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Effect of Caffeine-Containing Beverages on Physicochemical and Release Properties of Halofantrine

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Received: 15 December 2013 Accepted: 1 January 2014 Published: 15 January 2014

Abstract

Halofantrine (Hf) is a poorly water-soluble drug for treating malaria in endemic areas like tropical Africa, where caffeine-containing products are habitually consumed. Previous reports showed that caffeine increased the aqueous solubility of Hf at room temperature over 3 days. The aim of this study was to determine the effect of caffeine and caffeinecontaining beverages on dissolution and solubility of Hf and to investigate any possible interactions. The aqueous solubility and dissolution of Hf alone and in the presence of caffeine was investigated at pH 1.3, 5.9 and 7.4 using standard methods. The solubility of Hf in the presence of aqueous extracts of cocoa, coffee, black tea and green tea at pH 5.9 was also investigated. In 1 hour, caffeine markedly increased the aqueous solubility of Hf at pH 1.3, 5.9 and 7.4. Caffeine and caffeine-containing beverages markedly increased the aqueous solubility of Hf by between 100- to more than 1600- fold, with a 1672-fold increase by caffeine (from 76.6 ±7.8 ng/mL to128.2 ± 4.5 mg/mL) at pH 5.9. The dissolution of Hf tablets at pH 1.3, 5.9 and 7.4 showed the respective amounts released as 3.57 ± 0.09, 0.95 ± 0.19 and 0.260 ± 0.043 mg, but introduction of caffeine increased these values to 9.51 ± 0.23, 3.70 ± 0.12 and 0.52 ± 0.10 mg respectively, representing 3-fold, 4-fold and 2-fold respectively. These results prove physico-chemical interaction between caffeine and halofantrine. The consequence of this finding is unknown but may affect malaria chemotherapy when Hf is administered concurrently with caffeine-containing products.

Index terms— caffeine, halofantrine, physicochemical interaction.

1 Introduction

alofantrine (Hf) is a phenanthrene methanol antimalarial currently marketed as halofantrine hydrochloride under the trade name Halfan®. Hf, a highly lipophilic drug [1] has been shown to be highly active against multidrug resistant isolates of Plasmodium falciparum in preclinical studies [2,3,4]. The drug has proven efficacy against multi-drug resistant malaria including infection with chloroquine and/or pyrimethamine resistant strains of P. falciparum [5].

Hf is highly lipophilic [1,6] with an erratic oral absorption pattern leading to high inter individual variations that have been shown to be associated with food intake **???** -10]. Lim and Go (2000) reported that caffeine, a non-toxic complexing agent that possesses stimulant effect on the CNS, enhanced the aqueous solubility of Hf [11] at room temperature for over 3 days by a 1:1 ratio complex formation. In a different study by Kolade et al. (2008) kolanut, a habitually consumed nut rich in caffeine, also increased the solubility of Hf in vitro but decreased the plasma concentrations of the drug in humans [12].

Aside of kolanut that contains caffeine, other caffeine-containing beverages such as, coffee, cocoa, black tea and green tea are also habitually consumed in the tropics where malaria is prevalent. There is thus a need for

investigations of Hf interactions with caffeine and caffeine-containing beverages especially at various pH values that are important in GIT for orally administered medicines. Therefore the aim of this study was to determine the effect of caffeine and caffeinecontaining beverages on the solubility and dissolution profile of Hf at physiologically important pH values of 1.3, 5.9 and 7.4 as well as to investigate any possible interactions.

