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Proton pump inhibitor administration via nasogastric tube in pediatric practice: Comparative analysis with protocol optimization

M.P. Ponrouch[a], V. Sautou-Miranda[a,b,*], A. Boyer[a,b], D. Bourdeaux[a], A. Montagner[a], J. Chopineau[a,b]

[a] CHU Clermont-Ferrand, Pharmacie, Hop G Montpied, 58 rue Montalembert, F-63000 Clermont-Ferrand, France
[b] Université d'Auvergne-Clermont I, Faculté de Pharmacie, Laboratoire de Pharmacie Clinique et Biotechniques, 28 place H Dunant, F-63000 Clermont-Ferrand, France

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ABSTRACT

Proton pump inhibitors (PPIs) are largely prescribed to children because their efficacy and tolerance are now well-established. One disadvantage resides in the absence of liquid form which causes problems for their administration in nasogastric tubes. Indeed, the absence of use recommendations involves many misuses responsible for inefficiency and/or tube obstruction. We tried to evaluate if PPIs can be administered through pediatric nasogastric tubes. We administered four PPIs (Omeprazole, esomeprazole, lansoprazole and lansoprazole orally disintegrating tablet) through nasogastric tubes. For each PPI a study plan was drawn up to assess the influence of different variables: the volume of water to dissolve or put in suspension the PPIs (2 ml or 5 ml), the volume of tube flush-through water post-PPI administration (2 ml, 5 ml or 10 ml), the length (50 cm or 125 cm) and the diameter (6 or 8 French) of the polyurethane tubes. For each assay an analysis of each active ingredient at the tube outlet by UV spectrometry was carried out. All 6 F tubes were obstructed by PPIs. Through 8 F tubes, we observed a mean recovery of active ingredient of 86.2% for lansoprazole orally disintegrating tablet, 36.9% for esomeprazole but only 7.1% for lansoprazole and 3.9% for omeprazole. It is disadvised using omeprazole and lansoprazole through 8 F nasogastric tubes because no condition ensures the transit of an efficient concentration of active ingredient. For esomeprazole, the best conditions of administration were a water volume of 5 ml and a rinse volume of 5 ml but only a half of the microgranules administered were recovered. The most satisfactory results were obtained with lansoprazole orally disintegrating tablet. A 5 ml volume of water diluent for suspension and a 10 ml volume of flush-through water made it possible to deliver the full lansoprazole dose administered.

1. Introduction

The efficacy and tolerance of proton pump inhibitors (PPIs) in children is now well-established (Faure, 2004; Barron et al., 2007; Tolia et al., 2008). In France, only omeprazole has been given marketing authorization for use in pediatrics, although the FDA has approved both lansoprazole and more recently esomeprazole for use in children (Lang, 2008). These molecules are unstable in acidic conditions, degrading rapidly on contact with the stomach's gastric juice. Pharmaceutical companies have addressed this issue by adapting the PPI dosage forms, developing capsules containing gastro-resistant granules or tablets incorporating gastro-resistant microgranules. Administration to infants can be made easier to deliver by opening the capsules and mixing the granules or tablets in water or fruit juice. However, in practice, it appears that these suspensions struggle to pass through nasogastric tubes, particularly the small-bore tubes designed for use in pediatric patients. The lack of guidelines on using these pediatric tubes leads to widespread improper use, with the result that the tubes are inefficient or become blocked. Several studies have been led on the in-tube transit of PPIs, particularly omeprazole but also esomeprazole (Messaouik et al., 2005; Sostek et al., 2003; Shah et al., 2006; White et al., 2002), but there has not yet been a comparative analysis on PPI transit in small-bore nasogastric tubes. This prompted us to study the transit of PPIs in pediatric nasogastric tubes under different sets of parameters (tube bore and tube length, volume of PPI diluent, volume of tube-flushing solvent) in order to determine the optimal set of PPI delivery conditions.

