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Artemisinin derivatives with long elimination half-life

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Dear Sir or Madam,

A recent article by Bigucci et al (2008) in this Journal describes the absorption of fluoroalkyl derivatives of dihydroartemisinin. Hereby, I would like to make a few comments on the general thoughts behind the development of these compounds and why, in my opinion, such compounds might create more problems than they solve.

Artemisinin and its derivatives have short elimination half-lives (1–2 h) after oral or intravenous administration. The short half-life is believed to be the main reason for rather high recrudescence rates observed 4 weeks after the end of the 5-day monotherapy regimens (Meshnick et al 1996), as there are no drug molecules present for a long enough time to kill all the parasites. The relation between the life-cycle of malaria parasites and duration of treatment has been discussed by White (1997), where it is argued that a drug presence over a minimum duration of 4 parasite life-cycles, equal to 8 days in the case of falciparum malaria, is necessary to decrease the recrudescence rate. A rather large study in 227 patients, however, showed no differences in recrudescence rates after 5 or 7 days monotherapy with artemisinin (Giao et al 2001). Interestingly, the short half-life of these compounds has not been associated with any need for repeated dosing during the course of treatment: artemisinins have successfully been used as once-daily dosing regimens (Ashton et al 1998) and there is no evidence that more frequent daily dosing would result in better parasite elimination or less recrudescence. A long treatment duration of 8 days will obviously result in poor compliance, especially since the infection becomes symptom-free and seemingly cured after 1–2 days of therapy initiation. Hence, artemisinin and its derivatives are increasingly used in combination therapy with conventional antimalarials, where the parasite load is significantly decreased through the action of the artemisinins (1–2 days dosing), while the longer half-life of the second drug decreases the recrudescence rates (Nosten & White 2007). These regimens result in 1–2 days total treatment duration and better therapy outcomes. Needless to say, they also result in improved compliance.

It might seem logical that artemisinin derivatives with longer half-lives would be desirable, as they eliminate the need of combination therapy with other compounds. Results of preclinical experiments, however, suggest the opposite. Several studies have shown artemisinin derivatives to be neurotoxic in rats (Genovese et al 1999), dogs (Brewer et al 1994) and monkeys (Petras et al 2000), when administered intramuscularly using oil vehicles. Such mode of administration results in prolonged absorption of these compounds, prolonging their presence in the blood over an extended period of time. This is practically what can be expected if artemisinins had a longer half-life. When given as oral, intravenous or water-based intramuscular injections, no toxicity is observed amid the fast elimination. The altered concentration–time profile of artemisinins due to the route of administration and its relation to the observed toxicity has been discussed in a review article (Gordi & Lepist 2004). In essence, the artemisinins are exceptionally safe and extremely effective, when they are cleared from the body rapidly. If the body is exposed to these compounds continuously over a long period of time, serious side-effects are inevitable.

Artemisinin derivatives with longer half-lives do not seem to add any benefit to the immediate antiparasitic effects of those already in clinical use. More importantly, available data suggest derivatives with a prolonged half-life result in increased risk of neurotoxicity.

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