Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 299 (2005) 65–72
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Comparative study and optimisation of the administration mode of three proton pump inhibitors by nasogastric tube

D. Messaouik [a], V. Sautou-Miranda [a,b,*], S. Bagel-Boithias [a], J. Chopineau [a,b]

[a] *Service Pharmacie, Hôpital G. Montpied, Rue Montalembert, BP69, 63003 Clermont-Ferrand, France*
[b] *Laboratoire de Pharmacie Clinique et Biotechnique, UFR Pharmacie, Place Henri Dunant, BP38, 63001 Clermont-Ferrand, France*

Received 22 November 2004; received in revised form 23 April 2005; accepted 23 April 2005

Abstract

Patients in intensive care often develop stress-induced ulcers. As a preventive measure, proton pump inhibitors (PPIs) are administered by nasogastric tube. However, some PPIs can block the tube. The aim of this study was to compare the behaviour of three PPIs (omeprazole, lanzoprazole and esomeprazole) during the transit of the granules through the tube and to optimise their modes of administration. For each IPP, the experiment was designed to study the influence of four variables: the tube material (silicone or polyurethane), the solvent used to dilute the granules (water or apple juice), the mode of administration (in two or three doses) and the rinse volume (10 or 20 ml). We counted the granules before transit and at the tube outlet, and assayed the active drug ingredient by UV spectrometry. The assay showed complete transit of esomeprazole through the tube, but average losses of omeprazole and lanzoprazole of 39 and 33%, respectively, were observed. No significant improvement was obtained by the variables 'diluent' and 'mode of administration'. The variable 'rinse' had a significant influence. For lanzoprazole, a polyurethane tube allowed recovery of on average 86% of the active ingredient. Esomeprazole is thus the choice PPI for the treatment of patients by nasogastric tube. Using a polyurethane tube and a rinse volume of 20 ml, the administration of lanzoprazole by tube can be considered. Use of omeprazole is not recommended because none of the modes of administration tested ensured that a sufficient concentration of active ingredient reached the stomach.

Keywords: Omeprazole; Lansoprazole; Esomeprazole; Nasogastric tube; Granule

1. Introduction

Stress-induced gastrointestinal tract bleeding (SGIB) is common in intensive care patients. In such patients, the preventive use of proton pump inhibitors (PPIs) decreases the occurrence of stress-induced ulcers, and reduces the associated mortality. The PPIs, which are sensitive to gastric acid, are formulated to resist breakdown in the stomach and favour intestinal absorption. In general, pharmaceutical suppliers advise against chewing or crushing solid drug forms. However, most patients in intensive care are unable to

* Corresponding author. Tel.: +33 4 73 75 17 63; fax: +33 4 73 75 17 57.
E-mail address: vmiranda@chu-clermontferrand.fr (V. Sautou-Miranda).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.04.034

swallow. For this reason, PPIs have to be administered by gastric tube after dissolution of tablets or dispersion of granules in water, or in some other solvent, such as fruit juice or sodium bicarbonate solution. PPI formulations supplied in gelatine capsules or in tablets containing stomach acid resistant granules may obstruct tubes.

A number of studies have already been conducted on the administration of omeprazole (Dunn et al., 1999; Larson et al., 1996; McAndrews and Eastham, 1999; Sharma et al., 2000), lansoprazole (Chun et al., 1996; Doan et al., 2001; Dunn et al., 1999; Freston et al., 2001; McAndrews and Eastham, 1999; Sharma et al., 2000) and esomeprazole (Sostek et al., 2003; White et al., 2002) through nasogastric tubes, but none of them sought to evaluate the impact of the different variables involved in the administration of these PPIs (tube material, dilution solvent, administration pattern, rinse volume, etc.). In addition, much published work has been carried out in conditions that are not always applicable in clinical practice. Also, the administration of these three PPIs through nasogastric tubes has never been compared in the same experimental conditions.

We thus set out first to compare the behaviour of these three PPIs when administered through nasogastric tubes in experimental conditions as close as possible to clinical practice. Second, we evaluated the influence of different variables on this behaviour, in order to optimise the mode of administration.