2. Materials and methods

2.1. Drugs and drug delivery systems

In order to ensure that our experimental design mirrored professional practice, we surveyed several pediatric departments in French hospitals (Necker Hospital in Paris, *Hospices Civils de Lyon*, Clermont-Ferrand University Teaching Hospital) to canvass

* Corresponding author at: Pharmacie, Hop G Montpied, 58 rue Montalembert, F-63000 Clermont-Ferrand, France. Tel.: +33 473751760; fax: +33 473751759.
E-mail address: vmiranda@chu-clermontferrand.fr (V. Sautou-Miranda).

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Table 1
Experiment design conducted to study the in-tube transit of each PPI tested.

Experiment	NG tube length (cm)	PPI solution volume (ml)	Tube flush-through volume (ml)
No. 1	50	2	2
No. 2	50	2	5
No. 3	50	2	10
No. 4	50	5	2
No. 5	50	5	5
No. 6	50	5	10
No. 7	125	2	2
No. 8	125	2	5
No. 9	125	2	10
No. 10	125	5	2
No. 11	125	5	5
No. 12	125	5	10

the techniques and equipment most widely used. The responses obtained highlighted significant variability in nasogastric tube-based drug delivery (variability in the volume of water diluent for PPI suspensions, in flush-through volume, etc.). These variations were dependent on both the care staff involved and the on ward-specific practices. These in-field differences are almost certainly due to the fact that there are no officially documented reference guidelines covering the issue. We opted to experimentally reproduce these techniques in order to elect the most satisfactory in terms of tube patency, efficacy, and speed of execution. The parameters studied were: tube bore (6 and 8 French), tube length (50 cm or 125 cm), tablet solution volume or the volume of solution used to suspend the PPI granules (2 ml and 5 ml of water), and volume of tube flush-through water post-PPI administration (2 ml, 5 ml or 10 ml of water). Since in pediatric care these flushing and solution volumes are kept intentionally low in order to prevent gastric overload, the sum of liquid volumes administered does not go over 15 ml.

The PPIs used were: Omeprazole (MOPRAL®) 10 mg (AstraZeneca), Esomeprazole (INEXIUM®) 20 mg (AstraZeneca), Lansoprazole (OGAST®) 15 mg (Takeda), and lansoprazole orally disintegrating tablet (LODT) (OGASTORO®) 15 mg (Takeda). The nasogastric tubes used are size 6 and 8 French 50-cm long and 125-cm long polyurethane tubes (Laboratoire Cair). The granule suspensions were administered using 20-ml capacity syringes (Laboratoire Cair).

2.2. Study methodology

An experimental design was carried out for each PPI tested in order to study the influence of each of the three abovementioned parameters (Table 1). A total of 12 experiments were run for each PPI tested. Each experiment was conducted in triplicate.

We first administered PPI granules in each nasogastric tube placed as in a child in semi-Fowler's position. Although this position does not offer a long-term guarantee against the occurrence of gastroesophageal reflux, it does prevent reflux aspiration. We therefore opted to fit the tubes in such a way as to mimic this semirecumbent angle. Each experiment was conducted by placing the tablets (esomeprazole or LODT) or granules contained in the capsules (omeprazole or lansoprazole) in the syringe barrel and sampling-in the volume of water required for that particular experiment. The syringe was then shaken to suspend the granules or dissolve the capsule to release the microgranules of PPI. The syringe was then fitted to the tube and drug administration was carried out. The mixture contained in the syringe was shaken constantly by small rotations throughout drug delivery to prevent granule build-up on the inner walls of the syringe barrel. Furthermore, we kept the injection flow constant in an attempt to minimize the occurrence of tube blockage.

Table 2
Percentage of active ingredient recovered at the tube outlet and the percentage of tubes blocked over the course of the experiment.

