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Current Opinion

Idiosyncratic quinoline central nervous system toxicity: Historical insights into the chronic neurological sequelae of mefloquine ☆

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ABSTRACT

Mefloquine is a quinoline derivative antimalarial which demonstrates promise for the treatment of schistosomiasis. Traditionally employed in prophylaxis and treatment of chloroquine-resistant *Plasmodium falciparum* malaria, recent changes to the approved European and U.S. product labeling for mefloquine now warn of a risk of permanent and irreversible neurological sequelae including vertigo, loss of balance and symptoms of polyneuropathy. The newly described permanent nature of certain of these neurological effects challenges the conventional belief that they are due merely to the long half-life of mefloquine and its continued presence in the body, and raises new considerations for the rational use of the drug against parasitic disease. In this opinion, it is proposed that many of the reported lasting adverse neurological effects of mefloquine are consistent with the chronic sequelae of a well characterized but idiosyncratic central nervous system (CNS) toxicity syndrome (or toxidrome) common to certain historical antimalarial and antiparasitic quinolines and associated with a risk of permanent neuronal degeneration within specific CNS regions including the brainstem. Issues in the development and licensing of mefloquine are then considered in the context of historical awareness of the idiosyncratic CNS toxicity of related quinoline drugs. It is anticipated that the information presented in this opinion will aid in the future clinical recognition of the mefloquine toxidrome and its chronic sequelae, and in informing improved regulatory evaluation of mefloquine and related quinoline drugs as they are explored for expanded antiparasitic use and for other indications.

1. Introduction

Mefloquine is a 4-quinolinemethanol antimalarial and antiparasitic drug that is structurally related to quinine. Although increasingly investigated for its promising antischistosomal properties (Keiser et al., 2010; Basra et al., 2013), mefloquine is associated with a diverse range of adverse neurological effects (Croft, 2007a) which, together with the drug's neuropsychiatric contraindications (Wooltorton, 2002), have limited the drug's utility for its original antimalarial indications, particularly for prevention of disease (Arznei-Telegramm, 2013b; Bisoffi et al., 2013).

According to recent European product labeling (Hoffmann-La Roche, 2013a) and the results of a randomized blinded trial (Overbosch et al., 2001), commonly reported neurological effects from mefloquine which occur in 1–10% of prophylactic users include vertigo and visual difficulties. Additional idiosyncratic neurological effects reported in both European and U.S. product labeling include balance disorder, peripheral neuropathy, paresthesias, tremor, and ataxia (Hoffmann-La Roche, 2013b, 2014; Roxanne Laboratories, 2013). Case reports also describe dysesthesias (Félix et al., 1985; Jha et al., 2006), disequilibrium (Patchen et al., 1989), nystagmus (Nevin, 2012a), and photophobia (Caillon et al., 1992).

Although adverse neurological effects had previously been considered fully reversible (Arznei-Telegramm, 2013a), diminishing in intensity with the slow elimination of the drug (Nevin, 2013), in 2012, the U.S. Food and Drug Administration (FDA) announced it was reevaluating mefloquine specifically for concerns of an association with lasting vestibular disorder based on new signals detected from its FDA Adverse Event Reporting System (FAERS) (U.S. Food and Drug Administration, 2012). In 2013, European regulators updated the drug's core safety profile to warn that symptoms of polyneuropathy developing during mefloquine use were associated with risk of an irreversible neurological condition (Bundesinstitut für Arzneimittel und Medizinprodukte, 2013), and FDA updated the U.S. product labeling with a boxed warning that

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other neurological effects including vertigo and loss of balance could be permanent in some cases (Arznei-Telegramm, 2013b; McGuire and Wilson, 2013).

Originally developed by the U.S. military and first licensed in Europe over a quarter century ago by F. Hoffmann-La Roche as Lariam® (Croft, 2007a), the innovator product was recently withdrawn from the U.S. market without explanation (Strauch et al., 2011). Generic formulations of mefloquine remain recommended in the U.S. (Centers for Disease Control and Prevention, 2013), but are decreasingly prescribed for the drug's original antimalarial indications (LaRocque et al., 2012; Kersgard and Hickey, 2013). Similarly, while the innovator product remains licensed in many European countries (Arznei-Telegramm, 2013a), certain authorities now recommend its use only as a drug of last resort (Arznei-Telegramm, 2013b; Bisoffi et al., 2013).