2. Materials and methods

2.1. Drugs and medical materials

Omeprazole (Mopral®) and esomeprazole (Inexium®) were supplied by AstraZeneca and lansoprazole (Ogast®) by Takeda. The omeprazole and lansoprazole were formulated in gelatine capsules containing gastroresistant granules. The esomeprazole was formulated in tablets of gastroresistant granules. The granules were dispersed in apple juice or natural mineral water, and injected into the nasogastric tube using a 60 ml blunt cannula syringe (Becton Dickinson).

Two types of 16 French gauge gastroduodenal tubes were used: polyurethane tubes (Salem type, length 120 cm, internal diameter 3.8 mm, Rüsch-Pilling) and silicone tubes (Levin type, length 125 cm, internal diameter 3 mm, Vygon).

The solvents and tubes used in our experiments were chosen to correspond as closely as possible to those commonly used in intensive care for the administration of medication by nasogastric tube. Apple juice is used less often than water, but much published work (Freston et al., 2001; Chun et al., 1996; Phillips et al., 1996; Tsai et al., 2000) has made use of it for studying the bioequivalence or efficacy of PPIs administered by nasogastric tube.

2.2. Study design

We administered the PPI granules through the nasogastric tube positioned, as it would be in a reclining patient. For each PPI a study plan was drawn up to assess the influence of four variables: the 16 French gauge tube material (silicone or polyurethane), the nature of the solvent (water or apple juice), the rinse volume (10 or 20 ml) and the administration pattern ($1\times$ 30 ml or $3\times$ 10 ml). We thus carried out 16 separate experiments (Table 1), each repeated three times.

Before each administration, the tubes were rinsed with the solvent chosen to carry the granules. The granules were then dispersed in the solvent (water or apple juice): for omeprazole and lansoprazole, the contents of each capsule were dispersed in the solvent using a beaker, and the resulting mixture was drawn through a syringe (60 ml blunt cannula syringe); for esomeprazole, the capsule contents were placed in the syringe, the solvent was drawn in, and dispersion was performed by shaking the syringe. After dispersion in the solvent, the granules were injected into the tube. The syringe containing the mixture was always shaken during the administration to prevent granules adhering to the syringe wall. In addition, we maintained a constant injection flow rate to limit tube obstruction. The granules were then recovered in a beaker placed under the end of the tube.

2.3. Analysis of samples

The granules collected were analysed to determine whether PPI was lost during transit through the tube. Granules were counted and the active ingredient was assayed. In addition, the granules were examined and measured under a microscope to evaluate their dimensional homogeneity.

Table 1
Experiments performed to compare the impact of material-related and administration pattern-related parameters on PPI transit through nasogastric tubes

Experiment number[a]	Tube material	Solvent	Administration pattern (ml)	Rinse volume (ml)
1	Silicone	Water	1× 30	10
2	Polyurethane	Water	1× 30	10
3	Silicone	Apple juice	1× 30	10
4	Polyurethane	Apple juice	1× 30	10
5	Silicone	Water	3× 10	10
6	Polyurethane	Water	3× 10	10
7	Silicone	Apple juice	3× 10	10
8	Polyurethane	Apple juice	3× 10	10
9	Silicone	Water	1× 30	20
10	Polyurethane	Water	1× 30	20
11	Silicone	Apple juice	1× 30	20
12	Polyurethane	Apple juice	1× 30	20
13	Silicone	Water	3× 10	20
14	Polyurethane	Water	3× 10	20
15	Silicone	Apple juice	3× 10	20
16	Polyurethane	Apple juice	3× 10	20

[a] For each experiment, three assays were done.

2.3.1. Assay of active ingredient

The suspension of granules collected at the tube exit was filtered on a 0.125 mm screen to recover the granules. These were then dissolved in a mixture of 3.813 g/l sodium tetraborate and 95° ethanol (80/20, v/v) for omeprazole and esomeprazole, and pure methanol for lansoprazole. After complete dissolution by sonication, the suspensions of omeprazole, esomeprazole and lansoprazole were filtered a second time and centrifuged at 4500–5000 rpm. The clear solutions obtained were then diluted 10-fold and assayed by UV spectrophotometry (VIS JASCO V 530 spectrophotometer) at 303 nm for omeprazole, 307 nm for esomeprazole and 285 nm for lansoprazole.