Active ingredient	Active ingredient recovered at tube outlet (%)	Tubes blocked (%)
Omeprazole	3.9 ± 4.2	33.3
Lansoprazole	7.1 ± 5.9	22.2
Esomeprazole	36.9 ± 28.4	30.5
LODT	86.2 ± 17.3	0

The suspension containing granules or microgranules was then recovered into glass labware fitted at the end of the tube.

The dosage of PPI delivered was measured on the recovered suspension. This required the samples to be preprocessed. Each suspension was filtered through a 0.125 nm pore-size filter in order to separate out the microgranules. To separate active ingredient from gastro-resistant coating, the granules were then dissolved in an appropriate solution: a mixture of sodium tetraborate at 3.183 g/l and pure ethanol (80/20 v/v) for omeprazole, esomeprazole and lansoprazole orally disintegrating tablet, or in pure methanol for lansoprazole.

After completely dissolving the granules obtained by running them through an ultrasonic bath and a sonicator, the omeprazole, esomeprazole and lansoprazole solutions were then centrifuged for 5 min at 4500–500 rpm. The fully clear solutions thus obtained were then diluted to 1 in 10 in sodium tetraborate/ethanol mixture or in methanol and then spectrophotometrically assayed on a Jasco V-530 UV-Vis spectrophotometer at 303 nm for omeprazole, 307 nm for esomeprazole and 285 nm for lansoprazole (Messaouik et al., 2005). The concentrations measured through this spectrophotometric analysis were used to determine the percentage of active ingredient recovered at the tube outlet in relation to the initial dose administered. These initial doses were 20 mg for esomeprazole, 10 mg for omeprazole, and 15 mg for lansoprazole. We then studied the influence of each parameter, i.e. 'suspension volume', 'flush-through volume' and 'tube length', on the through-tube transit of each PPI. The statistical analyses run on the results were performed using Excel software on one-way ANOVAs.

3. Results and discussion

All the 6 French-bore tubes became blocked during trialing, regardless of PPI administered. Consequently, the only workable results were those from the 8 French-bore tubes.

Table 2 presents the percentages of PPIs recovered at the tube outlet with all parameters pooled, and the percentage of tubes that became completely blocked by the suspension.

The different PPIs showed significantly different behavior, with most of them also presenting significant variability in through-tube transit. Three of the 4 PPIs tested also recorded a significant percentage of tubes blocked by suspension transit. LODT proved easy to deliver via a gastroduodenal tube, since none of the tubes suffered blockage and a very satisfactory quantity of active ingredient could be recovered, regardless of the PPI administration parameters. The other PPIs were, however, poor in comparison, presenting apparently highly random through-tube transit. This prompted us to finetune our analysis in an attempt to evaluate whether certain parameters (tube length and water volumes used) could impact on these general conclusions.

3.1. Influence of tube length

Table 3 presents the results obtained for all the 4 PPIs on transit through the 50 cm and 125 cm tubes:

Across all the PPIs studied, the 'tube length' parameter showed no statistically significant influence on PPI transit through 8

Table 3
Percentage of active ingredient recovered at the tube outlet in relation to PPI and tube length after transit through 50 cm and 125 cm tubes.

Active ingredient	50 cm PU tube	125 cm PU tube	*p*
Omeprazole	3.7 ± 4.6	4.2 ± 3.9	0.74
Lansoprazole	5.7 ± 5.9	8.4 ± 5.8	0.17
Esomeprazole	42.1 ± 19.4	30.1 ± 35.0	0.28
LODT	84.3 ± 19.7	88.0 ± 14.3	0.52

French-bore polyurethane tubes. A 125 cm tube is therefore able to deliver a quantity of active ingredient that is comparable to that of a tube 2.5 times smaller. This result can be put to beneficial use in pediatric wards whose policy is to employ long NG tubes to avoid cluttering up the space around the patient's head with tubes and tube system equipment.

3.2. Influence of liquid volumes

The results were analyzed for each active ingredient. We studied the influence of volume of water diluent used for PPI suspensions (called 'administration volume') and volume of water used to flush the tubes (called 'flush-through volume').