Although the adverse neurological effects of mefloquine have been known for nearly a quarter century (World Health Organization, 1989a), the recent emphasis by regulatory authorities of the permanent nature of some of these effects challenges the conventional belief that they are due merely to the long half-life of the drug (Schlagenhauf et al., 2010) and its continued presence in the body. The possibility of permanent neurological sequelae from the use of mefloquine introduces important new considerations for the continued rational use of the drug and calls for an improved effort to better characterize the pathophysiology of these effects.

In this opinion, it is proposed that many of the lasting adverse neurological effects of mefloquine are consistent with the chronic sequelae of a well characterized but idiosyncratic central nervous system (CNS) toxicity syndrome (or toxidrome) common to a number of historical antimalarial and antiparasitic quinolines and associated with a risk of permanent neuronal degeneration within specific CNS regions including the brainstem. Issues in the development and licensing of mefloquine are then considered in the context of historical awareness of the CNS toxicity of related quinoline drugs.

It is anticipated that the information presented in this opinion will aid in the future clinical recognition of the mefloquine toxidrome and its chronic sequelae, and in informing improved regulatory evaluation of mefloquine and related quinoline compounds, particularly as these drugs are investigated for expanded use worldwide for antiparasitic and other indications.

2. Historical evidence of quinoline CNS toxicity

Although not well described in the contemporary literature, the neurological toxidrome observed with mefloquine appears not to be unique to the drug, but instead shares a number of clinical characteristics in common with idiosyncratic CNS toxicity syndromes produced by certain related quinoline derivatives, including drugs that had historically been widely employed as antimalarials and antiparasitics.

While the naturally occurring cinchona alkaloid quinolines were historically well known to cause seemingly reversible neurological effects including symptoms of cinchonism (Taylor and White, 2004), the potential for lasting neurological effects from quinoline drugs was recognized in the mid 1940s, when certain synthetic quinoline antimalarials were found to cause irreversible CNS toxicity. In particular, the synthetic 8-aminoquinolines pamaquine and plasmocid, then both in common use as antimalarials (Manwell, 1949; Benazet, 1963), were linked to an idiosyncratic neurological syndrome accompanied by direct histopathological evidence of CNS neuronal degeneration in human and animal subjects. These drugs induced in the most extreme cases "highly localized degenerative changes in the (CNS) associated with functional derangement" (Smith and Schmidt, 1947). Nearly three decades later the synthetic hydroxyquinoline clioquinol, then in common use as an antiparasitic (Kono, 1971), had also been linked to a related idiosyncratic neurological syndrome again accompanied by histopathological evidence of CNS neuronal degeneration (Shiraki, 1971; Kono, 1975).

In the following sections, the clinical manifestations and histopathological findings associated with idiosyncratic intoxication with these three drugs are reviewed. Although comparable effects have been observed with a large number of other synthetic quinoline derivatives (Schmidt and Schmidt, 1951; Schmidt, 1983), the well-characterized and fairly conserved nature of the extensive CNS neuronal degeneration caused by these three drugs, together with their widespread historical use in antimalarial and antiparasitic therapy, are of greatest relevance in demonstrating the potential for lasting but previously unrecognized neurological effects from mefloquine.

2.1. Pamaquine

Pamaquine, known chemically as 8-(4-diethylamino-1-methylbutylamlno)-6-methoxyquinoline, originally developed by the Germans (British Medical Journal, 1926; The Science News-Letter, 1926) and also known as praequine, plasmochin, or plasmoquine, was initially thought to be free of cinchona-like neurological effects. In use as an antimalarial since the late 1920s (Hardgrove and Applebaum, 1946), a large review of 258 cases of toxic reactions to the drug failed to identify any symptoms suggestive of CNS toxicity (Hardgrove and Applebaum, 1946). However, pamaquine was found in some users to induce similar symptoms of vertigo and photophobia (U.S. Army Medical Department, 1943; Hardgrove and Applebaum, 1946) and visual disturbance (West and Henderson, 1944) to those commonly attributed to the cinchona alkaloids. Benign perceptions of the safety of pamaquine were challenged when a fatal case of human overdose, marked by blurred vision and facial paresthesias, was found at autopsy to have significant neuronal degeneration within specific brain structures including the brainstem. Careful histopathological study revealed extensive focal degeneration of the pontine nuclei, with mild to moderate degeneration of the vestibular nuclei, particularly the medial vestibular nuclei, as well as the nuclei of cranial nerves III, IV, and VI (Loken and Haymaker, 1949).

