Caffeine Metabolism

Disposition in Liver Disease and Hepatic-Function Testing

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Introduction

Caffeine is probably the most commonly consumed drug in the world. Caffeine is 1,3,7-trimethylxanthine (137X) and is metabolized by N-de-methylation to dimethylxanthines (Fig. 1). All these compounds are pharmacologically active. This chapter will describe the metabolism of caffeine and the changes in caffeine metabolism that occur in people with liver disease. We will also examine the use of caffeine to assess cytochrome P-450 function, acetylator status, and liver function in general.

Metabolism

Oral absorption of caffeine is rapid and complete. Only a small fraction (1–4%) of caffeine is excreted unchanged in the urine. Caffeine is extensively metabolized by the liver. Evidence to support hepatic metabolism includes in vitro studies demonstrating biotransformation of caffeine by human liver microsomes, observations of impaired clearance of caffeine in people with liver disease, and the well-known effects of induc-
ers and inhibitors of hepatic microsomal enzymes on caffeine metabolism.\textsuperscript{17-19} Since caffeine is completely bioavailable, the extent of extraction from the blood in each pass through the liver must be low (i.e., a low-extraction drug). Caffeine is bound to plasma proteins (presumably albumin) with binding reported to range from 10 to 35\%.\textsuperscript{1,20,21}

Table 1 lists the pharmacokinetic parameters of caffeine from nine studies in healthy subjects given single doses of caffeine.\textsuperscript{6,10,13,15,22-26} There is a wide interindividual variation in clearance with values ranging almost ninefold. Although some of this variation is attributable to the influence of cigarette smoking on caffeine metabolism, studies in nonsmokers showed a three- or fourfold difference.

The known metabolic pathways of caffeine in humans are illustrated in Fig. 2. The major routes of metabolism are indicated by the heavy arrows. Details of the discovery of these metabolic pathways have been reviewed by Arnaud.\textsuperscript{27} The primary and major pathway for the metabolism of caffeine is $N_3$-demethylation to paraxanthine (17X).\textsuperscript{5} About 80\% of caffeine is metabolized via 17X. Approximately 10\% of caffeine is $N_1$-demethylated to theobromine (37X) and 4\% is $N_7$-demethylated to theophylline.\textsuperscript{28} These dimethylxanthenes undergo further $N$-demethylation to