Evaluation of Effects of Altered Gastric pH on Absorption of Dapsone in Healthy Volunteers

GAIL A. BREEN,1 JOSEPH M. BROCAVICH,1,2* JOSEPH V. ETZEL,1,2 VIJAY SHAH,3 PETER SCHAEPER,4 AND SUSAN FORLENZA3

Departments of Pharmacy,1 Medicine,2 and Surgery,4 Nassau County Medical Center, East Meadow, and The College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, 2 New York

Received 17 November 1993/Returned for modification 12 February 1994/Accepted 19 June 1994

A prospective, randomized, crossover study was performed with seven healthy volunteers to address the effect of increased gastric pH on dapsone absorption. Subjects were randomized to receive a single 100-mg dose of dapsone or a single 100-mg dose of dapsone in addition to 30 ml of a high potency antacid 1 h before dapsone administration and hourly thereafter for a total of 10 doses. Dapsone concentrations in serum were measured periodically for 48 h. No statistical differences between the two regimens were noted when mean dapsone maximal initial concentrations, times to peak, and areas under the curve were compared. These data suggest that an increase in gastric pH has little or no effect on the absorption of dapsone in healthy subjects.

Dapsone is frequently employed in the prophylaxis and treatment of Pneumocystis carinii pneumonia in patients infected with human immunodeficiency virus (4, 13). Metroka et al. reported that dapsone's efficacy was significantly reduced in patients who received concomitant didanosine therapy. The mechanism postulated for this interaction was that the buffering agents in didanosine elevated gastric pH, resulting in decreased dapsone absorption (12). This hypothesis was based on in vitro findings that have shown dapsone to be insoluble in a neutral pH environment and completely soluble in an acidic environment (17). Since this report, the effect of increased gastric pH on dapsone absorption has been debated (7, 8).

The speculation that dapsone may require an acidic environment for absorption is potentially significant, especially in AIDS patients, since chlorhydria has been described in this population (9-11). However, clinical studies to evaluate the absorption characteristics of dapsone in the presence of elevated gastric pH have not yet been performed. As such, this prospective, crossover study was performed with healthy volunteers to evaluate the effect of increased gastric pH via concomitant antacid administration on dapsone absorption.

The study protocol was approved by the Institutional Review Boards at Nassau County Medical Center and St. John's University. Healthy volunteers over 18 years old were enrolled after giving informed written consent. The study subjects underwent an initial physical exam as well as a routine serum chemistry work-up which included routine laboratory monitoring. Additionally, their glucose-6-phosphate dehydrogenase level was evaluated. Human chorionic gonadotropin levels in blood and urine were evaluated prior to the first and second stages of study for all female subjects. Subjects were excluded from the study if they (i) were taking any scheduled medications; (ii) had an estimated creatinine clearance of less than 30 ml/min as determined by the equation of Cockcroft and Gault (5); (iii) had liver impairment, which was defined biochemically by liver function test results reported to be greater than two times higher than laboratory normal values or by a history of end-stage liver disease and/or cirrhosis; (iv) had a known adverse reaction to dapsone; (v) were found to be glucose-6-phosphate dehydrogenase deficient; (vi) were found to be pregnant; (vii) were on any medication which might alter gastric pH; or (viii) had any underlying disease states which might alter gastric pH.

The study was designed as a prospective, open-label, crossover trial. All subjects were randomized by the use of a table of random numbers to receive either treatment A (dapsone alone) or treatment B (dapsone with antacids). The second phase of the study occurred after a 1-month wash-out period. With treatment A, individuals received a single 100-mg dose of dapsone (Jacobus Pharmaceutical, Princeton, N.J.) orally after an overnight fast. Before dapsone administration, a venous catheter was placed in an antecubital vein and flushed with 3 ml of sterile normal saline. After the first 3 ml of blood was drawn and discharged, 5 ml of blood was collected and centrifuged for 20 min. Following each blood draw, the venous catheter was flushed with 3 ml of sterile normal saline. Blood samples were taken before administration of the drug and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 h postadministration. Study subjects were fed a standardized meal 8 h after dapsone administration.

For treatment B, individuals received 100 mg of dapsone orally following an overnight fast in addition to 30 ml of a high-potency antacid (Mylanta II; Johnson & Johnson, Skillman, N.J.) 1 h before drug administration, at time zero, and every hour for 8 h following dapsone administration. Blood samples were obtained by the same technique and at the same times as those for treatment A.

For both treatments A and B, gastric pH was measured by a rapid gastric string test (Gastro-Test; HDC Corporation, San Jose, Calif.) at 0, 4, and 6 h post-dapsone ingestion.

The quantification of dapsone and monoacetyldapsone (MADDS) in plasma was accomplished by high-performance liquid chromatography (HPLC) according to the method described by Carr and associates (3). A Waters Associates HPLC was employed for all assays. The assay sensitivity ranged from 0.1 to 5 μg/ml. The coefficient of variation for dapsone and MADDS between runs was 1.25%.

Dapsone (lot 2810), MADDS (lot 2811), and monopropionydapsone (lot 2813) were obtained from Jacobus Pharmaceuticals for analytical purposes.

Initial peak serum dapsone concentrations following absorp-
tion prior to presumed enterohepatic recirculation ($C_{\text{initial}}$), the corresponding times at which these concentrations occurred, and the areas under the plasma concentration-time curve (AUCs) were compared. These initial maximal concentrations and corresponding times were determined graphically and visually with a plot of concentration versus time. AUCs for dapsone and MADDS were calculated by using the trapezoidal rule. Each AUC was calculated from time zero to infinity. The paired Student $t$ test was utilized to make comparisons between the two phases of the study (with and without antacids) with regard to dapsone AUCs, $C_{\text{initial}}$ values, times to maximal concentration ($T_{\text{max}}$), and the gastric pH of the subjects. A $P$ value of less than 0.05 was considered statistically significant.