Although comparable neurological reactions to pamaquine observed in rhesus monkeys had been characterized as reversible (Schmidt and Smith, 1947), on histopathological testing, the drug in small doses was found to produce strikingly similar effects to those observed later in man (Loken and Haymaker, 1949), causing swelling and subtle degeneration in scattered neurons throughout various brainstem nuclei including within the vestibular, supraspinal, ruber, ambiguus, dorsal motor, lateral cuneate, and lateral reticular nuclei, as well as those of cranial nerves III, IV, and VI (Schmidt, 1947). At higher doses, the drug produced more extensive degeneration in these areas (Schmidt, 1947; Schmidt and Schmidt, 1951).

2.2. Plasmocid

The related 8-aminoquinoline plasmocid, known chemically as 8-(3-diethylaminopropylamino)-6-methoxyquinoline, originally developed by the Russians (Findlay, 1950a) and also known as rhodoquine or Fourneau 710 (Findlay, 1950b) was also found in early human use to cause cinchona-like neurological effects including vertigo, paresis and diplopia (Decourt, 1936). A 1945 review of the foreign literature cited a diverse range of more serious neurological effects including severe ataxia, convergence disorder, smoothing of the nasolabial fold, and deviation of the tongue

(Board for the Coordination of Malarial Studies, 1945) suggestive of focal brainstem dysfunction. A review of 76 human cases of neurological effects attributed to plasmocid toxicity found a range of lasting deficits, including in equilibrium, coordination, and eye muscle movement; some of these symptoms "persisted for months or years after termination of treatment" (Schmidt and Schmidt, 1949).

In the absence of published neurohistopathological testing of fatal human cases of plasmocid intoxication, early neurological effects were commonly attributed to cerebellar ataxia, polyneuritis, and optic atrophy (Findlay, 1950b). However, histopathological testing in rhesus monkeys following administration of high doses of plasmocid revealed almost complete destruction of the nuclei of cranial nerves III, IV, and VI and of the vestibular nuclei; further administration produced variable patterns of injury extending into other brainstem nuclei (Schmidt and Schmidt, 1947; Lyle and Schmidt, 1962), with highly scattered lesions extending throughout the medulla, pons, striatum, and limbic system (Schmidt and Schmidt, 1948; Sipe et al., 1973). Authors speculated that "the effect of plasmocid on the human brain would be quite similar" to that observed in monkey (Sipe et al., 1973), and that multiple human cases of CNS toxicity were "doubtless similar to these in origin" (Schmidt, 1983).

2.3. Clioquinol

By the early 1970s, accumulating evidence with the antiparasitic hydroxyquinoline clioquinol, known chemically as 5-chloro-7-iodo-8-quinolinol, had demonstrated a similar propensity for CNS toxicity to that observed with antimalarial 8-aminoquinolines. Although idiosyncratic cases of human toxicity, labeled subacute myelo-optic neuropathy (SMON) (Kono, 1971) are characteristically associated with symptoms attributable to peripheral neurotoxicity, cases of SMON have also featured disequilibrium (Ferrier and Eadie, 1973), visual disturbances (Kaeser, 1984), paresthesias and gait disturbances (Tsubaki et al., 1971), and vertigo and nystagmus (Yamasaki and Shibuya, 1968) equally attributable to CNS causes.

Although the neurohistopathology of SMON has been more typically characterized by extensive degeneration within the dorsal columns and the optic nerve, extensive evaluation of autopsy cases has also revealed degeneration of brainstem structures including the inferior olive and nucleus ruber (Kono, 1975); the roots of cranial nerves V, VIII, and X (Shiraki, 1971); and the nucleus gracilis (Ricoy et al., 1982). On histopathological study across animal models, the drug produces scattered and highly variable degenerative lesions including within the distal optic nerve and dorsal funiculus of the spinal cord (Hoover et al., 1981) and fasciculus gracilis (Tateishi et al., 1972a) in beagle dogs; the optic tract and fasciculus gracilis in cats (Tateishi et al., 1972b); and the nucleus gracilis in rats (Arasaki and Nakanishi, 1989).

