possible that variations in artesunate C_{max} could influence clinical response and overall cure rate (Ashley *et al.,* 2014). (See Chapter 169, Artemisinins.)

5d. Excretion

Although a number of metabolites of pyronaridine can be generated (including by CYP1A2, CYP2D6, and CYP3A4) and identified *in vitro* and *in vivo,* most of the drug is excreted from the body unchanged, and it seems unlikely that any active metabolites are of clinical significance (Ni *et al.,* 1982). Human volunteer studies have corroborated previous radiolabeling studies from animals, demonstrating that 47.3% of a given oral pyronaridine dose is excreted in the feces and 23.7% in urine over 86 days, with much of the remainder likely to remain in the body and be subject to ongoing slow elimination (Morris *et al.,* 2015).

The terminal elimination half-life of pyronaridine has been estimated at 14–18 days in adults with malaria treated with pyronaridine–artesunate (Methaneethorn *et al.,* 2011), and is therefore broadly similar to that in drugs such as piperaquine, mefloquine, and naphthoquine (Batty *et al.,* 2012; Karunajeewa *et al.,* 2008; Simpson *et al.,* 1999). However, because the decay in drug levels throughout the drug's long elimination phase may not be log linear, the half-life that is derived from sampling data may depend on the duration of the sampling schedule and the sensitivity of the assays used, with longer sampling schedules and high-sensitivity assays generating higher estimates of half-life. Therefore, earlier studies using less sensitive assay technology and shorter follow-up calculated much shorter elimination half-lives that probably failed to adequately describe the drug's elimination kinetics (Croft *et al.,* 2012). Pharmacokinetic studies in African children suggested a somewhat more rapid elimination of pyronaridine in children, with an estimated terminal elimination half-life of 9.6 days (Ramharter *et al.,* 2008).

Artesunate is extremely rapidly metabolized to a principal active metabolite, dihydroartemisinin (plasma half-life estimated at < 5 minutes) (Batty *et al.,* 1998). Dihydroartemisinin is also itself rapidly cleared (estimated half-life < 1 hour) (see Chapter 172, Dihydroartemisinin–piperaquine). This rapid elimination profile demonstrated in earlier studies of artesunate monotherapy does not seem to be altered when it is co-administered with pyronaridine (Shin Poong Pharmaceutical Company, 2015).

5e. Drug interactions

Studies of *in vitro* interactions between pyronaridine and a range of other anti-malarials (including antifolates, 4-aminoquinolines, and amino-alcohols) have shown synergism or additive effects, no interaction, or weak antagonism (Croft *et al.,* 2012). However, in practice, it is unlikely that pyronaridine–artesunate will be co-administered with any of these drugs. A number of *in vitro* studies have also examined interactions between the two components of pyronaridine–artesunate, also with conflicting results that range from synergism to weak antagonism between either artesunate or dihydroartemisinin and pyronaridine (Davis *et al.,* 2006; Gupta *et al.,* 2002; Ringwald *et al.,* 1999a). These differences are likely due to methodologic differences, and studies in *P. berghei* rodent malaria models (Peters and Robinson, 1997; Vivas *et al.,* 2008) have suggested that if anything, the relationship is likely to be synergistic *in vivo,* consistent with the demonstrated efficacy of the combination in clinical studies (Bukirwa *et al.,* 2014).

It is possible that pyronaridine–artesunate will be used either simultaneously or sequentially with 8-aminoquinoline drugs (primaquine and tafenoquine) for radical cure of *P. vivax* infections. One study showed a synergistic effect between pyronaridine and primaquine on blood stage parasites *in vitro* (Ringwald *et al.,* 1999b). A pharmacokinetic interaction study using a crossover methodology in healthy Thai volunteers did not demonstrate any differences in pyronaridine, artesunate, or dihydroartemisinin exposures when pyronaridine–artesunate was co-administered with primaquine (Jittamala *et al.,* 2015). However, co-administration resulted in significantly higher primaquine C_{max} (by 30%) and AUCs (by 15%) compared with primaquine given alone. Nonetheless, primaquine's hypnozoiticidal activity and dose-dependent toxicity are probably primarily dependent on short-lived active metabolites that are difficult to measure in practice. Therefore it is not clear how these moderate increases in observed concentration of the prodrug primaquine translate to actual exposure to its biologically active metabolic products. Given the importance of adjunctive hypnozoiticidal therapy to malaria control in *P. vivax*–endemic settings (Robinson *et al.,* 2015), this is a potentially important issue. However, reassuringly, one recent clinical trial demonstrated good radical cure efficacy when pyronaridine–artesunate schizonticidal treatment was used concurrently with primaquine hypnozoiticidal therapy in 60 Indonesian adults with *P. vivax* (Nelwan *et al.,* 2015). Current manufacturer recommendations are that pyronaridine–artesunate can be co-administered with primaquine (Shin Poong Pharmaceutical Company, 2015).

Pyronaridine inhibits cytochrome P-450 2D6 *in vitro* (Shin Poong Pharmaceutical Company, 2015). Therefore it may lead to an increase in exposure to a number of drugs that are CYP2D6 substrates, including tricyclic antidepressants, serotonin reuptake inhibitors, neuroleptics, codeine, beta-blockers, and antiarrhythmics. Particular caution is recommended with metoprolol (pyronaridine–artesunate has been shown to increase metoprolol C_{max} by 50%) (Morris *et al.,* 2014) and the antiarrhythmics flecainide and propafenone (Shin Poong Pharmaceutical Company, 2015). Pyronaridine also shows *in vitro* inhibition of P-glycoprotein (P-gp) and therefore may necessitate therapeutic monitoring of digoxin and dabigatran concentrations (Shin Poong Pharmaceutical Company, 2015).

Dihydroartemesinin is a weak inhibitor of CYP1A2 and therefore may have mild, short-lived effects on drugs such as