2 II.

3 Materials and Methods

4 a) Chemicals and Reagents

Halofantrine hydrochloride (Hf) was received as a gift from Smithkline Beecham (Welwyn Garden City, United Kingdom). Caffeine, coffee (Coffee arabica), cacao (Theobroma cacao), black tea Ccamellia sinensis), and green tea Ccamellia sinensis) were obtained commercially. Potassium dihydrogen phosphate (analar) and sodium chloride (analar) were obtained from VWR International (Darmstrdt, Germany). Instruments used were basket type Easy-lift dissolution test station, Mettler Delta 340, pH meter, Uniscope SM b) Preparation of 0.05M KH 2 PO 4 (ionic strength = 0.08)

Standard solutions of 0.05M potassium dihydrogen phosphate were prepared and adjusted to pH 1.3, 5.9 and 7.4 respectively

5 c) Calibration line for Hf

The HPLC method for determination of Hf in plasma previously described [12] was adapted for this study. Mobile phase samples (1mL) were spiked with standard solutions of Hf to give predetermined concentrations of 200, 500, 1000, 2000, 4000, and 8000ng/mL. 40mL of 1mg/mL chlorprothixen was measured into a 100mL volumetric flask and diluted to volume with methanol to produce 400µg/mL chlorprothixen solution. To each 1mL mobile phase sample was added 20µL of 400µg/mL internal standard solution (chlorprothixen) to produce 8000ng/mL. Aliquots of 20 µL were then injected into the HPLC. The peak area ratio (Hf/IS) obtained for each sample was plotted against the corresponding concentration to obtain the calibration line.

6 d) Determination of solubility of Hf in KH 2 PO 4 buffers

(pH 1.3, 5.9, 7.4) To 5mg of Hf weighed into a test tube, 5mL of phosphate buffer (pH 5.9) was added to it. The mixture was then shaken in a water bath at 37 o C for 1h after which it was centrifuged at 4000 rpm for 15 minutes to get a clear supernatant. The procedure was repeated with buffers of pH 1.3 and 7.4. After centrifuging, 20µL of the supernatant were injected into the HPLC and the concentrations of Hf were extrapolated from the calibration line.

7 e) Interactions of Hf with caffeine

0.6063g of caffeine was weighed into a volumetric flask and made up to 25mL with phosphate buffer (pH 5.9). 5mL each of this preparation was placed in three different test tubes. An excess of Hf was weighed into each test tube and the test tubes were placed on a water bath adjusted to 37 o C and shaken for 1h. The solutions were centrifuged at 4000rpm for 15 minutes and the supernatants collected and analyzed for Hf. The procedure was repeated using phosphate buffers pH 1.3 and 7.4.

8 f) Preparation of extracts of caffeine-containing beverages

The seeds of Coffee arabica were powdered using a mortar and pestle. 2.5g of the powdered coffee seeds were dissolved in 25mL of KH 2 PO 4 buffer (0.05M, ionic strength 0.08, pH 5.9) and mixed in a vortex mixer for 20 minutes at room temperature. The mixture was then centrifuged at 4000 rpm for 15 minutes to give a clear supernatant. The same procedure was followed using cocoa powder, black tea leaves and green tea leaves to get the extracts of cocoa, black tea and green tea respectively. g) Interactions of Hf with coffee, cocoa, black tea and green tea 5mg each of Hf was weighed into different test tubes. 5mL of each of the extracts of coffee, cocoa, black tea and green tea equivalent to 2.5g/25mL (100mg/mL) prepared above was then added to the test tube containing the Hf. The mixture was shaken in a water bath at 37 o C for 1h after which it was centrifuged at 4000 rpm for 15 minutes to get a clear supernatant. 20µl of the supernatant was injected into the HPLC. Triplicates of the above samples were prepared and the concentrations of Hf extrapolated from the calibration line.

9 h) Dissolution profile of Hf tablets alone and in the presence of caffeine

A dissolution medium consisting of phosphate buffer : methanol (75:25, v/v) was prepared using buffers at three different pH values (1.3, 5.9 and 7.4) representing gastric, duodenal and plasma pH values.

Six dissolution vessels containing 500 mL each of buffer (pH 5.9) : methanol (75:25, v/v) was set up. Three of the vessels contained a single tablet of halofantrine hydrochloride (250 mg) alone while the other three vessels contained both a tablet of Hf and 1.95 mg/mL of caffeine. The dissolution stations were maintained at 100 rpm,

and 37 o C for 1h. Samples were taken for analysis at different time intervals of 5, 10, up to 60 minutes. The procedure was repeated using buffers pH 1.3 and 7.4 respectively. All the determinations were performed in triplicate and the amount of Hf dissolved was thereafter determined spectrophotometrically.

