
	Cholestyramine + ^{99m}Tc pertechnetate	Sucralfate + ^{99m}Tc DTPA	Carbopol		
			^{99m}Tc tin colloid	^{99m}Tc DTPA	^{111}In DTPA
Distilled water (pH 4.74)	99.42	98.07	98.68	78.38	67.12
0.03 M HCl (pH 1.5)	99.39	95.33	90.10	36.32	50.43
Simulated gastric juice (pH 1.5)	98.39	90.15	90.53	62.46	57.92

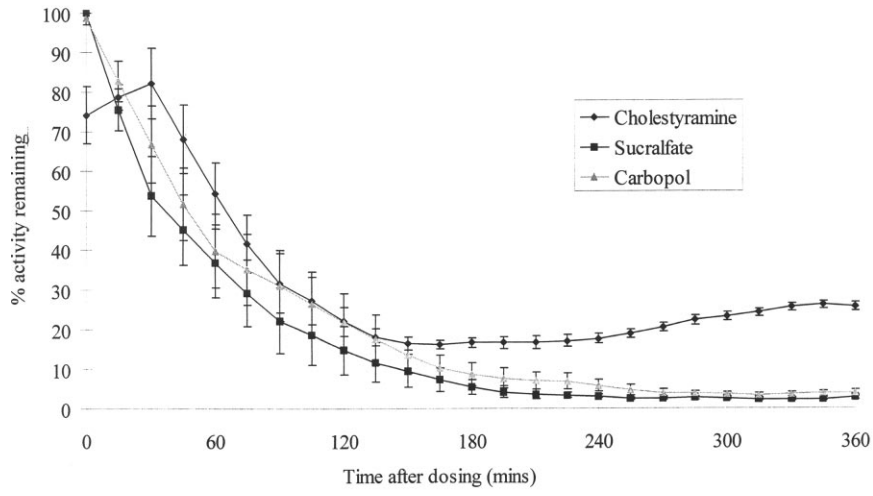

Fig. 1. Mean gastric emptying curves for cholestyramine, Carbopol and sucralfate ($n = 10$: mean ± S.E.M.).

there was no difference between the three formulations in the antrum (T-test, $P > 0.05$).

4. Discussion

Cholestyramine has previously been shown to exhibit prolonged gastric retention and uniform coating of the stomach (Burton et al., 1995; Thairs et al., 1998). More recent in vitro investigations have shown that this retentive behaviour is due to the mucoadhesion of the resin to the gastric mucus (Jackson, 1999) and that the surface charge of the resin contributes to this adhesion (Jackson and Perkins, 2000). The mucoadhesion of cholestyramine to gastric mucus via an electrostatic attraction has resulted in extended gastric residence of the resin whilst being distributed throughout the stomach (Jackson et al., 2000).

Whilst the radiolabelling of sucralfate with ^{99m}Tc for studies of this nature is well established and documented, the radiolabelling of Carbopol is not. Different studies have adopted different methods for radiolabelling to suit their purpose. For example, Durrani and co-workers used ^{111}In labelled Carbopol microspheres to investigate ocular disposition (Durrani et al., 1995), whilst Harris et al. added ^{99m}Tc labelled Amberlite® resin to Carbopol for gastrointestinal scintigraphy (Harris et al., 1990). As there was no standard procedure for the radiolabelling of Carbopol, stability testing on some of the common radiolabels used in studies of this type was performed to determine which method was most suitable. From these stability tests, ^{99m}Tc tin colloid was found to be a suitable label because as a colloid it bound well within the structure of the Carbopol. It was therefore concluded that this was a suitable method for the radiolabelling of Carbopol to be used in gastric emptying studies.

When compared to Carbopol and sucralfate, under in vivo conditions, cholestyramine performed well. Initial gastric emptying of the three formulations was not found to be significantly different although cholestyramine did empty more slowly than Carbopol or sucralfate. Carbopol and sucralfate had virtually emptied from the stomach within 4 h, while the overall gastric residence of cholestyramine was significantly longer with 25% of

Table 2
T_{50} and AUC_{0-6} values (mean ± S.E.M.) for cholestyramine, Carbopol and sucralfate

Formulation	T_{50}	AUC_{0-6}
Cholestyramine	66.93 ± 9.39	11 516 ± 686
Carbopol	56.57 ± 11.96	7657 ± 1170
Sucralfate	48.33 ± 11.07	6170 ± 998
P-value	0.548	0.004

