Neuroparmacokinetic Heterogeneity of Mefloquine in the Treatment of Progressive Multifocal Leukoencephalopathy

Key words: mefloquine, PML, P-gp, clioquinol, SMON


To the Editor I read with interest the report by Naito and colleagues describing successful treatment of a case of progressive multifocal leukoencephalopathy with mefloquine (1). Their results stand in apparent contrast to those of the larger American trial referenced in their report, which although pending publication has reportedly failed to demonstrate efficacy (2). The relatively large number of cases reported from Japan of progressive multifocal leukoencephalopathy successfully treated with mefloquine suggests the intriguing possibility that genetic and environmentally-linked neuropharmacokinetic heterogeneity may be playing a significant role in predicting successful response to treatment.

The neuropharmacokinetics of mefloquine may plausibly be influenced by variation in the expression and function of the P-glycoprotein transmembrane transporter, a key constituent of the blood-brain barrier responsible for the active efflux of mefloquine across barrier membranes (3). Polymorphisms in the ABCB1/MDR1 gene coding for P-glycoprotein which result in decreased mefloquine efflux across the blood-brain barrier might plausibly result in therapeutic concentrations against JC virus being achieved in brain parenchyma as a result of lipophilic accumulation. Conversely, in cases of unsuccessful treatment of progressive multifocal leukoencephalopathy, it may be that active efflux as a result of drug-induced upregulation of P-glycoprotein expression in the blood-brain barrier may be preventing therapeutic concentrations of mefloquine being achieved despite high serum concentrations of the drug (3).

This proposed heterogeneous susceptibility to central nervous system effects is reminiscent of the epidemiology of adverse effects from clioquinol, a structurally-related quinoline compound that was causally associated with an epidemic of central nervous system toxicity including subacute myelo-optical neuropathy predominantly affecting those of Japanese ancestry (4). A similar genetic predisposition to central nervous system accumulation of clioquinol, suggested by reports of differences in central nervous system toxicity across species and even breeds of experimental animals administered the drug, might readily explain the epidemiology of this epidemic as well (4).

As the quinolines are highly lipophilic and there is evidence that absorption and tissue bioavailability may be affected by the fatty acid milieu (5), environmental factors, such as heterogeneity in dietary consumption of omega-3 fatty acids may be another plausible explanation for the differences in the central nervous system effects of quinolines observed across populations.

The author states that he has no Conflict of Interest (COI).

Acknowledgement

The author acknowledges the valuable assistance of Ms. Cecelia Higginbotham of the Bayne-Jones Army Community Hospital Medical Library.

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References