concentration of free drug ranging between 2 and 6 μg/ml after 8–10 days of therapy (Zuidema *et al.,* 1986). A dose of 2 mg/kg daily or 4 mg/kg weekly in children achieves concentrations similar to those in adults receiving 100 mg daily (Mirochnick *et al.,* 1999).

Dapsone's pharmacokinetic parameters do not appear to be appreciably altered in patients with *falciparum* malaria (Simpson *et al.,* 2006), adults with advanced HIV infection (Falloon *et al.,* 1994), or children with HIV infection (Mirochnick *et al.,* 1999). Acetylator status does not affect the half-life or efficacy of the drug (Peters *et al.,* 1975; Crook *et al.,* 1983); however, it may be correlated with the development of adverse effects (Bluhm *et al.,* 1999).

5b. Drug distribution

Dapsone is widely distributed throughout all tissues and, in particular is concentrated in the skin, muscle, liver, and kidney. It crosses the blood–brain barrier and is also excreted in breast milk (Edstein *et al.,* 1986; Pieters and Zuidema, 1986; Gatti *et al.,* 1997).

Dapsone penetrates the central nervous system, achieving levels between 0.3 and 1.61 μg/ml (Rich and Mirochnick, 1996).

Dapsone gel 5%, when topically applied twice daily for acne, is systemically absorbed and reaches a steady state plasma level after 2 weeks. Mean plasma concentrations ranged from 7.5 to 11 ng/ml over 12 months. The authors estimated that systemic exposure was over 100-fold less than that of oral dapsone at a standard dosage (Thiboutot *et al.,* 2007).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Correlation between the pharmacokinetic and pharmacodynamic parameters of dapsone and its clinical efficacy have not been assessed in detail.

5d. Excretion

Once absorbed, dapsone is rapidly acetylated in the liver into the nontoxic monoacetyl and diacetyl forms, and steady state equilibrium among the three forms ensues. It is also *N*-hydroxylated by a number of hepatic microsomal cytochrome P-450 enzymes, producing the hydroxylamine metabolite, which is the likely cause of the toxic side effect of methemoglobinemia (see section 6, Adverse Reactions and Toxicity) (Mitra *et al.,* 1995; Winter *et al.,* 2000). The level of expression of these enzymes appears to be under genetic control and may explain the variability in individual susceptibility to the development of this side-effect (Gill *et al.,* 1995).

Dapsone is excreted in the bile but undergoes enterohepatic circulation, which is substantially interrupted by the administration of activated charcoal, markedly decreasing the drug's elimination half-life (Neuvonen *et al.,* 1980). This feature is useful in the overdose situation. Ultimately, the majority of the drug is excreted by the kidneys after glucuronidation by the glucuronosyl transferases UGT1A4 and UGT1A9, with about 10% excreted in the bile (Ellard, 1966; Green and Tephly, 1998).

5e. Drug interactions

Renal excretion of dapsone is blocked by probenecid, resulting in a corresponding increase in serum dapsone levels, and consequent increase in adverse effects (Goodwin and Sparell, 1969). Rifampicin increases the metabolism of dapsone, reducing serum levels and potentially affecting its antimicrobial effects in all but Hansen's disease (Gelber and Rees, 1975).

Clofazimine does not appear to have an effect on the pharmacokinetics of dapsone, despite there being some initial suspicion of increased hepatotoxicity (Venkatesan *et al.,* 1986). Trimethoprim increases levels of dapsone by 40% when administered simultaneously in patients with AIDS (Lee *et al.,* 1989). Dapsone simultaneously increased trimethoprim levels as well, increasing the rate of toxic side effects of both drugs.

Disulfiram has been used experimentally to determine the relative roles of cytochrome P-450 enzymes in the metabolism of dapsone; however, its overall effect has not yet been fully elucidated (Frye and Branch, 2002).

Drugs such as erythromycin, omeprazole, and ketoconazole inhibit cytochrome CYP3A, potentially decreasing the production of the hydroxylamine and its consequent toxicity. On the other hand, glucocorticoids, carbamazepine, and phenytoin induce the P-450 enzymes, with the potential of increasing the production of the hydroxylamine and its consequent toxicity. Interactions with these drugs are subject to such significant inter-individual variation that the interactions may or may not have a strong influence on the efficacy and toxicity of dapsone in any particular individual case (Zhu and Stiller, 2001).

Cimetidine, a potent inhibitor of cytochrome P-450, has been investigated for its potential to reduce the side effects and also potentially increase the efficacy of dapsone in inflammatory disorders such as dermatitis herpetiformis, in which patients often experience dose-limiting toxicity. Cimetidine was administered to seven volunteers who also took 100 mg of dapsone daily in a crossover study. In the presence of cimetidine, the area under the concentration-time curve (AUC) of dapsone was increased by almost 30%, and peak methemoglobin levels fell by more than half. The percentage of dapsone excreted in the urine as dapsone hydroxylamine glucuronide was reduced by one third (Coleman *et al.,* 1990). In a 6-week study of patients with dermatitis herpetiformis who received a wide range of dapsone dosages, methemoglobin levels fell by 27% after commencement of cimetidine 400 mg thrice daily. Four of six patients reported a significant reduction in side effects (Coleman *et al.,* 1992).

Interactions with a number of antiretroviral drugs have been predicted or reported. Amprenavir is metabolized by