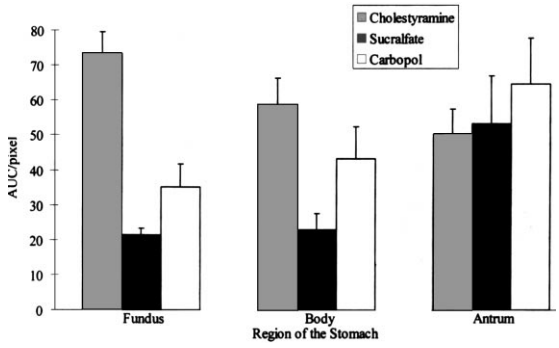

Fig. 2. Distribution of cholestyramine, Carbopol and sucralfate throughout the regions of the stomach ($n = 10$: mean $\pm$ S.E.M).

the activity still remaining at 6 h. More cholestyramine was also distributed throughout the fundus than Carbopol and sucralfate.

Although the overall gastric emptying of 50% of cholestyramine may not have been significantly delayed in comparison to sucralfate and Carbopol, the mode of gastric emptying was different. There appeared to be two phases to the gastric emptying of cholestyramine. The initial linear phase, in which approximately 70–80% of the resin emptied over 2 h, could represent the water phase of the suspension. This mode was similar to the gastric emptying of a water-wash administered in a previous study, although the emptying of the water-wash was almost complete within 90 min ($T_{50} \pm$ S.E.M. = 31.01 $\pm$ 3.58 min; Jackson, 1999). The linear phase was then followed by a lag phase, in which the gastric emptying of the remaining 20–30% was retarded. This may be as a result of the resin adhering to the mucus. These results indicate that there was a separation of particles from the water in which they were suspended, the water phase containing some suspended resin emptied quickly while the resin particles in contact with the gastric mucosa remained.

Carbopol and sucralfate did not perform as well as expected despite being established bioadhesive or gastro-retentive agents. The time taken for 50% of the Carbopol to empty was less than an hour, which was similar to the results presented by a separate group in a previous study (Harris et al., 1990). The reason Carbopol emptied so quickly could be due to the loss of viscosity encountered when Carbopol was acidified. From the manufacturer's instructions, maximum thickening occurs between pH 5 and pH 10. In the fasted stomach, the pH would have been considerably lower due to gastric acid secretions, between pH 1 and pH 2. The Carbopol at this pH would have lost viscosity and emptied as a liquid. Sucralfate gel has been shown to empty more slowly from the stomach than sucralfate suspension, with mean T_{50} values ranging from 61 to 72 and 33 to 66 min, respectively (Hardy et al., 1993; Vaira et al., 1993) and with sucralfate still evident in the stomach at 5 h (Hardy et al., 1993). The present study showed sucralfate suspension to have a T_{50} value of approximately 48 min, which concurred with the previous studies. Sucralfate, although thought to coat the stomach and exhibit gastro-retentive properties, has little interaction with normal mucosa but has been shown to have a greater affinity for and preferentially bind to damaged and inflamed mucosa associated with ulceration (Vasquez et al., 1987; Vaira et al., 1993). As healthy subjects, assumed to have normal gastric mucosa, were used in this study, the sucralfate would have adhered only to a minimal extent. This could explain the poor performance seen herein.

Once the cholestyramine had adhered to the gastric mucus, it would seem that the only limiting factor would be mucus turnover. The adherent resin did not appear to be dislodged by the normal contractions of the fasted or fed stomach, with approximately 25% of the particles still remaining within the stomach at 6 h compared to only 2.65% sucralfate and 3.84% Carbopol. Dur-ing the 4 h prior to ingestion of a standard meal, the stomach would have been in a fasted pattern of motility and as such at least one cycle of the migrating motor complex (MMC) must have been encountered since these occur approximately every 2 h. Constant washing from food, drink and gastric secretions also failed to dislodge the resin. The adherent resin could therefore be responsible for the overall prolonged gastric residence.

In conclusion, cholestyramine was found to have a comparable emptying time to Carbopol and sucralfate but exhibited greater overall gastric residence and was distributed throughout the stomach. This could therefore provide a potential

mucoadhesive drug delivery system for targeting the gastric mucosa; one that is capable of withstanding gastric motility and providing distribution throughout the stomach, in particular to the fundus. This could be of potential use in the topical treatment of conditions such as *H. pylori* infection.

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