Pediatric patients have shorter lansoprazole half-life than previously reported

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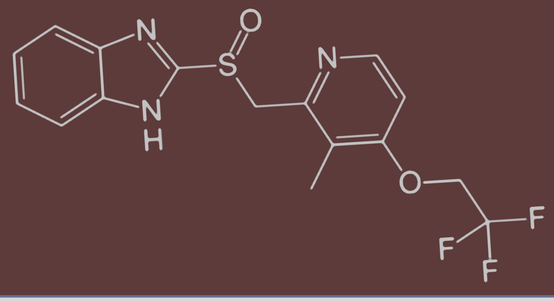

Background

The Proton pump inhibitor drugs are the medications of choice in managing gastric-acid related disorders due to their potency, safety, and ability to control acid production regardless of the source of stimulus. For these reasons, they have been used increasingly to treat reflux disease in pediatric as well as adult populations. PPIs have been used successfully in children not only to manage gastroesophageal problems, but also to manage extra-esophageal manifestations of reflux disease such as asthma, laryngitis, laryngomalacia, subglottic stenoses, sinusitis and otitis media. Omeprazole and lansoprazole are currently the only two PPIs approved by the FDA for use in children under 5 years of age, which is the group that is most likely to suffer from acid-related disorders. For children in this age group, the dose recommended by the package labeling for each drug is about half of what is recommended for adults.

Several studies have shown that the per-weight doses required to achieve healing in children are, contrary to the package insert's recommendation, higher than ranges typically required for adults. A recent large-scale retrospective observational study of off-label use of omeprazole or lansoprazole in infants less than a year old showed that doses of omeprazole and lansoprazole required to achieve 95% efficacy were 3.1 and 3.5 mg/kg/day, respectively. The package insert for commercial lansoprazole, meanwhile, recommends a 15mg daily dose for children under 30 kg (as little as 0.5 mg/kg/day) and a 30mg dose for children over 30 kg (at most 1.0 mg/kg/day).

Many pediatric pharmacokinetic studies have attributed this higher dose requirement to the finding that lansoprazole is eliminated from the bloodstream faster in young children than what has been previously reported for adults and studies of older children. In contrast to these observations, several investigators have concluded that there is no pharmacokinetic basis for the assertion that children require higher doses than adults and that no modifications of dosing regimens are necessary for children beyond weight-based adjustment of the standard adult dose; these conclusions directly contradict the findings of the aforementioned pediatric clinical studies. A significant concern in these conflicting results should be that failure to identify age-specific differences in PPI metabolism might result in treatment failures due to underdosing in pediatric patients.

Summary

The widespread underdosing of PPIs in children necessitates a reassessment of the effect of age on PPI disposition. In particular, this study investigates the relationship between age and the elimination half-life of lansoprazole by employing a regression analysis of data combined from several different pediatric and adult studies, including additional newly-collected pediatric data. These data provide further support for the conclusion that pediatric PPI pharmacokinetics are, in fact, different from adult pharmacokinetics and that dosing regimens should be adjusted accordingly.

Methods

- Based on a literature search, lansoprazole was chosen for further analysis because of the abundance of relevant pediatric pharmacokinetic data.
- Published data involving healthy patients were plotted on a graph of age (± SEM) vs. lansoprazole half-life (± SEM) (figure 1).
- Additional patient data was collected as follows for patients under 9 years of age:
  - > The patient was given a single dose of lansoprazole in caracream, a flavored sodium bicarbonate-based immediate-release suspension.
  - > Subsequent blood samples were taken for 5 hours and immediately centrifuged.
  - > Lansoprazole was extracted from the plasma and analyzed by HPLC.
  - > HPLC data was used to determine pharmacokinetic parameters.
- Lansoprazole half-life values from this new study were added to the age vs. half-life plot.

Results

- Mean half-lives from this clinical study were calculated:
  - 0.51 hr for patients aged 0.5 - 4.0 years (n = 3, SEM = .054)
  - 0.63 hr for patients aged 4.0 - 9.0 years (n = 2, SEM = .044)
  - Mean correlates closely with data published by Tran et al, but SEM is significantly lower.
- Previously-published studies were compared with one another and with this study; lansoprazole half-life trends can be summarized as follows:
  - t1/2 ≈ 0.6 hr for children of age 0.5 - 9 years.
  - t1/2 ≈ 0.8 hr for pre-adolescent children.
  - t1/2 ≈ 1.0 - 1.5 hr for young and middle-aged adults.
  - t1/2 ≈ 2.0 or higher in the elderly.
- The left panel of Figure 1 displays the trend when considering all previously-published arithmetic mean half-life values (± SEM) with respect to age (± SEM)
- The right panel of Figure 1 displays a similar trend when considering both arithmetic and harmonic mean half-life values for increased statistical power.

Discussion

-The evident trend suggests that age has a significant impact on PPI elimination.
-The youngest patients in the analysis eliminated the drug approximately three times as fast as the oldest patients.
-The lansoprazole package insert fails to establish a clear relationship across all age groups because of the large amount of variation that is often seen in the data. This is usually caused by one of four factors:

1. Genetic polymorphisms in Cytochrome P450 2C19 (CYP2C19), which is responsible for about 50% of lansoprazole metabolism. Certain genotypes are considered "poor metabolizers" and exhibit significantly higher plasma half-lives than normal individuals.
2. Immature hepatic function can lead to unusual pharmacokinetic measurements; this is typically a concern in patients under 6 months of age. Data from neonates and young infants, for this reason, were not considered in the meta-analysis.
3. Hepatic dysfunction can, for obvious reasons, also significantly affect drug clearance rates. Since any studies that included patients with hepatic dysfunction (or any other conditions that may affect clearance) are skewed, such studies were not considered.
4. The use of delayed-release PPIs, which are commercially available as enteric-coated drugs, can make the timing of blood draws more difficult because the exact time of complete drug release into the blood stream is unknown. Also, delayed-release drugs pose the problem of simultaneous uptake and metabolism; when drug metabolism starts before absorption is complete, measured half-life values will be impacted significantly.

-Since therapeutic success increases with the AUC of the plasma concentration vs. time curve, the trend found in this study explains the aforementioned finding that children require higher per-weight doses of PPIs. AUC is related to plasma half-life as follows:

$$AUC = (f)(Dose) \times (t_{1/2}) \times (V_d) / (0.693)$$

Where V_d is volume of distribution of the drug and the dose is corrected for bioavailability (f).

Conclusions

A trend was clearly evident with a reasonable variance. The difference between the youngest and the oldest patients is more than significant when considering the corresponding dosing requirements. Elderly patients eliminated the drug nearly four times slower than younger children, so the dosing requirements suggested in the lansoprazole package insert are clearly questionable. Physicians should immediately consider that, especially because of the high specificity (and consequent safety) of PPI drugs, pediatric doses should be increased in order to heal the disorders in question.