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Mini-review

The toxicology of Clioquinol☆

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ABSTRACT

5-Chloro-7-iodo-quinolin-8-ol (Clioquinol) is a halogenated 8-hydroxyquinoline that was used in 1950–1970s as an oral anti-parasitic agent for the treatment and prevention of intestinal amebiasis. However in the 1970s oral Clioquinol was withdrawn from the market due to reports of neurotoxicity in Japanese patients. Recently, reports have demonstrated that Clioquinol has activities beyond its use as an antimicrobial. For example, Clioquinol inhibits the function of the proteasome and displays preclinical efficacy in the treatment of malignancy. In addition, due to its ability to bind copper and dissolve beta-amyloid plaques in the brain, Clioquinol has been investigated for the treatment of Alzheimer's disease. As such, efforts are underway to repurpose Clioquinol. In light of the reemergence of oral Clioquinol, we review the toxicology of this compound in animals and humans with an emphasis on its neurotoxicity. Such information will aid in the design of clinical trials of oral Clioquinol for new indications such as cancer therapy.

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1. Introduction

5-chloro-7-iodo-quinolin-8-ol (Clioquinol) (Fig. 1) is a halogenated 8-hydroxyquinoline that was used in the 1950s–1970s as an oral anti-parasitic agent for the treatment and prevention of intestinal amebiasis, but its mechanism of action as an antimicrobial was unknown. In the 1970s oral Clioquinol was withdrawn from the market due to reports of neurotoxicity in Japanese patients. However, topical formulations of Clioquinol are still available for the treatment of topical fungal and parasitic infections. Recently, Clioquinol has reemerged for the treatment of non-infectious indications including malignancy (Daniel et al., 2005; Ding et al., 2005; Chen et al., 2007; Mao et al., in press) and Alzheimer's disease (Cherny et al., 2001; Mao et al., in press; Ritchie et al., 2003). Given the potential reintroduction of oral Clioquinol for these new indications, an understanding of Clioquinol's toxicology is important to fully appreciate the potential side effects of this drug

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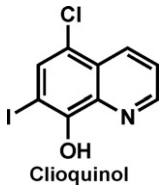

Fig. 1. Clioquinol. The chemical structure of Clioquinol (5-chloro-7-iodo-quinolin-8-ol) is shown.

in these new patient populations. Here, we review the toxicology of Clioquinol.

2. Repurposing oral Clioquinol for new indications

Recently, we and others have demonstrated that Clioquinol induces cell death in malignant cells by inhibiting the proteasome (Daniel et al., 2005; Ding et al., 2005; Chen et al., 2007; Mao et al., in press). The proteasome is necessary to rid cells of excess and mis-folded proteins as well as regulate levels of proteins responsible for processes such as cell cycle progression, DNA repair and transcription (reviewed in Goldberg, 2003). The proteasomal protein degradation pathway is initiated by the sequential activity of E1, E2 and E3 enzymes that mark proteins for degradation by adding chains of ubiquitin molecules to proteins' lysine residues (reviewed in (Passmore and Barford, 2004; Nalepa et al., 2006)). Once tagged with ubiquitin, proteins are degraded by the proteasome (Fig. 2).

The proteasome is a 2000 kDa multimeric enzymatic complex located in the nucleus and cytoplasm. The 26S proteasome contains a 20S proteolytic core capped by two 19S regulatory subunits. Inhibition of the proteasome induces cell death through a variety of mechanisms including accumulation of mis-folded proteins and inhibition of NFKβ activation (Hideshima et al., 2001; Chauhan et al., 2005; Bazzaro et al., 2006; Meister et al., 2007). To date, all of the known proteasome inhibitors act at the 20S subunit.