10 i) Determination of amount of dissolved halofantrine

from tablets UV analysis of the samples was carried out at a wavelength of 310nm. Corresponding concentrations of the absorbance readings were obtained using a calibration curve equation constructed from six concentrations (2.5 -25µg/mL) of Hf.

11 III.

12 Results

The calibration line of Hf in mobile phase was linear over a concentration range of 100ng/mL to 8000ng/mL with an r 2 of over 0.999. The aqueous solubility of Hf determined at 37 o C for 1 h at pH of 1.3, 5.9 and 7.4 was found to be 323 ± 41, 77 ± 8 and 27 ± 11 ng/mL, respectively indicating highest solubility at pH 1.3. Caffeine increased the solubility of Hf at pH 1. 11ng/mL to 6646 ± 712 ng/mL. Coffee, cocoa, black tea and green tea extracts at a concentration of 2.5g/25mL also increased the solubility of Hf by over a 100-fold in pH 5.9 as shown in Table **??**. Coffee and cocoa extracts increased the solubility from 77 ± 8 ng/mL to 11525 ± 593 and 17270 ± 1680 ng/mL respectively while black For the dissolution rate studies, the amount of Hf dissolved at pH 1.3, 5.9 and 7.4 were 3574.48 ± 92.53, 947.93 ± 194.12, and 259.9 ± 43.15 µg respectively, but with the addition of caffeine to the dissolution medium, the amount dissolved increased to 9506.93 ± 226.6, 3703.13 ± 117.98, and 522.42 ± 104.54 µg of Hf at the same pH values indicating 3-, 4and 2-folds increment respectively. A plot of amount of Hf dissolved at 60 mins against the physiologic pH revealed the degree of impact caffeine had on the dissolution of Hf.

IV.

13 Discussion

The ionic strength of 0.08 was used for the solubility studies of Hf studies because it is at this strength that optimum results was obtained in previous studies [11]. The effect of caffeine on the solubility of Hf investigated at three pH values of 1.3, 5.9 and 7.4 represents gastric, duodenal and physiological pH respectively. pH 5.9 is a good approximation of duodenal pH with or without food and since Hf is administered orally for the treatment of malaria, its solubility profile at this pH will be useful. pH 5.9 was chosen as the pH medium for the interaction of the caffeine-containing beverages with Hf since it gave the optimum results observed with caffeine. The extracts of these beverages increased the solubility of Hf at this pH in the following order: Green tea>Cocoa>Coffee>Black tea. The caffeine contents of these beverages from literature vary and in some cases, the % content overlaps. For example, the % content are; coffee (1-2%), cocoa (0.6-0.36%), green tea and black tea (1-5%) [13,14]. Cocoa which is reported to have the lowest caffeine content was expected to cause minimum solubility on interaction with Hf if the interaction is solely based on caffeine content. However it was placed 2 nd in this study. Cocoa also contains cocoa butter which is fatty and since Hf is lipophilic and affected by fatty foods [1,8], it is likely that the cocoa butter may be contributing to the increase in solubility of Hf.

Preliminary investigations were carried out to find out the effect of some of the other constituents present in the extracts such as theophylline and trigonelline but these were found to have no effect on the solubility of Hf.

The dissolution profile of a drug is an important parameter in evaluating its bioavailability since dissolution precedes absorption. Earlier studies of the aqueous solubility of halofantrine, a poorly soluble and weakly basic drug conducted by Lim and Mei [11] shows that the solubility is greatest at the low pH range of 2.5-3.5 and shows a steep hundred fold decline as the pH is increased to 8.0. This was attributed to a change in the state of protonation of halofantrine.

However, the aqueous solubility of halofantrine in phosphate buffer pH 5.9 and 7.4 was found to be increased by the addition of caffeine and nicotinamide; of which pH 5.9 showed the greatest solubility [11].

Fig. **??** shows the calibration curve generated for the absorbance measurement of Hf at 310nm. The curve was linear over a range of 2.5-25µg/mL with a regression coefficient and coefficient of determination of 0.996 & 0.993 respectively.