3. Evidence of mefloquine CNS toxicity

The most prominent neuropsychiatric effects identified during the development of mefloquine including vertigo initially resembled those of cinchonism induced by quinine (Stockwell, 1982; World Health Organization, 1989b). Presumably due to lack of direct histopathological evidence of quinine neurotoxicity and the presumed transient nature of neurological effects from drugs of the 4-quinolinemethanol class (Schmidt et al., 1978a,b), the drug appears to have been assumed free of the known permanent CNS toxicity of pamaquine, plasmocid, and clioquinol.

The neurotoxicity of mefloquine was only first reported in papers published more than three decades after the drug's reported synthesis (Ohnmacht et al., 1971), following experiments in cultured rat neuroblastoma and embryonic rat neuron cell lines (Dow, 2003) over a range of neurophysiologically plausible concentrations (Dow et al., 2003). In subsequent years, confirmatory evidence of the drug's neurotoxicity was also obtained (Dow et al., 2004, 2005; Caridha et al., 2008).

In direct histopathological testing in a rat model, high dose mefloquine induced neuronal degeneration evocative of the effects of clioquinol in the nucleus gracilis, nucleus cuneatus, and solitary tract (Dow et al., 2006), and was accompanied by "anxiousness/hyperactivity" and functional changes in motor activity (Dow et al., 2006). Study authors noted that the brainstem injury induced by mefloquine was "permanent in nature" (Dow et al., 2006). Independent authors subsequently demonstrated mefloquine neurotoxicity in rat cortical neurons (Hood et al., 2010; Milatovic et al., 2011) and in human neuronal cell lines (Geng et al., 2010; Shin et al., 2012). While recommended confirmatory human neurohistopathological testing has yet to be performed (Nevin, 2009), clinical observations following intoxication from mefloquine at prophylactic doses have demonstrated lasting deficits consistent with brainstem lesions or dysfunction in the vicinity of the oculomotor and vestibular nuclei (Nevin, 2012a).

While a variety of pathological mechanisms may be evoked to explain many of the signs and symptoms associated with mefloquine use, CNS neuronal degeneration similar to that observed in the animal model and similar to that caused by pamaquine and clioquinol in humans provides a highly parsimonious theoretical explanation for many of the drug's reported chronic neurological effects, including lasting cases of vertigo (Grupp et al., 1994), disequilibrium (Nevin, 2012a), and paresthesias (Lobel et al., 1998).

For example, although mefloquine is a known peripheral ototoxicant (Yu et al., 2011; Ding et al., 2013), focal neuronal degeneration in the vicinity of the oculomotor and vestibular nuclei (Nevin, 2012a), as observed at human autopsy with pamaquine and in animal models from plasmocid, provides a parsimonious pathophysiological explanation for at least some of the reported chronic vestibular effects of mefloquine. Similarly, while symptoms of mefloquine neuropathy have frequently been attributed to peripheral causes (Watt-Smith et al., 2001; Jha et al., 2006) including to C-fiber irritation (Chester and Sandroni, 2011), the lack of direct evidence of specific peripheral neurotoxicity, together with the drug's demonstrated degenerative effects in the animal model in areas of the brainstem involved in the processing of sensory inputs including the nucleus gracilis, cuneatus and solitary tract (Dow et al., 2006) suggest that CNS toxicity, analogous to that observed historically with clioquinol, may provide a more plausible and parsimonious pathophysiological explanation for these symptoms.

In spite of the large and growing body of neurotoxicity data from *in vivo* and *in vitro* studies, broader acceptance of the possibility of clinically significant CNS neurotoxicity from mefloquine has remained strangely elusive in the literature, possibly owing to the absence of published human neurohistopathology studies (Nevin, 2009). Interestingly, in the absence of comparable human neurohistopathology, and on the basis of animal studies alone, clinically significant human CNS neurotoxicity from plasmocid was never seriously contested and was even deemed "doubtless" by leading historical authorities (Sipe et al., 1973; Schmidt, 1983). In contrast, some contemporary authors have appeared less inclined to acknowledge the possibility of similar effects from mefloquine, particularly at the relatively low doses encountered during prophylactic use, claiming that extrapolation of high dose neurotoxicity data from animal studies to human cases still requires the "bridging of a large knowledge gap" (Schlagenhauf et al., 2010).