3.2.1. Omeprazole

The results obtained are illustrated in Fig. 1.

3.2.1.1. Influence of administration volume. The results obtained, all parameters pooled together, were 4.05 ± 3.86% omeprazole recovered with 5 ml of diluent and 3.78 ± 4.64% with 2 ml of diluent. Quantity of active ingredient recovered at the tube outlet was not statistically influenced by the volume of water used to administer the omeprazole granules ($p = 0.85$).

3.2.1.2. Influence of flush-through volume. The percentages of omeprazole recovered for the 3 flush-through volumes studied (2 ml, 5 ml and 10 ml) were respectively: 2.28 ± 3.40%, 2.35 ± 2.50% and 7.12 ± 4.67%. Statistical analysis highlighted that a 10 ml flush-through volume was able to significantly improve through-tube omeprazole transit compared to the 2 ml ($p = 0.008$) and 5 ml ($p = 0.005$) volumes, but the quantities involved remained far too small to be clinically satisfactory.

Messaouik et al. reported only limited transit of omeprazole granules through nasogastric tubes (Messaouik et al., 2005). These results nevertheless proved more satisfactory than those observed in our present study, although their experimental conditions were less restrictive: 16 French-bore tubes, a 30 ml administration volume and either a 10 ml or a 20 ml flush-through volume. These conditions would not be realistically applicable in pediatric practice. Reports have been published on the through-tube transit of omeprazole dissolved in different solvents, particularly 8.4% sodium bicarbonate (Reilly, 1999; Song et al., 1999). Satisfactory percentages of active ingredient were recovered. We elected not to use this solvent, since there are currently no validated data on the quantity of bicarbonate required in order to neutralize gastric acidity in children and newborns. Furthermore, a previous study conducted internally in our laboratory showed that a 1.4% sodium bicarbonate solution had a significant impact on the internal bore surface of the NG tubes after a 7-day period of contact exposure. For these reasons, we opted to conduct our experiments using a water diluent only. The poor results yielded by our trials with omeprazole are mainly due to size of the granules in the capsules, which have a diameter of 1.90 ± 0.64 mm whereas the internal bore size of 8 French tubes is around 1.5 mm, so many of the granules would have been unable to penetrate the tube. It is therefore unadvisable to use this formulation for administration via NG tubes.

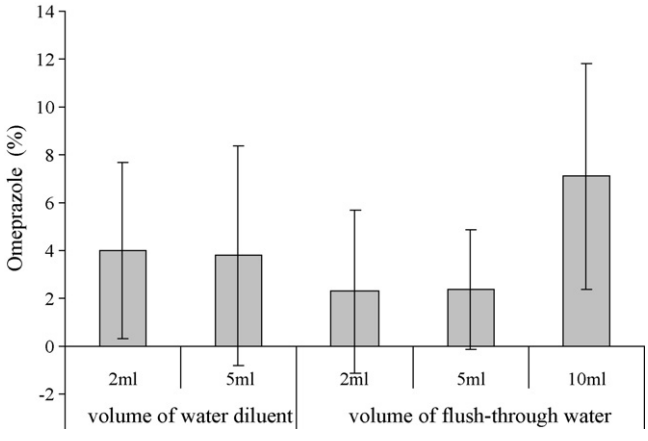

Fig. 1. Percentage omeprazole recovered according to administration volume and flush-through volume.

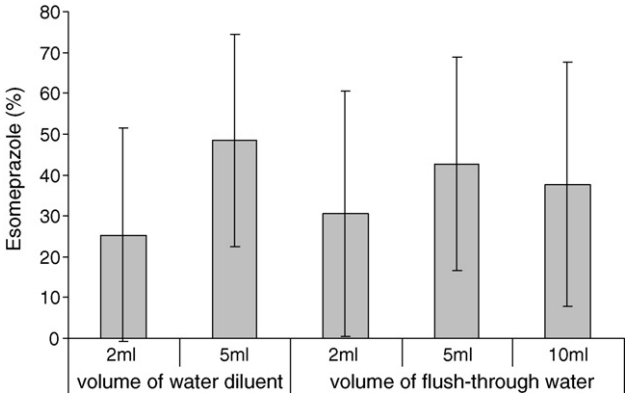

Fig. 2. Percentage esomeprazole recovered according to administration volume and flush-through volume.

