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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