Fortunately, human neuropharmacokinetic data is available that may effectively bridge this gap. For example, human autopsies have demonstrated mefloquine CNS accumulation at prophylactic dosing

rates (Jones et al., 1994; Clifford et al., 2013) to concentrations comparable to those after treatment (Pham et al., 1999) and well beyond *in vitro* human cell line neurotoxicity thresholds (Geng et al., 2010; Shin et al., 2012). Additional *in vivo* (Barraud de Lagerie et al., 2004) and pharmacogenetic studies (Aarnoudse et al., 2006) provide further neuropharmacokinetic insights into known CNS drug transport (Pham et al., 2000) and metabolism (Fontaine et al., 2000) pathways that may plausibly mediate idiosyncratic accumulation in CNS to neurotoxic concentrations during routine use.

Despite both toxicological and pharmacokinetic plausibility, demonstrating incontestable evidence of mefloquine CNS toxicity in individual clinical cases remains challenging. With use of mefloquine at higher doses for treatment of malaria, the possible confounding of signs and symptoms of CNS toxicity by those of comorbid cerebral malaria (Weiss, 1985) creates challenges for their attribution uniquely to the drug. Similarly, with use of mefloquine at lower prophylactic doses, a lack of sensitive prospective ascertainment, particularly in resource-constrained settings, may result in neurological effects not being identified (Rønn et al., 1998). Even when such effects are identified, demonstrating incontestable evidence of CNS toxicity may be made challenging by the microscopic and highly focal nature of most expected neuronal degeneration (Dow et al., 2006), which as with presumed cases of clioquinol CNS toxicity (Kimura et al., 2011), would be frequently undetectable by conventional neuroimaging. Despite these limitations, reports of highly specific clinical findings, including central vestibulopathy (Nevin, 2012a) occurring among those without any history of malaria or other plausible neurological etiologies establishes mefloquine CNS toxicity as a probable pathophysiological entity worthy of significant further investigation, particularly as the drug is considered for expanded use against parasitic disease and for other indications.

4. Mefloquine CNS toxicity in historical context

The long delayed recognition of the possibility of clinically significant CNS toxicity from mefloquine calls for an examination of the historical context of the drug's development and licensing as an antimalarial. Although the first synthesis of mefloquine, known chemically as 2,8-bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanol, was reported in 1969 (Ohnmacht et al., 1971), the drug was very closely related to the synthetic 4-quinolinemethanol compound 4-quinolyl-α-piperidylcarbinol first reported over three decades earlier in 1938 (Ainley and King, 1938). Mefloquine differs from this previously synthesized compound (later known as SN 2549) (Berliner et al., 1946, p. 1062) solely by addition of two trifluromethyl groups (CF_3) at the 2 and 8 positions of the quinoline nucleus.

During early human testing of the 4-quinolinemethanols during the U.S. military's World War II era drug discovery program (Alving et al., 1948) these drugs exhibited some evidence of the CNS toxicity observed from related synthetic quinoline compounds (Schmidt and Schmidt, 1951), including producing visual photosensitivity or photophobia (Pullman et al., 1948). One particularly efficacious 4-quinolinemethanol known as SN 10,275 induced headache and visual photosensitivity (Pullman et al., 1948) but also induced phototoxicity which may have masked recognition of underlying CNS effects. Presumably owing to concerns of phototoxicity (Rozman and Canfield, 1979; World Health Organization, 1984), investigation of 4-quinolinemethanols as antimalarials was formally abandoned in favor of the more promising 4-aminoquinolines (Schmidt et al., 1978a).

However, by the early 1960s (Tigertt, 1969), owing ostensibly to concerns of rising resistance to the 4-aminoquinoline chloroquine, the U.S. military had initiated a new large scale drug discovery program (Modell, 1968), during which time hundreds of thousands of compounds were evaluated for their antimalarial activity. Over 300 4-quinolinemethanols were evaluated in this effort, including some that had been previously tested during the earlier wartime program (Schmidt et al., 1978a). Mefloquine (initially known as WR 142,490) quickly emerged as the favored of these drugs based the results of limited human testing in prisoners (Rieckmann et al., 1974; Trenholme et al., 1975) that suggested the drug was free of serious side effects. Soon after its first reported synthesis, mefloquine had been singled out by the U.S. military for larger-scale synthesis (Ohnmacht et al., 1971) and commercialization by F. Hoffmann-La Roche (Maugh, 1977). So rapid was the testing of the drug in field settings that one researcher noted "Phase II clinical trials threatened to outstrip needed Phase I testing" (Reba, 1977).