3.2.2. Esomeprazole

The results obtained are illustrated in Fig. 2.

3.2.2.1. Influence of administration volume. The results obtained, all parameters pooled together, were 51.6 ± 24.0% esomeprazole recovered with 5 ml of diluent and 26.8 ± 26.1% with 2 ml of diluent. The volume of water used for the administration of esomeprazole tablets had a significant influence on the through-tube transit of the microgranules ($p = 0.007$). This is probably one of the reasons why AstraZeneca recommends a 25 ml suspension volume for dissolving Inexium® tablets. A volume of this size, while ensuring good microgranule dispersion, cannot be recommended for use in young children since there is a risk of causing gastric overload.

3.2.2.2. Influence of flush-through volume. The percentages of esomeprazole recovered for the 3 flush-through volumes studied (2 ml, 5 ml and 10 ml) were respectively: 30.5 ± 30.0%, 42.4 ± 25.6% and 37.7 ± 30.0%. Statistical analysis was unable to highlight a significant influence of flush-through volume on the through-tube transit of esomeprazole ($p = 0.59$). The increase in flush-through volume is unable to flush through the microgranules stuck to the inner walls of the tube, which are therefore not delivered to the patient.

Esomeprazole posted disappointing results: even when opting for the liquid volumes giving the best results (a 5 ml administration volume and a 5 ml flush-through volume), on average only half of the microgranules administered are actually delivered, and under

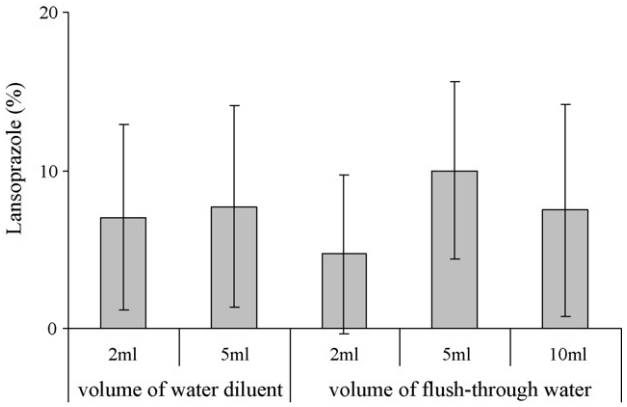

Fig. 3. Percentage lansoprazole recovered according to administration volume and flush-through volume.

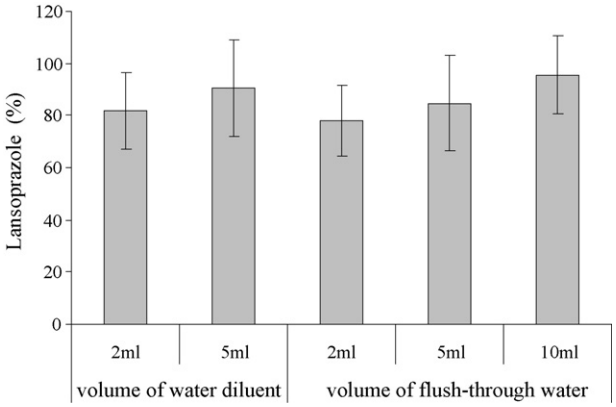

Fig. 4. Percentage LODT recovered according to administration volume and flush-through volume.

these conditions the esomeprazole showed 49% variability over the 6 experimental runs performed.