We determined the percentage of active ingredient recovered at the tube exit relative to the initial dose injected into the tube. These initial doses were 40 mg of omeprazole and esomeprazole and 30 mg of lansoprazole.

2.3.2. Counting of granules

In addition to the assay, the granules of omeprazole and lansoprazole were counted before and after transit through the tube. We did not count the granules of esomeprazole, because these could not be visualised before the dissolution of the tablet of Inexium® in the selected solvent, and because each tablet of Inexium® contains at least 1300 granules, making visual counting very difficult.

2.3.3. Measurement of granule size

We measured the mean length of 10 granules of omeprazole, lansoprazole and esomeprazole using an optical microscope (DAS Mikroskop Leica DM LB) fitted with a precision scale (0.01 mm).

2.4. Statistical analysis

The statistical analysis of the results was carried out using Excel software from one-way ANOVA tests. We studied the impact of each of the “tube”, “solvent”, “rinsing” and “administration pattern” parameters on the transit of each PPI through the tube. An ANOVA was performed to compare two groups of 24 values without setting subgroups to match to the other parameters. For each test, the two groups compared were homogenous.

3. Results

3.1. Overall results

In 48 tube administrations of granules of esomeprazole no case of obstruction was observed. By contrast,

Table 2
Comparison of the behaviour of the three PPIs administered by nasogastric tube

	Esomeprazole ($n = 48$)	Lansoprazole ($n = 48$)	Omeprazole ($n = 48$)
Recovered active ingredient (%)	$100.9 \pm 2.6^{*,\$}$	67.2 ± 39.4	60.8 ± 33.4
Recovered granules (%)		67.1 ± 41.3	63.0 ± 35.4

* $p < 10^{-7}$ compared with lansoprazole.
$ $p < 10^{-11}$ compared with omeprazole.

Table 3
Mean size (mm) of PPI granules

	Esomeprazole ($n = 10$)	Lansoprazole ($n = 10$)	Omeprazole ($n = 10$)
Size (mm)	0.6 ± 0.04	1.1 ± 0.19	1.9 ± 0.63
Coefficient of variation (%)	6	17	33

with omeprazole and lansoprazole about 20 cases of tube obstruction were observed out of the 48 tested (42%).

The assay of the active ingredient showed a recovery rate for esomeprazole of 100.9% with very slight variations between runs (<5%). For lansoprazole and omeprazole, respective average losses of 33 and 39% were observed. In all the experiments carried out with these two drugs we observed a very wide variability in loss rates, which ranged from 0 to 100%.

No statistically significant difference was found between omeprazole and lansoprazole as regards concentration of active ingredients or quantities of granules obtained at the tube exit (Table 2).

In addition, we noted that the mean size of a granule of omeprazole was about three times that of a granule of esomeprazole (1.78 mm versus 0.61 mm). The granules of lansoprazole were of intermediate size (Table 3).

3.2. Impact of different variables on the flow of PPIs through the tubes

3.2.1. Esomeprazole

All the experiments gave excellent results, with total doses collected at the tube exit practically equal to those administered (mean recovery rate 100.9% with a variability of 2.6%). The statistical analysis of the results showed significant differences with the 'solvent' and 'rinse' factors. However, these differences were slight (101.6% with 10 ml versus 100.1% with 20 ml) and did not influence the clinical result. For the 'administration pattern' factor, no significant difference was found between 3× 10 ml and 1× 30 ml. In addition, in a preliminary study carried out on esomeprazole, we found that the administration patterns recommended by AstraZeneca (2× 25 ml or 1× 50 ml) did not give significantly better results than those we tested. Thus, a lower administered volume gave equivalent results for a lower stomach load (Table 4).

Table 4
Influence of the volume of suspension on the quantity of esomeprazole collected at the tube exit

Administered volume (ml)	Recovered esomeprazole (%)
50	103.53 ± 0.64
2× 25	105.57 ± 4.07
30	99.91 ± 1.89
3× 10	101.93 ± 3.45

3.2.2. Lansoprazole (Fig. 1)

In all our experiments, we observed a very wide variability in the quantity of granules collected from one administration pattern to another (67% of lansoprazole recovered on average, with a variability of about 40%).