When the experimental 4-quinolinemethanol compounds WR-184,806 and WR-226,253 were noted in the early 1970s to evoke lightheadedness and difficulties in focusing (Schmidt et al., 1978b), these symptoms appear not to have been taken as evidence of possible CNS toxicity of the 4-quinolinemethanol class. Similarly, during testing of mefloquine, early and frequent reports of vertigo (Harinasuta et al., 1983; Björkman, 1989), "dizziness" (Trenholme et al., 1975; Harinasuta et al., 1983; Reisinger et al., 1985), and rare but sentinel reports of formication (Harinasuta et al., 1983), psychosis (Harinasuta et al., 1983; Björkman, 1989), confusion (Harinasuta et al., 1985; Nosten et al., 1987; Bernard et al., 1989; Björkman, 1989), amnesia (Lapras et al., 1989), and gait disturbance (Harinasuta et al., 1983) were seemingly also not considered in the context of earlier publications as evidence of potentially permanent CNS toxicity (Schmidt et al., 1978a). Importantly, and in marked contrast to the extensive testing conducted during earlier wartime drug development efforts (Schmidt and Coatney, 1955), no significant histopathological testing appears to have been undertaken prior to the U.S. licensure of mefloquine to rule out the drug's potential neurotoxicity.

Despite the lack of specific neurohistopathological testing, there nonetheless appears to have been clear awareness of the drug's potentially serious CNS effects. The original 1989 U.S. product insert acknowledged a risk of "disturbed sense of balance", and "visual disturbances", and cautioned that during prophylactic use, "if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to *a more serious event*" (emphasis added). Although this critical phrase was left undefined, the product insert warned of a risk of CNS disturbances including "encephalopathy of unknown etiology" during prophylactic administration (Hoffmann-La Roche, 1989). In subsequent years, absent empiric understanding of the molecular basis of mefloquine's CNS effects, multiple authors posited imaginative but ultimately untested theories to explain the drug's marked neuropsychiatric toxicity (Croft and Herxheimer, 2002; Nevin, 2009; Mawson, 2013).

Although evidence suggestive of the neurotoxicity of mefloquine was published in 1996 (Lee and Go, 1996), it was only in 2003, 14 years after the drug's U.S. licensure, that the first results of neurotoxicity testing in rats were published by U.S. military affiliated researchers (Dow et al., 2003). Recent attempts to mitigate mefloquine neurotoxicity, including efforts sponsored by the U.S. military to develop a human "safety test" (Walter Reed Army Institute of Research, 2006) to identify individuals with idiosyncratic susceptibility, have thus far failed to yield satisfactory results. Notwithstanding recent confusion over the absolute configuration of the currently marketed drug (Ding and Hall, 2013; Schützenmeister et al., 2013), randomized trials of enantiomeric mefloquine (Knight et al., 2011), originally thought less likely to

induce CNS effects owing to slightly lower average brain accumulation (Baudry et al., 1997; Dow et al., 2011), have also demonstrated a propensity similar to the currently licensed racemic mixture to induce idiosyncratic "centrally mediated" symptoms of "dizziness" and difficulties in concentration (Tansley et al., 2010).

With rising awareness of the drug's neurotoxicity, by 2009, the U.S. military had prohibited the widespread use of mefloquine for prophylaxis (Milatovic and Aschner, 2011), and had returned to a policy of first-line use of doxycycline (Nevin, 2012b), the drug of choice prior to the U.S. licensing of mefloquine 20 years earlier (Sánchez et al., 1993). In response to the FDA boxed warning, senior U.S. military officials recently emphasized that mefloquine should be used for prophylaxis only as a "drug of last resort" (Woodson, 2013), while elite U.S. military units prohibited such use of the drug outright (Reactions Weekly, 2013).

While never explicitly addressing the potential implications of permanent CNS toxicity from the drug, senior U.S. military medical authors have acknowledged that mefloquine's neuropsychiatric effects might "confound the diagnosis and management of post-traumatic stress disorder and traumatic brain injury" making "the continued routine use of mefloquine less desirable" (Magill et al., 2012), and noting that "with the availability of better-tolerated drugs, there is no need to use mefloquine for treatment unless other options are unavailable" (Magill, 2006).