Recently, we and others have demonstrated that Clioquinol is a potent inhibitor of the proteasome (Daniel et al., 2005; Ding et al., 2005; Chen et al., 2007; Mao et al., in press). We have also demonstrated that Clioquinol inhibits the proteasome through a dual copper-dependent and -independent mechanism. Through its actions as a proteasome inhibitor, Clioquinol induces cell death in leukemia and myeloma cell lines and primary patient samples preferentially over normal hematopoietic cells (Mao et al., in press). In addition, Clioquinol delays the growth of tumors in mouse models of malignancy (Mao et al., in press). Thus, Clioquinol may be a novel anti-cancer agent that could be repurposed for this new indication.

Clioquinol has also re-emerged as a potential therapy for Alzheimer's disease. The activity in Alzheimer's disease relates to the ability of Clioquinol to bind copper. Clioquinol binds copper and dissociates this metal from beta-amyloid protein aggregates that have been associated with Alzheimer's disease (Cherny et al., 2001). Upon removal of copper, the aggregation of these proteins is reversed (Cherny et al., 2001). A phase II study of oral Clioquinol in patients with Alzheimer's disease reported that the drug improved the cognition and behavior of their study patients (Ritchie et al., 2003).

Given the potential efficacy of Clioquinol as a therapeutic for the treatment of Alzheimer's disease and malignancy, oral formulations of this drug are being tested for these new indications. As such, prior toxicology studies of Clioquinol are important when making decisions about repurposing this drug. Here, we review the animal and human pharmacology and toxicology data for Clioquinol.

3. Pharmacokinetics and metabolism of Clioquinol

Pharmacokinetic studies of Clioquinol absorption and metabolism have been performed in animals and humans. For example, in rats given 100 mg/kg and 200 mg/kg of Clioquinol intraperitoneally, peak concentrations were reached 30 min–1 h after administration (Kotaki et al., 1983).

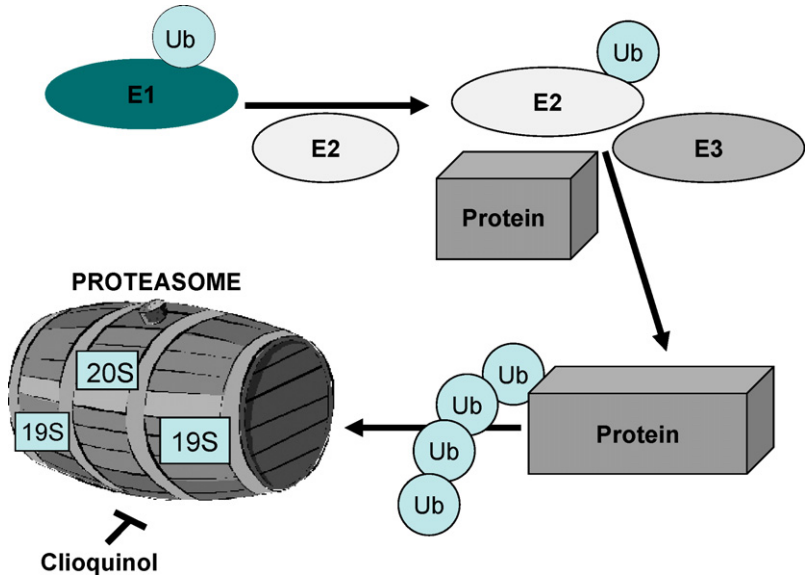

Fig. 2. The proteasomal pathway of protein degradation. The proteasomal degradation pathway is a multi-step enzymatic cascade in which ubiquitin is conjugated to target proteins to mark them for degradation. In the first step of this cascade, the E1 enzyme binds two ubiquitin molecules. The E1 enzyme then transfers a ubiquitin molecule to the E2 enzyme. The E2 enzyme transfers the ubiquitin to a lysine residue on the target protein with the help of the E3 ubiquitin ligase. K48-polyubiquitinated proteins are then recognized, unfolded, and degraded by the proteasome enzyme complex. The 26 proteasome is a barrel shaped structure that contains a 20S proteolytic core capped by two 19 regulatory subunits. Clioquinol inhibits the 20S proteasome through copper-dependent and -independent mechanisms.