Nine study subjects (six females and three males) were enrolled in the study after the screening for eligibility requirements. However, two subjects (both females) withdrew prior to completion of the study. The mean age of the subjects was 26 ± 3 years and their mean actual body weight was 67 ± 28 kg (range, 52 to 134 kg).

Individual subjects’ dapsone pharmacokinetic parameters with and without antacids are listed in Table 1. Table 2 lists the mean gastric pH values at 0, 4, and 6 h for both groups. Figure 1 depicts the mean dapsone concentrations versus time curve obtained from our study subjects.

The mean gastric pH without antacid administration was 2.3 ± 0.8, and when antacids were administered it was 5.9 ± 1.1 ($P < 0.01$). At no time during the antacid-dapsone arm of the study did gastric pH fall below 4.5 for any of the subjects.

The mean AUC when dapsone was administered alone was 65.15 ± 34.30 mg · h/liter, and when dapsone was administered with antacids the mean AUC was 61.04 ± 24.94 mg · h/liter. These values were not statistically different ($P > 0.5$). For three subjects, concentrations following presumed enterohepatic recirculation reached higher levels than those achieved immediately following absorption. For this reason, maximum concentrations in serum and $T_{\text{max}}$ were not measured directly; rather, the $C_{\text{initial}}$ values and the corresponding $T_{\text{max}}$ values immediately following absorption were compared. The mean $C_{\text{initial}}$ measured following dapsone administration alone was 1.82 ± 0.48 mg/ml, and when antacids were administered, the mean was 1.74 ± 0.44 mg/ml ($P > 0.2$). The mean corresponding times at which these concentrations were achieved were 2.1 ± 1.2 h for dapsone alone and 2.3 ± 0.8 h when antacids were administered ($P > 0.6$).

The mean AUC for dapsone's metabolite, MADDS, when dapsone was given alone was 24.96 ± 17.64 mg · h/liter, and when dapsone was given with antacids, the mean was 23.32 ± 17.52 mg · h/liter ($P > 0.05$).

The results of this study suggest that the absorption of dapsone is not significantly altered when the gastric pH is

### Table 2. Mean gastric pH values with and without antacids

<table>
<thead>
<tr>
<th>Postdose time (h)</th>
<th>pH (mean ± SD) for treatment:</th>
<th>With antacids</th>
<th>Without antacids</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.6 ± 1.1</td>
<td>2.3 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.9 ± 1.2</td>
<td>2.4 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6.1 ± 1.1</td>
<td>2.2 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.9 ± 1.1</td>
<td>2.3 ± 0.8 **</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4–7</td>
<td>1–3.5</td>
<td></td>
</tr>
</tbody>
</table>

*Time 0 indicates the measurement taken immediately preceding dapsone administration.

**$P < 0.01$.

![Dapsone Plasma Concentration (mg/L)](image_url)

**FIG. 1.** Mean dapsone concentrations in plasma versus time. □, without antacids; Δ, with antacids.
increased by the continuous administration of antacids. In addition, the mean AUC values for dapsone reported in this study are comparable with those reported in other pharmacokinetic studies following a single oral 100-mg dose (2, 6, 16).

Previous pharmacokinetic studies have shown that dapsone undergoes enterohepatic recirculation (14, 15). In three subjects, concentrations following presumed enterohepatic recirculation reached higher levels than those achieved following initial absorption. Though the mechanism is unclear, this phenomenon may have occurred as a result of enterohepatic recirculation superimposed on delayed absorption of the drug. This phenomenon occurred both when dapsone was administered alone and when it was given with antacids; thus, it does not appear to be a result of antacid administration.

The C_{initial} values and the corresponding times at which these concentrations were measured were not found to be statistically different. These values correlated with those reported in previous dapsone pharmacokinetic studies following a single 100-mg dose (2, 6, 16).

The gastric pH of all subjects was measured in both phases of the study. When the subjects received antacids, their gastric pH was higher than when they did not receive antacids. As anticipated, the two groups were statistically different when gastric pH values were compared (P < 0.01). On the basis of these data, it appears that dapsone absorption in this population of healthy volunteers was not statistically altered by elevated gastric pH.

Prior to Metroka and colleagues implicating didanosine’s buffers as decreasing dapsone bioavailability, no drug interactions with this agent during absorption were reported; rather, effects of other drugs on dapsone elimination and protein binding have been established (1). Because gastric pH was not found to have an effect on the absorption of dapsone, it could theoretically be extrapolated that other drugs which increase gastric pH, such as didanosine, H2 antagonists, and omeprazole, also do not alter the absorption of dapsone. However, other possible mechanisms of interaction need to be considered.

Extrapolation of this study’s results to patients with human immunodeficiency virus is difficult. Since up to 20% of this population may suffer from achlorhydria, these data suggest that dapsone is adequately absorbed for use in the prophylaxis of P. carinii pneumonia. However, other mechanisms besides alterations in gastric pH (e.g., altered gastric transit time or the effects of concomitant gastric lesions) that can alter the bioavailability of this agent may exist. Further study in a human immunodeficiency virus-infected population with elevated gastric pH is warranted to ultimately address this dilemma.

This study was supported in part by Jacobus Pharmaceuticals, which provided the dapsone, MADDS, internal standard, and Gastro-Test capsules, and by Johnson & Johnson, Inc., which provided the antacid.

REFERENCES