The solubility of halofantrine was then determined both in the absence and presence of caffeine. The dissolution profiles (Figs. **??** & 3) reveal an increase in the amount of Hf dissolved in the presence of caffeine for all the physiologic pH values.

The amount of Hf dissolved increased by 3-, 4and 2-folds in the presence of caffeine at pH 1.3, 5.9 and 7.4 respectively. This solubility enhancement has been attributed to complex formation between caffeine and Hf in accordance with the ? -donor ? -receptor mechanism proposed by Fawzi et al [18] and Abdul et al [19].

The amount of the drug dissolved at 60 mins at the various pH values also clearly shows that caffeine had a great impact on the dissolution of halofantrine. Fig. **??** shows r 2 of 0.972 with caffeine and 0.897 without caffeine. The decrease in the amount of halofantrine that dissolved at 60 mins with pH increase is as a result of the weakly basic nature of the drug. Since many drugs exist as either weakly basic or weakly acidic compounds,

their ionization in water which also influences their solubility and absorption is influenced by pH. In the presence of an acidic pH, a weakly basic drug dissolves better as it is able to form a soluble salt. However the dissolution diminishes as the pH is increased and the weakly basic drug tend to precipitate **??**20].

The analysis of variance (2-way ANOVA) on the amount of halofantrine dissolved at the 60 mins shows that a highly significant ($p<0.001$) interaction exists between the effect of caffeine and the pH effect on the dissolution of this drug.

V.

14 Conclusion

Caffeine enhances the solubility of halofantrine in a remarkable way and beverages that contain varying amounts of it also have similar effect as shown in the effects of coffee, cacao, black and green tea. It is obvious that these extracts that contain caffeine increased the in vitro solubility of Hf markedly. Although in vitro analyses of Hf in the presence of caffeine and caffeine-containing beverages show increase in the amount of Hf, an in vivo study recently carried out showed a decrease in the concentration of Hf when coadministered with kolanut -a caffeine containing nut (Kolade et al 2008). Whether in vivo studies involving coffee, cacao, black tea and green tea will give replicate results as kolanut still remains to be investigated.

Although in vitro results do not correspond with in vivo effect of caffeine on Hf, it still is evident that caffeine, either in pure form or as a constituent of food, does impact on the profile of Hf when co -administered and therefore the ingestion of the two together must be closely monitored in order to determine therapeutic importance of these findings.

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Figure 1:

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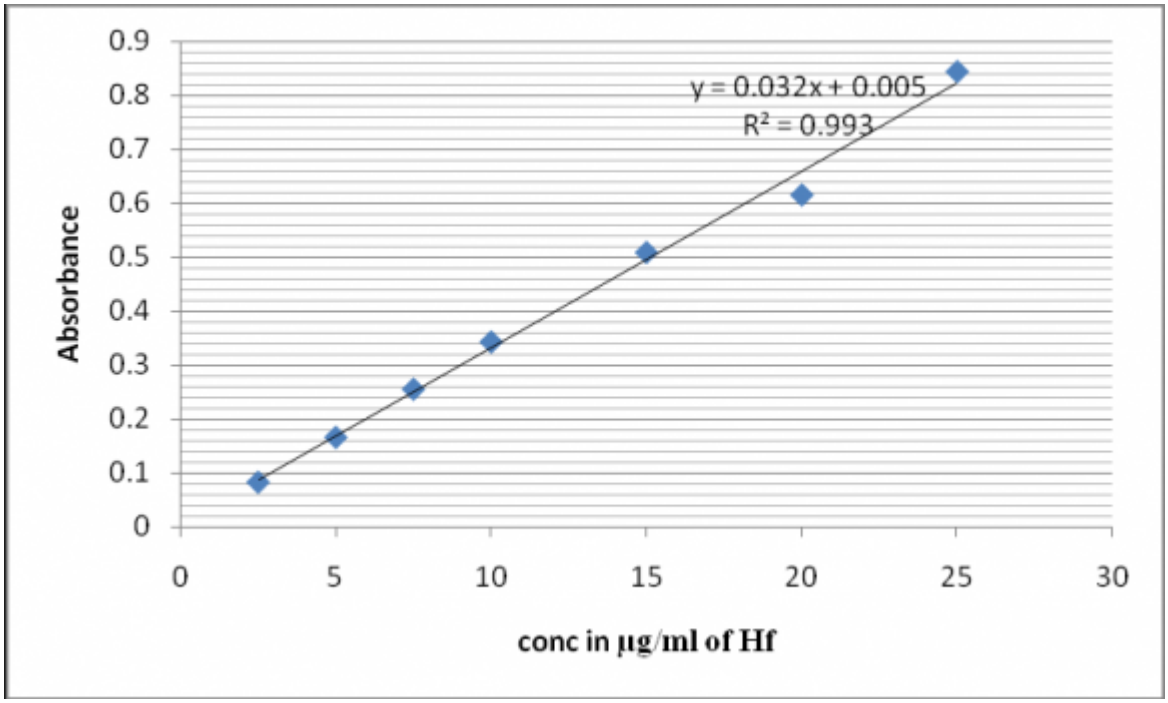

