Therapeutic Equivalence of Mesalamine Products

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No bioequivalence studies have been conducted for mesalamine because of differences in formulation. Based on U.S. Food and Drug Administration definitions for bioequivalence, none of these drugs can be classified as bioequivalent or therapeutically equivalent. No adequate comparative trials have been conducted with equivalent mesalamine doses to determine if any of the current formulations are superior in the treatment of ulcerative colitis. All of these mesalamine formulations are effective, but they differ with regard to where the drug is released in the intestinal tract, which may influence the outcome in some patients. Therefore, the selection of a mesalamine agent should be based on the results of the clinical trials, individual patient response, compliance issues, and price, until comparative clinical trials are published. [Rev Gastroenterol Disord. 2004;4(1):25-28]

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Key words: Bioequivalence • Mesalamine • Pro-drugs • Therapeutic equivalence

Therapeutic substitution of pharmaceuticals is commonplace in some health care settings. This practice often occurs with the various 5-aminosalicylic acid products used in the treatment of ulcerative colitis (UC) and Crohn’s disease.
The generic name for 5-aminosalicylate (5-ASA) is mesalamine. Various pro-drugs (e.g., sulfasalazine, olsalazine, balsalazide) are also used to deliver mesalamine to the intestinal tract. The pharmacologic effectiveness of all of these mesalamine agents is based on the bioavailability or release of mesalamine from the administered dosage form.

This review will evaluate the bioequivalence of these various products and the factors that might influence a practitioner’s decision to authorize a request for therapeutic substitution of one of these products for another.

Bioequivalence Terminology
Bioavailability refers to the rate and extent that a drug is absorbed from its dosage form. This information is derived from data obtained by a series of blood samples taken after administration of the compound. The data are then used to calculate the peak plasma concentration (Cp_max), time-to-peak plasma concentrations, the area under the plasma concentration time curve (AUC), and other pharmacokinetic parameters for orally absorbed drugs.1–4

Reference product is the term generally applied to the first branded product within a class of drugs. But it can also refer to a new formulation of the compound in a different dosage form or using a different delivery system that is considered the testing standard for a particular drug.1–4 In the case of mesalamine, each of the current formulations is classified as a reference product, with the exception of sulfasalazine.1

Bioequivalence refers to the comparison of the bioavailability of different drug products using the same type of dosage form (e.g., tablet vs tablet, sustained-release tablet vs sustained-release tablet, capsule vs capsule). One of these products is arbitrarily classified as the reference product and the other is considered the comparator product. This means that tablets cannot be bioequivalent to capsules and sustained-release dosage forms can only be compared to other sustained-release dosage forms using the same delivery system.1–4 No mesalamine products are recognized as bioequivalent due to the differences in the various formulations. The only mesalamine-like compound for which bioequivalence data exists is sulfasalazine.1

In order to be assured that a switch from one product formulation to another is without potential clinical consequence, the products must be bioequivalent and the individual bioequivalence should be the same. This type of situation requires that the products also have therapeutic equivalence. In order for the products to be considered therapeutically equivalent, they must be pharmacologically equivalent, bioequivalent, have the same clinical effect and safety profile when administered to patients under conditions specified in the labeling, and have consistent in vitro quality control from lot to lot.1–4

Bioequivalence of Mesalamine Products
The U.S. Food and Drug Administration guideline for bioequivalence requires that a number of parameters be in place for two drugs to be considered bioequivalent. For example, the differences in the means of the AUC and the Cp_max must be within −20% and +25%.2,3 Currently, none of these guidelines applies to the mesalamine formulations or their pro-drugs because they are marketed in different dosage forms (capsules vs tablets). None of the mesalamine products or pro-drugs is classified as narrow therapeutic index medication; therefore, small differences in the plasma concentration or the bioavailability of a particular mesalamine product should not produce big changes in its

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Site of Absorption for Various Mesalamine Products and Pro-Drugs</th>
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<tbody>
<tr>
<td><strong>Generic Name</strong></td>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Colazal</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Asacol</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Pentasa</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Dipentum</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Azulfidine, azulfidine EN-tabs</td>
</tr>
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Data from Wickersham7 and Sandborn.12
safety or effectiveness. However, these products do differ in their release characteristics, which demonstrates why one formulation may be more effective for some patients and less effective for others (Table 1). In addition, traditional bioequivalence studies may be of limited value with these compounds. What is not clear with mesalamine therapy is whether the majority of its activity is based on systemic absorption or its effects within the intestinal tract. If the latter effect is the most important determinant of efficacy, then all traditional bioequivalence studies will be of limited value since they are based on absorption and the measure of plasma concentrations, not on topical effects at the site of action.