Statistical analysis showed that the 'solvent' and 'administration pattern' factors gave no significant improvement in the quantity of granules collected or the final concentration of lansoprazole. By contrast, the 'rinse' and 'tube' factors both had a significant influence: a 20 ml rinse improved yield by about 23% ($p < 0.05$) and a polyurethane tube increased it by 32% ($p < 0.005$). Thus, with both these conditions met 86% of the active ingredient could be recovered on average (coefficient of variation 24%).

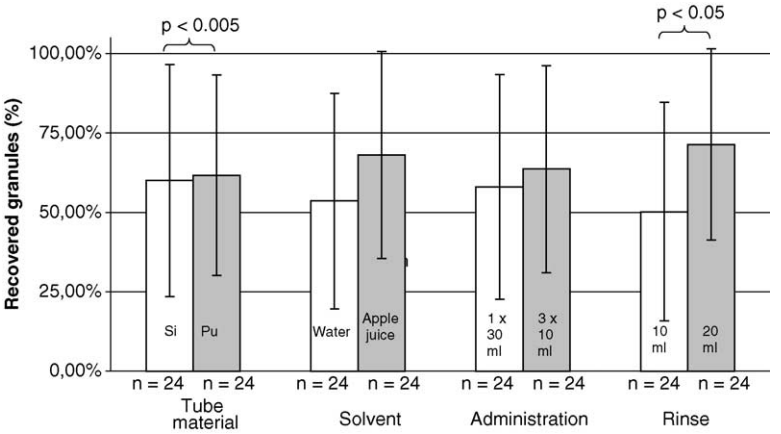

Fig. 1. Impact of different parameters on the flow of granules of lansoprazole through a nasogastric tube.

3.2.3. Omeprazole (Fig. 2)

Like for lansoprazole, a very wide variability was found in the quantity of omeprazole collected from one administration to another. No significant improvement was given by the 'tube', 'solvent' or 'administration pattern' on the quantity of granules collected or on the final concentration of omeprazole. Only the 'rinse' variable had a significant influence ($p < 0.03$), allowing an average increase of 20% in the final concentration of omeprazole. However, this variable did not significantly influence the number of granules recovered: this difference between concentration and quantity of granules can be explained by the high variability in the size of the omeprazole granules (coefficient of variation 33% versus 17% for lansoprazole and 6% for esomeprazole). Rinsing with 20 ml statistically influenced the concentration obtained, but did not systematically prevent obstruction of the tube.

4. Discussion

4.1. General comments on the behaviour of the three PPIs

4.1.1. Influence of administration pattern

We investigated whether it was preferable to administrate the IPP granules in one or several doses. No

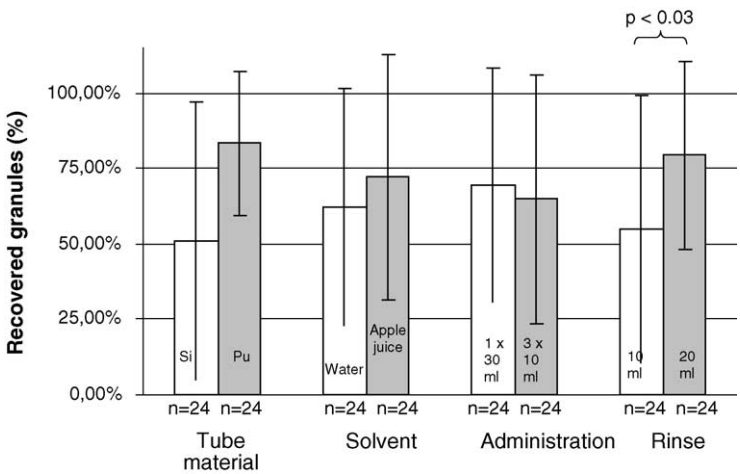

Fig. 2. Impact of different parameters on the flow of granules of omeprazole through a nasogastric tube.

Fig. 3. Comparison of PPIs' granule size (magnification ×2.5).

study of this variable was found in the literature for omeprazole or lansoprazole. However, White et al. (2002) assessed it for esomeprazole, and their results are consistent with ours; no significant difference was found that indicated the superiority of either pattern over the other (1× 50 ml versus 2× 25 ml). The same conclusion was drawn for our two patterns (1× 30 ml and 3× 10 ml), for esomeprazole and for the two other PPIs. Hence, the administration pattern did not influence the quantity of granules collected at the tube exit for any of the PPIs we tested.

