

**DRUG DISPOSITION & PHARMACOKINETICS**

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# The Effect of Food on the Absorption of Oral Ziprasidone

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**ABSTRACT** ~ Oral ziprasidone bioavailability is increased when taken with food. Here we describe two pharmacokinetic studies to quantify the impact of food on ziprasidone absorption in healthy volunteers. The first, an open-label, six-way crossover study, investigated ziprasidone absorption in eight healthy men. Subjects received oral ziprasidone (20, 40, and 80 mg) after an 8-hour fast or immediately following a US Food and Drug Administration standard meal (50% fat). In this study, area under the serum concentration-time curve (AUC) was greater in fed than in fasting states at each dose (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). Under fasting conditions, increases in AUC and maximum drug concentration ( $C_{max}$ ) were less than dose-proportional; under fed conditions, they were dose-proportional. The second, an open-label, randomized, three-way crossover study, explored the impact of dietary fat on ziprasidone absorption in 14 healthy subjects. Subjects received ziprasidone (40 mg) under three conditions: fasting, with a high-fat meal (60% fat), and with a moderate-fat (30% fat) meal. AUC and  $C_{max}$  under fed conditions increased by 104% and 84% (60%-fat meal) and 79% and 98% (30%-fat meal), respectively, relative to the fasting state. There was no clear difference in ziprasidone bioavailability between the fed groups, suggesting that meal fat content is not a major determinant of bioavailability. Less pharmacokinetic variability was observed in the fed state, suggesting more consistent absorption of ziprasidone. These results demonstrate that administration of ziprasidone with food is crucial to ensure optimal, reliable dose-dependent bioavailability and thus predictable symptom control and tolerability. *Psychopharmacology Bulletin*. 2007;40(3):58-68.

## INTRODUCTION

Food, particularly the fat content of meals, influences the absorption of many orally administered drugs.<sup>1</sup> For many lipophilic drugs, absorption is enhanced when taken with food.

Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2-*H*-indol-2-one) is a widely used atypical antipsychotic indicated for the treatment of schizophrenia<sup>2</sup> and bipolar disorder.<sup>3</sup> It is a highly lipophilic compound, and this property impacts its absorption profile with respect to food.

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The prescribing information for ziprasidone specifies that the capsules should be taken with food.<sup>4</sup>

Previous pharmacokinetic studies have shown that under fasting conditions, oral doses of ziprasidone (0.5–40 mg) resulted in approximately dose-proportional increases in mean maximum observed serum concentration ( $C_{\max}$ ) and mean area under the serum concentration–time curve from time 0–12 hours ( $AUC$ )<sub>0–12</sub>. Under these fasting conditions, this dose proportionality was lost at higher doses, although there was evidence of some increase in overall exposure. When the dose of ziprasidone was taken after food, dose proportionality was seen in the dose range between 20 and 60 mg.<sup>5</sup> A further study showed that the administration of a single 20-mg dose of ziprasidone in the fed state produced total AUC ( $AUC$ )<sub>0–∞</sub> and  $C_{\max}$  values 69% and 67% greater, respectively, than values in the fasting state, and that taking ziprasidone 2 hours after a meal reduced drug absorption compared with taking it with food.<sup>6</sup>

The aims of the pharmacokinetic studies described here were to extend previous investigations of the effect of food and, specifically, to quantify the impact of the fat content of food on ziprasidone absorption, and to evaluate the pharmacokinetic linearity and dynamics of drug absorption in relation to fed and fasting conditions at drug doses above 40 mg.

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