Examples of the mesalamine formulations are Pentasa (mesalamine capsule, extended release, Shire Laboratories), Asacol (mesalamine tablet, delayed release, Proctor & Gamble), Canasa (mesalamine suppository, Axcan Scandipharm), and Rowasa (mesalamine enema, Solvay Pharmaceuticals, Inc.). Because all of these formulations use different delivery systems (ie, capsules, tablets, suppositories, and enema), none can be considered bioequivalent.

Some of the products are designed to release the mesalamine throughout the intestinal tract (Pentasa). Others (Asacol) are designed to release the mesalamine in the intestinal tract below the terminal ileum, which alters their ability to be considered therapeutically equivalent agents. The mesalamine capsules are coated with ethylcellulose. The ethylcellulose coating produces a controlled-release formulation that is designed to release mesalamine throughout the gastrointestinal tract.

The mesalamine tablets are coated with an acrylic-based resin. This resin coating is designed to delay the release of mesalamine until it reaches the terminal ileum. This may explain why this product’s absorption is unaffected by administration with food, and why the time to reach maximum plasma concentration is 4 to 12 hours.

Various pro-drugs of mesalamine are designed to release the mesalamine in the colon. Balsalazide is designed to be delivered to the colon where it is cleaved by bacteria in an azoreduction reaction. This azoreduction causes the release of equimolar quantities of mesalamine. Less than 1% of an oral dose is recovered as parent compound, 5-aminosalicylic acid, in the urine of healthy subjects. Olsalazine is bioconverted into two molecules of mesalamine by colonic bacteria. Serum concentrations of mesalamine are detected after 4 to 8 hours and urinary recovery is less than 1%.

Sulfasalazine, the oldest of the mesalamine pro-drugs, is metabolized by intestinal bacteria to mesalamine and sulfapyridine, an inactive metabolite, in the intestine. Peak plasma concentrations of mesalamine occur approximately 10 hours after oral dosing, but the majority of the drug actually stays within the colonic lumen.

A recent systematic review of the pharmacokinetic studies of the oral mesalamine products concluded that the various formulations of mesalamine and its pro-drugs produce comparable ranges of systemic absorption of mesalamine. Similar reviews of the efficacy studies have concluded that all of the mesalamine compounds are effective. Insufficient data is available to determine if any one of these formulations is superior due to differences in the formulations, doses, and dosing schedules used in the clinical trials.

Main Points
- There is a lack of bioequivalence or therapeutic equivalence studies with mesalamine because it is made in a variety of formulations.
- A recent systematic review of the pharmacokinetic studies of the oral mesalamine products concluded that the various formulations of mesalamine and its pro-drugs produce comparable ranges of systemic absorption of mesalamine.
- A decision pertaining to the comparability of these agents should not be based on pharmacokinetic differences, but instead on the safety and efficacy information derived from controlled clinical studies using similar doses and dosing schedules.
ative trials with equivalent doses using the commercial formulation are not available for most of these agents. Thus, the choice of agent should be based on individual response, compliance, dosing regimens, performance for particular dosage forms (eg, tablet vs capsule), and price.

**Conclusion**

No pharmacokinetic equivalency studies of mesalamine compounds have been conducted because—due to the various formulations—none of these drugs can be classified as bioequivalent. Because no adequate comparative trials have been conducted with equivalent mesalamine doses to determine if any of the current formulations are superior in the treatment of UC, therapeutic equivalency data is not available for the various mesalamine formulations.

All of these mesalamine formulations are effective in the treatment of UC, but differ with regard to where the drug is released in the intestinal tract. This may influence the outcome in some patients. Thus, until comparative clinical trials are published, the selection of a mesalamine agent should be based on response data from clinical trials, individual patient response, compliance issues, and price.

**Note:** The author has no association with, nor has he received any financial assistance from, any of the manufacturers of mesalamine or its pro-drugs.

**References**