Stability of an extemporaneously prepared clopidogrel oral suspension

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Thrombotic disease is predominately recognized and studied in the adult population; until recently, the occurrence of pediatric thrombotic disease has been limited to patients with hereditary coagulation defects. An enhanced understanding of thrombotic risks in a variety of pediatric disorders, including Kawasaki disease, ischemic stroke, congenital defects with single-ventricle physiology, placement of intracardiac stents and devices, and the advancement of pediatric cardiac surgery, has increased the need for antithrombotic therapies in the pediatric population. Aspirin is routinely used as a first-line agent in the prevention of thrombotic events in these patients. However, aspirin only affects one of the pathways of platelet activation and is not always sufficient in preventing arterial clot formation.

Clopidogrel has marketing approval for the reduction of atherosclerotic events in adult patients with recent myocardial infarction or stroke, established peripheral arterial disease, or acute coronary syndrome. Clopidogrel is a prodrug that undergoes extensive metabolism by the liver; the active thiol metabolite works as an irreversible inhibitor at the P2Y_{12} adenosine diphosphate (ADP) receptor and ultimately inhibits platelet aggregation.

Purpose. The stability of an extemporaneously prepared clopidogrel oral suspension was studied.

Methods. Clopidogrel oral suspension (5 mg/mL) was prepared using clopidogrel bisulfate tablets, Ora-Plus, and Ora-Sweet. Six 2-oz samples were prepared; three were stored at room temperature and three under refrigeration. One milliliter was withdrawn from each sample, diluted to 10 mL with methanol, and exposed to high-frequency sound waves in a water bath to ensure complete dissolution of clopidogrel. A 300-μL sample was then withdrawn, diluted with mobile phase to an expected concentration of 15 μg/mL, and assayed in duplicate using high-performance liquid chromatography immediately after preparation and at 7, 14, 28, and 60 days. The stability of the clopidogrel suspension was determined by calculating the percentage of the initial concentration remaining on each test day. Stability was defined as retention of at least 90% of the initial concentration.

Results. At least 97% of the initial clopidogrel concentration remained throughout the 60-day study period, regardless of storage conditions. There were no detectable changes in color, odor, taste, or pH and no visible microbial growth in any sample. The preparation was palatable, with a slightly gritty consistency and a slightly bitter aftertaste; the bitterness intensified slightly between 28 and 60 days but remained fairly mild.

Conclusion. Extemporaneously compounded suspensions of clopidogrel, 5 mg/mL, in a 1:1 mixture of Ora-Plus and Ora-Sweet were stable for at least 60 days when stored in amber plastic bottles at room temperature and under refrigeration.

Index terms: Clopidogrel bisulfate; Chromatography, liquid; Compounding; Concentration; Dissolution; Platelet aggregation inhibitors; Stability; Storage; Suspensions; Taste; Temperature; Vehicles

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role for clopidogrel in this patient population. No prospective studies have been completed to address the efficacy of clopidogrel in pediatric patients at risk for arterial thrombotic events, although enrollment is currently ongoing for a Phase III placebo-controlled trial to determine the efficacy for prevention of shunt thrombosis in patients with cyanotic congenital heart disease.

Clopidogrel bisulfate tablets (75 mg and 300 mg) are the only commercially available dosage form, but pediatric patients are often not able to swallow tablets and may require doses not easily or accurately measured from splitting a tablet. In 2007, a dose-ranging study was performed in pediatric patients less than 24 months of age to determine the dose of clopidogrel that would achieve the same level of ADP-induced platelet aggregation inhibition as that seen in adult studies. In this dose-ranging study, clopidogrel powder, which is not commercially available, was provided by the manufacturer to allow individualized dosing for patients randomized to the treatment group. Clopidogrel is a treatment option for young infants; but to be applicable in practice, it will be necessary to have a drug formulation that allows for accurate oral dosing.

The objectives of this study were to prepare an extemporaneous clopidogrel suspension and determine the short-term chemical stability of the formulation over a 60-day period at room temperature and under refrigeration.

Methods

Sample preparation. An oral suspension of clopidogrel bisulfate 5 mg/mL (a concentration that allows an adequate volume of suspension for accurate measurement and easy ingestion) was prepared by thoroughly grinding four 75-mg clopidogrel bisulfate tablets, USP, in a glass mortar. Thirty milliliters of Ora-Plus and 30 mL of Ora-Sweet were added to the powder to make a final volume of 60 mL. Details of the procedure are provided in the appendix.

Six identical samples were prepared and placed in 2-oz amber plastic bottles with child-resistant caps. Three bottles were stored at room temperature (23–25 °C) and three bottles were stored under refrigeration (2–8 °C). A 1-mL volume was withdrawn from each of the six bottles with a micropipette immediately after preparation and at 7, 14, 28, and 60 days. Samples were diluted with methanol to 10 mL and then exposed to high-frequency sound waves in a water bath for 10 minutes to ensure clopidogrel dissolution. A 300-μL sample was further diluted with mobile phase to 10 mL (expected concentration, 15 μg/mL) and assayed in duplicate by high-performance liquid chromatography (HPLC).

