Physicochemical and *In Vitro* Evaluation of Anti-Leishmania Activity of Parvaquone and Related Compounds

Ronoh Kiplangat Wesley

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ABSTRACT

Leishmaniasis is a widespread parasitic disease caused by protozoa of the genus Leishmania. The control of leishmaniasis remains a problem and it is emerging as an important opportunistic infection in immuno-compromised patients especially those infected with HIV. The current treatment use pentavalent antimony as primary therapy, which must be administered parenterally and requires long duration of therapy. It also has toxic side effects and variable efficacy with treatment failures being reported in India and Kenya. The most widely used secondary treatment is amphotericin B which is highly active but has extensive toxicity complications with the newer formulations being too expensive for use by the majority of endemic countries. A real need exists for improved anti-leishmanials as the current chemotherapy is inadequate and expensive. This study evaluated the physicochemical profiles comprising solubility, ionization constant ($pKa_)$ and partition coefficient (Log P) of parvaquone, buparvaquone, 2- Hydroxy-1, 4-Naphthoquinone (NQ) and 2-Hydroxy-3- (2-phenylbutyl)-1, 4- Naphthoquinone (PNQ). Parvaquone and buparvaquone are hydroxynapthoquinones that were developed for treatment of East coast fever (ECF) in cattle and being tested here against leishmaniasis. The anti-leishmanial activity of these compounds was also determined in cell free media and infected macrophages. Aqueous Solubility, pKa and Log P measurements were done following literature methods of poorly soluble drugs. Amphotericin B and Pentostam were used as standard drugs in *in vitro* evaluation of anti-leishmania activity. The compounds under test exhibited low aqueous solubility as all were below 65 µg/ml. According to literature most drugs that are orally active have aqueous solubility greater than 65 µg/ml but when the solubility is 20 µg/ml or less as was the case here, the probability of useful oral activity is very low. In cell free and macrophage assay, buparvaquone displayed the most potent activity while 2- hydroxy-1, 4-Naphthoquinone

(NQ) had the least potency among the test drugs. The *in vitro* activity of buparvaquone was comparable to standard drugs unlike parvaquone that exhibited weak activity compared with the positive control. The results further showed that the mode of action of the test drugs was not through nitric oxide production. In cytotoxicity assays, buparvaquone had the lowest minimum inhibitory concentration (MIC) among test drugs and a high selectivity index (SI). The test compound, 2-hydroxy-3- (2-phenylbutyl)-1, 4- Naphthoquinone (PNQ) had the lowest SI. In conclusion, buparvaquone exhibited the most favourable physico chemical parameters and *in vitro* activity among the test drugs. However, the challenge for oral and topical formulation of this drug is its poor aqueous solubility which will lead to low bioavailability.