The near complete withdrawal of mefloquine within the U.S. military both for prophylaxis and treatment clearly marks the demise of the drug for the military indications for which it was original developed (Croft, 2007a). Interestingly, in 1978, a leading authority involved in the development of mefloquine had noted that the drug "promises to be broadly useful" in the treatment and prophylaxis of malaria, but that "[if] this promise is not realized, it will doubtless not be for lack of antimalarial activity, but rather because of toxicological attributes not identified in the small-scale studies pursued to date" (Schmidt et al., 1978a). Two decades earlier, during testing of related 8-aminoquinoline antimalarials (Schmidt and Coatney, 1955), this same authority had presciently cautioned that since "...in doses well below the lethal level [these drugs] produced striking symptoms of [CNS] injury associated with severe lesions in the principal nuclei of the proprioceptive, visual-reflex, and vestibulo cerebellar pathways... their capacity to evoke reactions which might mask symptoms of low grade neuronal injury, plus the likelihood of their widespread use in malaria therapy, make a detailed search for CNS lesions highly desirable" (Schmidt and Schmidt, 1951). With awareness of the potential for lasting CNS toxicity finally emerging over 40 years after mefloquine's initial development, it appears worthy of further investigation to determine precisely why such a "highly desirable" search was never performed, and why pre-licensure testing appears to have been limited only to "small-scale" studies.

5. Conclusions

In this opinion, it has been argued that many of the idiosyncratic chronic neurological sequelae associated with mefloquine use not only have a solid biological basis, but are consistent with a more generalized CNS toxicity syndrome common to certain historical quinoline drugs and associated in both animal and human studies with a risk of neuronal degeneration particularly within specific brainstem nuclei. In the four decades since the development of mefloquine, and absent seeming awareness of its potential to induce permanent CNS toxicity, many of the drug's most severe idiosyncratic neuropsychiatric effects have been attributed by influential authors to the stresses of travel or to latent or pre-existing mental illness (Lobel, 1996; Schlagenhauf et al., 1997; Schlagenhauf, 1999; Schlagenhauf and Steffen, 2000), or to "media hype" (Schlagenhauf, 1996). With the benefit of the insights presented in this opinion, these prior explanations for many of mefloquine's reported adverse effects now appear unsatisfactory.

The recent emphasis by regulatory authorities of the potential for permanent neurological effects from mefloquine, coming four decades too late to rationally inform most antimalarial use of the drug, underscores the need for sensitive prospective evaluation (Rønn et al., 1998) of neurological endpoints during clinical testing as the drug is repositioned for possible widespread antiparasitic use, including in the treatment of schistosomasis. However, given the clinically occult CNS toxicity that may result from use of mefloquine, the insights of this opinion also underscore the critical importance of better characterizing the molecular basis of quinoline neurotoxicity, and emphasize the need to ensure comparable neurohistopathological testing (Schmidt and Schmidt, 1951) is performed in appropriate animal models prior to the future licensing of related quinoline drugs.

Such testing appears particularly needed for tafenoquine (Nasveld et al., 2010), an 8-aminoquinoline initially developed by the U.S. military (Kitchen et al., 2006) and related structurally both to pamaquine and plasmocid, and associated in pre-licensing trials with a similar risk of vertigo as mefloquine (Nasveld et al., 2010). While tafenoquine has been eagerly anticipated for its utility against vivax malaria (Baird, 2012) and potentially against leishmaniasis (Manzano et al., 2011a,b), the recent granting by the U.S. FDA of Breakthrough Therapy (Sherman et al., 2013) status, in the absence of any published neurohistopathological testing, risks recreating the sense of urgency that contributed to the approval of mefloquine in the absence of appropriate CNS safety data (Croft, 2007a,b).

Lastly, although of incidental interest to the parasitology community, these insights also suggest the need for caution as mefloquine (Nevin, 2011) and other currently licensed antiparasitic and antimalarial quinoline drugs are increasingly evaluated for treatment of neuropsychiatric and neurologic conditions, including behavioral dyscontrol (Daly and Caplan, 2012), affective dysregulation (Stahl, 2013), chorea (Ondo, 2012), progressive multifocal leukoencephalopathy (Clifford et al., 2013), multiple sclerosis (Nevin, 2012c), and glioblastoma (Geng et al., 2010), which might plausibly mask or make difficult the recognition of CNS toxicity and low grade neuronal injury.

Disclaimer

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