4.1.2. Influence of solvent

In intensive care units the solvent most often used is water (mineral water, sterile water, etc.). However, some studies conducted to compare the activity of PPIs administered by tube and by the oral route used solvents, such as fruit juice (e.g., apple juice) or sodium bicarbonate solution. We consider apple juice to be more appropriate than bicarbonate solution because apple juice maintains an acidic medium that conserves the granules to be administered. These retain their gastroresistant coating and therefore their properties when they arrive in the stomach. Conversely, bicarbonate dissolves the granule coating, exposing the active ingredient to stomach acids, and so may inactivate PPIs and impair their action. The study of Sharma et al. (2000) reports evidence of this effect: the absorption of omeprazole was lower from a suspension of granules in 8.4% sodium bicarbonate than from an intact gelatine capsule. It has been suggested that bicarbonate neutralises stomach acidity, but no validated data is currently available on the quantity of bicarbonate needed to do this. Accordingly, we preferred to focus our study on the two solvents recognised as being suited to the administration of PPIs by nasogastric tube: water and apple juice. In addition, our study shows no significant difference between these two solvents: the same quantities of granules were collected for PPIs dispersed in water and in apple juice.

4.1.3. Influence of dosage form (Fig. 3)

The analysis of granule size suggested some possible explanations for the tube obstruction observed with lansoprazole and omeprazole:

- The granules of esomeprazole were much smaller than those of lansoprazole, which in turn were smaller than those of omeprazole.
- The granules of omeprazole were very variable in size. This was demonstrated by measurement of the granules and by the inconsistency of the statistical results based on concentrations and quantities of granules obtained. All the administrations of omeprazole and lansoprazole were accompanied by a dual evaluation of the final quantity recovered: by assay and by counting of granules. This dual evaluation revealed the variations in granule size. Hence, the size heterogeneity of the omeprazole granules may be an additional risk factor for tube obstruction.

4.2. Specific comments

4.2.1. Esomeprazole

Our study shows how esomeprazole granules can be administered in ways that are better suited to the physiology of the patients under treatment. First, a volume of 10 ml is sufficient to dissolve the tablet. Second, 30 ml is enough to administer the whole dose (instead of 50 ml). This is important when the total volume delivered to the patient through a nasogastric tube has to be minimised.

4.2.2. Lansoprazole

Most of the studies performed on the efficacy of suspensions of lansoprazole administered by nasogastric tube have been clinical trials with either stomach pH over a period of time or plasma levels of lansoprazole as the main dependent variable. It is surprising to obtain systematically positive clinical results even though tube obstruction occurs quite frequently, and none of the administration patterns guarantees that the dose administered is fully delivered.

We found that the nature of the tube played a significant role in the delivery of lansoprazole granules (polyurethane tubes favoured the flow of lansoprazole granules). However, it is impossible to correlate this difference to the tube material because for the same gauge (16 French), the two types of tube used did not have the same internal diameter. The 16 French gauge silicone tube had a smaller internal diameter than the 16 French polyurethane tube (3 mm versus 3.8 mm). Thus, the influence of the tube material on the behaviour of the lansoprazole granules is not precisely known.

4.2.3. Omeprazole

In the studies of Larson et al. (1996) and Chun et al. (1996) conducted in vivo, no significant difference was found between the plasma levels of omeprazole in patients given an intact gelatine capsule and in those given a suspension of omeprazole granules through a nasogastric tube. However, in these two studies the volumes administered were rather large (140 ml in Larson et al. and 120 ml in Chun et al.) in view of the patients' limited stomach capacity. For this reason, we decided not to exceed a maximum administered volume of 70 ml (including tube rinse). Our study shows that in such conditions it is impossible to know whether a sufficient quantity of omeprazole will reach the stomach. The study of Balaban et al. (1997) supports our conclusion: it shows that that a dose of 20 mg of omeprazole administered through a tube is not clinically efficacious.