HPLC method. A modification of the reverse-phase stability-indicating HPLC method described by Gandhimathi and Ravi was adapted for use. The instrumentation included a constant-flow solvent delivery system and a 5-μm particle column (150 mm × 3.9 mm). A variable-volume injector, an ultraviolet (UV) light detector set at 225 nm, and a recording integrator were also used. The mobile phase consisted of 0.1% triethylamine in water adjusted to pH 4 with dilute phosphoric acid and UV-grade acetonitrile (25:75, v/v) delivered at a flow rate of 1 mL/min.

The stability-indicating capability of the assay was reevaluated in the laboratory. Degradation of clopidogrel bisulfate was forced by preparing three separate samples; 1-mL volumes of 5-mg/mL suspension were mixed with three drops of 3% hydrogen peroxide, adjusted to pH 2 with 1 N hydrochloric acid or to pH 12 with 1 N sodium hydroxide, and stored at room temperature for 60 days. Samples were then heated to 90 °C for two hours. The pH was adjusted to 7, and the samples were diluted with methanol and mobile phase to an expected concentration of 15 μg/mL and assayed. Approximately 40% degradation was achieved with the hydrogen peroxide and basic solutions and 16% with the acidic solution. No interfering peaks were identified at three different wavelengths (225, 240, and 254 nm). The peak for clopidogrel appeared at 3.16 minutes, with small peaks for unknown degradation products at 1.7 and 2.9 minutes with the hydrogen peroxide at a wavelength of 225 nm.

Standard solutions and standard curve. A 750-μg/mL stock solution was prepared on each day of sample analysis by crushing one 75-mg tablet, dissolving it in 100 mL of methanol, and exposing it to high-frequency sound waves in a water bath for 10 minutes to ensure full dissolution of clopidogrel (analytical-grade powder was not available). Standard samples of clopidogrel were prepared by diluting the stock solution with mobile phase to expected concentrations of 7.5, 11.25, 15, 18.75, and 22.5 μg/mL. A standard curve was produced by linear regression of the peak heights of clopidogrel against clopidogrel concentration. The standard curve was linear (r2 > 0.999) over the working range of concentrations. A 15-μg/mL concentration of clopidogrel was assayed in duplicate approximately every 10th sample as an external control. The intraday and interday coefficients of variation for the clopidogrel assay were 1% and 5.6%, respectively.

Sample analysis. Each clopidogrel sample was gently shaken by hand for approximately 15 seconds immediately before assay. Ten microliters of each sample was injected into the HPLC system, and each sample was assayed in duplicate. Samples were evaluated for visual and pH...
changes on each day of analysis, as well as for changes in odor and taste at the beginning, middle, and end of analysis. Microbiological testing was not performed, since each commercial vehicle contained effective preservatives.

Data analysis. The stability of clopidogrel in an oral suspension at room temperature and with refrigeration was determined by calculating the percentage of the initial concentration remaining at each time interval. Stability was defined as retention of at least 90% of the initial concentration.

Results and discussion

At least 97% of the initial concentration of clopidogrel remained throughout the 60-day study period in all suspensions (Table 1). There was no detectable change in color, odor, or taste, and no visible microbial growth was observed in any sample. The preparation was a well-distributed suspension after gentle shaking. The preparation was palatable with a slightly gritty consistency and a slightly bitter aftertaste that remained for approximately 30 seconds; the bitterness intensified slightly between 28 and 60 days but remained fairly mild. No appreciable change in mean ± S.D. pH occurred in any of the samples, regardless of storage at room temperature (2.65 ± 0.09) or with refrigeration (2.65 ± 0.05).

The bioavailability of the clopidogrel formulations in the current study was not evaluated; however, the absorption and therapeutic effectiveness of a drug in a suspension compounded from crushed tablets are unlikely to differ appreciably from those of the original dosage form.

Conclusion

Extemporaneously compounded suspensions of clopidogrel 5 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet were stable for at least 60 days when stored in 2-oz amber plastic bottles at room temperature and under refrigeration.

<table>
<thead>
<tr>
<th>Suspension</th>
<th>Actual Initial Drug Concentration (mg/mL)</th>
<th>% Initial Concentration Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.97 ± 0.08</td>
<td>98.4 ± 1.1</td>
</tr>
<tr>
<td>B</td>
<td>5.04 ± 0.05</td>
<td>98.9 ± 1.9</td>
</tr>
</tbody>
</table>

1 A = clopidogrel, Ora-Plus, and Ora-Sweet stored at room temperature, B = clopidogrel, Ora-Plus, and Ora-Sweet stored under refrigeration.

Appendix—Procedure for compounding clopidogrel bisulfate suspension, 5 mg/mL

1. Triturate four 75-mg clopidogrel bisulfate tablets in a glass mortar to produce a fine powder.
2. Mix 30 mL of Ora-Plus with 30 mL of Ora-Sweet.
3. Levigate 30 mL of diluent into the clopidogrel powder via geometric dilution until a smooth suspension is formed.
4. Transfer the mixture into a 2-oz, child-resistant, amber plastic prescription bottle.
5. Rinse the contents of the mortar into the bottle with enough diluent to bring the final volume to 60 mL.
6. Label the bottle “Shake Well Before Use” with an expiration date of 60 days after preparation.