SYNOPSIS

Industry: Laboratoires HOUDE
Product name: LANZOR®
Active ingredient: LANSOPRAZOLE

Study title: Pharmacokinetic and pharmacodynamic study after orally administered, single or repeated doses of lansoprazole capsules to children.

Investigators: Pr. PONS and Pr. DUPONT

Study centre: Hôpital Saint-Vincent de Paul, 75014, Paris, France


Study period: 1993-1995
Study type: Phase II A clinical trial

Objectives:
- To determine the pharmacokinetic and pharmacodynamic parameters of lansoprazole administered as a single (group A) or repeated (group B) dose of 17 mg/m²/day to children aged between 0-15 years.
- To study the influence of age on the pharmacokinetic and pharmacodynamic parameters
- To study the relationship between kinetics and efficacy
- To evaluate biological and clinical safety

Method: non-randomised, single centre, open study

Number of subjects:
Included: 43 (group A, n = 18; group B, n = 25)
Included for kinetic analysis: 40 (group A = 18; group B = 22)
Included for intragastric pH-measurement: 39 (group A = 18; group B = 21)

Diagnostic and inclusion criteria:
- Children aged from 0-15 years
- Having a pathology requiring lansoprazole treatment
- Written parental consent

Dose and administration mode of product; batch number:
Capsules of microgranules containing 5, 10 or 15 mg Lansoprazole, administered with a liquid; theoretical dose: 17 mg/m², actual dose administered, 17.7 ± 2.5 mg/m² [11.6-23.8 mg/m²], oral administration; batch numbers: JMP 24801-509, CG 24896-026.

Treatment duration: Group A = single dose, Group B = 7-15 days

Treatment reference: none

Evaluation criteria
- Pharmacokinetic parameters of lansoprazole
- Intragastric pH-measurement
- Clinical and biological tolerance (standard parameters and blood gastrin levels)

Statistical methods
- Descriptive analysis
- Research for an influence of age on kinetic and intragastric pH parameters using the Spearman test
- Research for a link between kinetic and intragastric pH parameters using the Spearman test
Conclusions

The pharmacokinetics of lansoprazole administered orally as gastroresistant microgranules was studied in 18 children aged from 4.9 ± 4.1 years [2 months–13.5 years] as a single dose of 17.2 ± 2.4 mg/m² [12.2-21.7 mg/m²] (group A) and in 22 children aged 5.3 ± 4.2 years [18 days–14.1 years] as a repeated dose of 17.5 ± 2.7 mg/m² [11.6-23.8 mg/m²] after 9-14 days treatment (group B). These children presented with a digestive pathology warranting treatment by a proton pump inhibitor.

Eight venous blood samples were taken just before and at 1 h, 2 h, 3 h, 4 h, 5 h, 8 h and 10 h after drug administration.

The following parameters (means ± SE [range]) were obtained:

Group A: Cmax, 1,068 ± 883 μg/l [220-3,812 μg/l]; tmax, 1.8 ± 0.8 h [0.97-3.52 h]; AUC0–∞, 3,796 ± 6,763 μg.l/h/l [476-16,446 μg.l/h/l]; t½, 1.5 ± 2.0 h [0.4-8.9 h]; Clapp, 0.57 ± 0.47 l/h/kg [0.03-1.79 l/h/kg]; Vdapp 0.61 ± 0.36 l/kg [0.28-1.65 l/kg]

Group B: Cmax, 769.2 ± 583.9 μg/l [87.7-2,248.0 μg/l]; tmax, 1.8 ± 1.1 h [0.88-4.02 h]; AUC0–∞, 2,581 ± 4,616 μg.l/h/l [342-20,447 μg.l/h/l]; t½, 1.2 ± 1.1 h [0.43-4.76 h]; Clapp, 0.71 ± 0.50 l/h/kg [0.08-1.76 l/h/kg]; Vdapp 0.9 ± 0.7 l/kg [0.22-3.57 l/kg]

No evidence was found for an influence of age on any of the kinetic parameters in either group.

Twenty-four hour intragastric pH-measurements were carried out to evaluate the antisecretory activity of lansoprazole:

- In group A i.e. after a single dose of lansoprazole, the percentage of time at pH < 4 and pH < 3 was respectively, (means ± SE) 61 ± 21% and 51 ± 21% over 24 hours, 55 ± 19% and 44 ± 18% over the first 12-hour period (midday to midnight) and 67 ± 28% and 57 ± 30% over the second 12-hour period (midnight to midday)
- In group B i.e. after 9-14 days treatment with lansoprazole, the percentage of time at pH < 4 and pH < 3 was respectively, (means ± SE) 47 ± 24% and 37 ± 21% over 24 hours, 36 ± 24% and 24 ± 19% over the first 12-hour period (midday to midnight) and 58 ± 28% and 49 ± 27% over the second 12-hour period (midnight to midday)

A significant correlation was found between age and intragastric pH parameters in both groups, with the antisecretory activity of lansoprazole appearing to be greater in the youngest children.

A significant correlation was found between intragastric pH parameters and 2 pharmacokinetic parameters, the antisecretory activity of the drug increasing with the Cmax and of AUC0–∞ of lansoprazole.

Two adverse events were reported:

- Diarrhoea, linked to a corona-like virus and not lansoprazole that appeared after 3 days treatment in a 5-month old boy who was receiving 13.5 mg/m² lansoprazole and no concomitant treatment.
- Iterative skin flushes, attributed to lansoprazole that appeared after 5 days treatment in an 8.5-year old girl who was receiving 17.7 mg/m² lansoprazole and no concomitant treatment.

Both adverse events led to withdrawal from the study and had a favourable outcome after stopping treatment.

ASAT, ALAT, creatine, prothrombin time and blood gastrin levels were measured for all the children in group B just before the start of treatment and at the end of treatment. Biological tolerance was good.

Fasting gastrin levels were measured at D0 and on the last day of treatment for 21 children from group B: the values rose from 78.7 pg/ml at D0 to 103.0 pg/ml at 12.6 ± 1.5 days (p < 0.01)