Several studies (Messaouik et al., 2005; Sostek et al., 2003; Shah et al., 2006; White et al., 2002) have demonstrated that esomeprazole could be administered via NG tube as an alternative to the parenteral route. However, the NG tubes employed in these studies (14 or 16 French) are very-wide-bore tubes. Tube bore remains a pivotal parameter for in-tube microgranule transit. However, 14 French or 16 French tubes cannot be used in pediatrics and should not even be used in adult patients fed via enteral route. Furthermore, the volumes of water used in this study to dissolve the tablets were too small to give a sufficiently fluid suspension, the result being a sort of 'paste' that was not only difficult to administer but blocked the tube. Pediatric nurses should follow the laboratory's recommended water volume of 25 ml when administering esomeprazole via nasogastric tube. However, while this is a practicable volume in adult patients, it remains too large for use in a number of pediatric indications.

Devlin et al. reported 88.9 ± 8.6% recovery through 8 French-bore NG tubes (Devlin et al., 2006). The authors specified that esomeprazole was a fast-delivery PPI that remained uninfluenced by operator experience, but they omitted to give data on the liquid volumes used to dissolve the tablets or flush through the tube. Since all the patients included in this study were adults, liquid volume was unlikely to have been a limiting factor.

3.2.3. Lansoprazole

The results obtained are illustrated in Fig. 3.

3.2.3.1. Influence of administration volume. The results obtained, all parameters pooled together, were 7.7 ± 5.9% lansoprazole recovered with 5 ml of diluent and 7.1 ± 6.4% with 2 ml of diluent. Quantity of active ingredient recovered at the tube outlet was not statistically influenced by the volume of water used to administer the lansoprazole granules ($p = 0.77$).

3.2.3.2. Influence of flush-through volume. The percentages of lansoprazole recovered for the 3 flush-through volumes studied (2 ml, 5 ml and 10 ml) were respectively: 4.7 ± 5.0%, 10.0 ± 5.6% and 7.5 ± 6.7%. Statistical analysis highlighted a significant influence of flush-through volume on the quantity of lansoprazole recovered ($p = 0.097$). It is not the largest volume that yields the best results: 5 ml gave a better flush-through, as was the case with esomeprazole. However, the percentages of active ingredient recovered remained mediocre at best, peaking at only 23% even when liquid volumes were optimized.

All lansoprazole experiments taken together, the PPI demonstrated very poor through-tube transit associated with strong variability. The quantities of lansoprazole actually reaching the tube outlet were too insignificant to expect any kind of therapeutic efficacy whatsoever. This is despite the fact that several studies (Doan et al., 2001; Chun et al., 1996; Freston et al., 2001) had previously demonstrated the efficacy of tube-delivered lansoprazole. The main criterion measured in these studies was either gastric pH or plasma levels. Since the results showed good efficacy, it was natural to conclude that a clinically satisfactory quantity of product actually transited through the tube. These studies were run on wider-bore tubes (16 French), and both administration volume and flush-through volume were also higher.

The poor results recorded here with lansoprazole were essentially due to the size of the granules contained in the capsule formulation, which have a diameter of 1.1 ± 0.1 mm (Messaouik et al., 2005) whereas the internal bore size of 8 French tubes is around 1.5 mm, so a number of granules may have been unable to penetrate the tube. Hence, Ogast® administration via NG tubes of 8 French bore size or less cannot be considered an alternative to the parenteral route in cases where the oral route is not a viable option.

3.2.4. Lansoprazole orally disintegrating tablets

The results obtained are illustrated in Fig. 4.

3.2.4.1. Influence of administration volume. The results obtained were 90.5 ± 18.4% lansoprazole recovered with 5 ml of diluent and 81.8 ± 14.8% with 2 ml of diluent. Quantity of active ingredient recovered at the tube outlet was not statistically influenced by the volume of water used to administer the tablets ($p = 0.39$). The mean quantity recovered using a 5 ml administration volume was 13.6 mg of the original 15 mg theoretically administered, i.e. 90% of the initial dose. The quantity delivered is therefore clinically satisfactory.