Figure 2: B

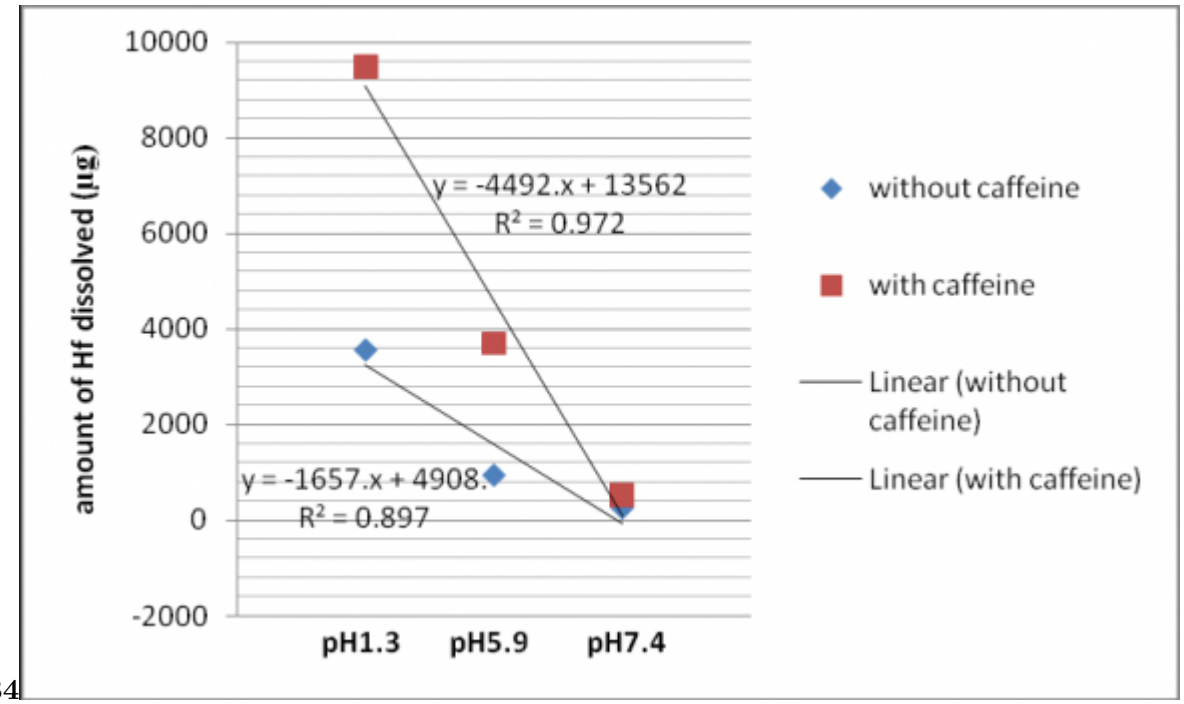

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Figure 3: Figure 3 :Figure 4 :

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