The rinsing, as our results show, is an important factor. Rinsing is a necessary part of any administration of medication through a nasogastric tube. It washes out all traces of active material from the tube, and in our case it appreciably increased the delivery of granules of both omeprazole and lansoprazole. For omeprazole, we observed that a large number of granules stuck to the plastic surfaces of the syringe; these could be detached by rinsing. However, rinsing with 20 ml did not prevent obstruction of the tube by granules of omeprazole.

5. Conclusion

Esomeprazole is the PPI of choice for the treatment of patients through a nasogastric tube. Using a polyurethane tube and a 20 ml rinse, the administration of lansoprazole by tube can be considered. It is not advisable to use omeprazole by this route because no administration pattern will guarantee that a sufficient concentration of active ingredient will be delivered.

Our study is only one step towards improving the administration of PPIs by nasogastric tube. Other factors, not taken into account here, can also affect the flow of granules through tubes. Among these are the re-use of a tube to deliver granules daily for periods ranging from days to months, administering other medication together with PPIs and administering round-the-clock enteral nutrition of ranging viscosity in parallel with PPI granules. Pediatric administration of PPIs via a nasogastric tube represents another target for study, given the small internal diameter of the nasogastric tubes. These different situations are being studied.

References

Balaban, D.H., Duckworth, C.W., Peura, D.A., 1997. Nasogastric omeprazole: effects on gastric pH in critically ill patients. Am. J. Gastroenterol. 92, 79–83.

Chun, A.H.C., Shi, H.H., Achari, R., Dennis, S., Cavanaugh, J.H., 1996. Lansoprazole: administration of the contents of a capsule dosage formulation through a nasogastric tube. Clin. Ther. 18, 833–842.

Doan, T.T., Wang, Q., Griffin, J.S., O'Dea, R.F., Pan, W.J., 2001. Comparative pharmacokinetics and pharmacodynamics of lansoprazole oral capsules and suspension in healthy subjects. Am. J. Health-Syst. Pharm. 58, 1512–1519.

Dunn, A., White, M., Reddy, P., Quercia, R.A., Chow, M.S.S., 1999. Delivery of omeprazole and lansoprazole through a nasogastric tube in vitro. Am. J. Health-Syst. Pharm. 56, 2327–2330.

Freston, J., Chiu, Y.-L., Pan, W.J., Lukasik, N., Taubel, J., 2001. Effect on 24-hour intragastric pH: a comparison of lansoprazole administered nasogastrically in apple juice and panto-

prazole administered intravenously. Am. J. Gastroenterol. 96, 2058–2065.

Larson, C., Cavuto, N.J., Flockhart, D.A., Weinberg, R.B., 1996. Bioavailability and efficacy of omeprazole given orally and by nasogastric tube. Dig. Dis. Sci. 41, 475–479.

McAndrews, K.L., Eastham, J.H., 1999. Omeprazole and lansoprazole suspensions for nasogastric administration. Am. J. Health-Syst. Pharm. 56, 81.

Phillips, J.O., Metzler, M.H., Palmieri, M.T., Huckfeldt, R.E., Dahl, N.G., 1996. A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage. Crit. Care Med. 24, 1793–1800.

Sharma, V.K., Peyton, B., Spears, T., Raufman, J.P., Howden, C.W., 2000. Oral pharmacokinetics of omeprazole and lansoprazole after single and repeated doses as intact capsules or as suspensions in sodium bicarbonate. Aliment. Pharmacol. Ther. 14, 887–892.

Sostek, M.B., Chen, Y., Skammer, W., Winter, H., Zhao, J., Andersson, T., 2003. Esomeprazole administered through a nasogastric tube provides bioaailability similar to oral dosing. Aliment. Pharmacol. Ther. 18, 581–586.

Tsai, W.L., Poon, S.K., Yu, H.K., Chang, C.S., Yeh, H.Z., Ko, C.W., Chen, G.H., 2000. Nasogastric lansopraole is effective in suppressing gastric acid secretion in critically ill patients. Aliment. Pharmacol. Ther. 14, 123–127.

White, M.C., Kalus, J.S., Quercia, R., Fortier, C., Piotrowski, A., Roach, H.A., Sostek, M.B., 2002. Delivery of esomeprazole magnesium enteric-coated pellets through small caliber and standard nasogastric tubes and gastrostomy tubes in vitro. Am. J. Health-Syst. Pharm. 59, 2085–2088.