3.2.4.2. Influence of flush-through volume. The percentages of lansoprazole recovered for the 3 flush-through volumes studied (2 ml, 5 ml and 10 ml) were respectively: 78.0 ± 13.8%, 84.8 ± 18.5% and 95.7 ± 14.9%. Statistical analysis highlighted a significant influence of flush-through volume on the transit of this formulation ($p = 0.032$). The dose of lansoprazole delivered to the stomach can be optimized using a 10 ml flush-through volume.

Combing a 5 ml volume water diluent for suspension and a 10 ml volume of flush-through water makes it possible to deliver the full lansoprazole dose administered (102.1 ± 3.2%).

It should also be underlined that throughout the experiment, none of the tubes became blocked with the LODT formulation. Fur-

thermore, there was relatively little inter-experiment variability (<20%), meaning that the parameters studied had little influence on the through-tube transit of this PPI.

These results therefore confirm the results of Devlin et al. (2006), who reported a $95.7 \pm 3.2\%$ lansoprazole recovery rate following administration of the LODT through 8 French tubes.

4. Conclusion

This study shows that among the PPIs that can be used in children, only LODT can be reliably and reproducibly delivered through small-bore (8 French) nasogastric tubes, even when using small volumes of water to dissolve the tablet and to flush the tube after the PPI has transited through. Omeprazole, lansoprazole and esomeprazole cannot be indicated for use via this route of administration since the quantity of active ingredient made bioavailable in the stomach is too little and/or too variable to expect any real therapeutic efficacy.

References

Barron, J.J., Tan, H., Spalding, J., Bakst, A.W., Singer, J., 2007. Proton pump inhibitor utilization patterns in infants. J. Pediatr. Gastroenterol. Nutr. 45, 421–427.

Chun, A.H., 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.

Devlin, J.W., Bakshi, A., Bungat, K., Olsen, K.M., 2006. An in vitro comparison of different providers to deliver four proton pump inhibitor products through a feeding tube. Aliment. Pharmacol. Ther. 24, 1603–1611.

Doan, T.T., Wang, Q., Griffin, J.S., Lukasik, N.L., 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.

Faure, C., 2004. Indications for proton pump inhibitors. Arch. Pédiatr. 11, 674–676.

Freston, J., Chiu, Y.L., Pan, W.J., Lukasik, N., Taubel, J., 2001. Effects on 24-hour intragastric pH: a comparison of lansoprazole administered nasogastrically in apple juice and pantoprazole administered intravenously. Am. J. Gastroenterol. 96, 2058–2065.

Lang, L., 2008. FDA approves Nexium for use in children 1–11 years. Gastroenterology 134, 1282.

Messaouik, D., Sautou-Miranda, V., Chopineau, J., 2005. Comparative study and optimisation of the administration mode of three proton pump inhibitors by nasogastric tube. Int. J. Pharm. 299, 65–72.

Reilly, J.P., 1999. Safety profile of the proton pump inhibitors. Am. J. Health Syst. Pharm. 56 (Suppl. 4), S11–S17.

Shah, S.A., Sander, S., Coleman, C.I., White, C.M., 2006. Delivery of esomeprazole magnesium through nasogastric tube and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. Am. J. Health Syst. Pharm. 63, 1882–1887.

Song, J.C., Quercia, R.A., Fan, C., Tsikouris, J., White, M., 1999. Pharmacokinetics comparison of omeprazole capsules and a simplified omeprazole in children. Dig. Dis. Sci. 44, 134–139.

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

Tolia, V., Boye, R.K., 2008. Long-term proton pump inhibitor use in children: a retrospective review of safety. Dig. Dis. Sci. 53, 385–393.

White, C.M., Kalus, J.S., Quercia, R., Fortier, C., Piotrowski, A., Roach, 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.