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Amodiaquine less sensitive than chloroquine to photochemical reactions

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Amodiaquine is receiving more attention now that there is increase in the spread of chloroquine-resistant *Plasmodium falciparum* in different parts of the world. Indeed amodiaquine has been found to be active against *P. falciparum* (Watkins et al., 1984; Spencer et al., 1984). Amodiaquine, like chloroquine, is a derivative of 4-aminoquinoline. The effect of sunlight, heat and ultraviolet (UV) irradiation on chloroquine has been reported (Sams and Carroll, 1966; Owoyale and Elmarakby, 1982). A similar study had also been carried out on proguanil by Owoyale and Elmarakby (1989). In continuation of the studies on the stability of antimalarials, it was decided to examine the effects of sunlight, heat and UV irradiation on amodiaquine more especially in the light of amodiaquine's increasing role in malaria chemotherapy.

It has been shown recently that UV irradiation with a 366 nm UV lamp is more effective than with a 254 nm lamp (Owoyale, 1989). Accordingly amodiaquine was irradiated with a 366 nm UV lamp.

Hydrated amodiaquine hydrochloride was obtained from camoquine tablets manufactured by Pharma-Deko (Nig) Ltd after dissolution of the tablets, filtering, concentration of the filtrate and recrystallization of the crystals obtained from water–ethanol. The presence of the water of hydration was confirmed by differential thermogravimetry using a Mettler TA 3000 thermal analysis system. UV irradiation was performed with a Camag UV lamp Type 2900 Ger No.850459 with a 366 nm fixed wavelength. The UV spectra were run on a Pye Unicam SP8-200 UV/visible spectrophotometer.

Phosphate buffer (0.1 M) solutions (pH 5.6, 7.4, 8.0 and 10.0) were prepared and used separately to obtain 1 μg/ml of amodiaquine hydrochloride upon dilution from a 1 mg/ml aqueous solution. The UV spectrum of each sample in the different pH buffer solutions was run in quartz cells. The samples were then exposed to sunlight, UV (at 366 nm) and heat (50 °C oven and water bath) for at least 8 h and their UV spectra were run.

The effect of pH on amodiaquine is shown in Fig. 1 (a,c,e) and Fig. 2 (a,c,e). At pH 10, the UV spectrum is similar to that at pH 8 (Figs. 1e and 2e) except that the absorbance is lower and the 342 nm peak is flattened. Accordingly the various effects on pH 10 buffer solutions of amodiaquine have not been shown throughout this investigation. At pH 5.6, the 342 nm peak was the highest and this peak decreased through pH 8.0 (and pH

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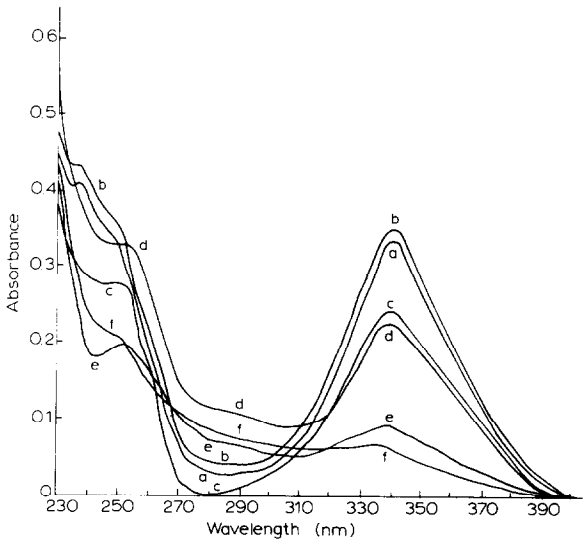

Fig. 1. Amodiaquine hydrochloride in phosphate buffer heated on a water bath for 8 h. a = pH 5.6 (control); b = pH 5.6; c = pH 7.4 (control); d = pH 7.4; e = pH 8.0 (control); f = pH 8.0.

10). In the lower wavelength region, the two inflections at 237 nm and 250 nm at pH 5.6 gave way to a new 252 nm peak at pHs 7.4 and 8.0 (and

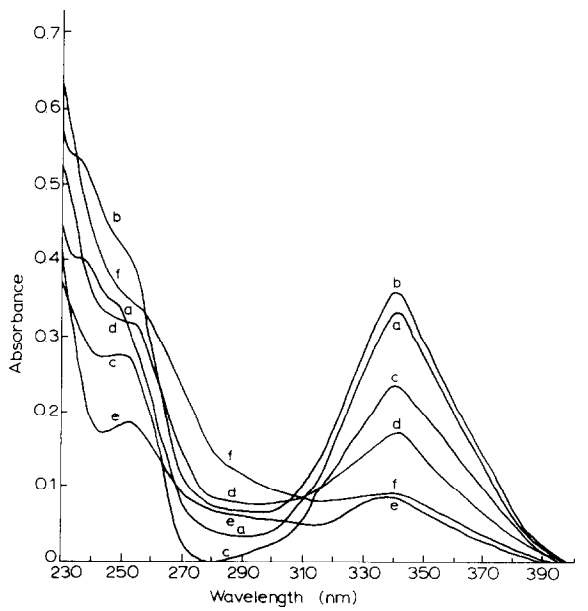

Fig. 2. Amodiaquine hydrochloride in phosphate buffer exposed to sunlight for 8 h. a = pH 5.6 (control); b = pH 5.6; c = pH 7.4 (control); d = pH 7.4; e = pH 8.0 (control); f = pH 8.0.

pH 10.0). The new peak could be due to the ionization of the phenolic hydroxyl group of amodiaquine at pH greater than 7.

The spectra of amodiaquine heated in a darkened oven were identical to those of the controls (Fig. 1a,c,e). Fig. 1, however, shows the effect of heat (50 °C on a water bath at laboratory illumination as supplied by daylight fluorescent tubes) on amodiaquine in the different pH buffer solutions. At pH 5.6, there was no effect on amodiaquine. At pH 7.4, there appeared to be some increase in only the absorbance in the region 230–320 nm while at pH 8.0 the 252 nm peak was becoming an inflection but without any appreciable increase in absorbance. These spectral differences could be due to the illumination from the daylight fluorescent tubes.

The effect of sunlight is presented in Fig. 2. The region 230–320 nm was mainly affected while the characteristic peak at 342 nm was not generally affected. In all pHs, there were some increases in absorbance in the 230–320 nm region. There was, however, no change in peak characteristics at pH 5.6 whereas at pH 7.4 and particularly pH 8.0, an inflection was recorded at 252 nm. The cell temperature of the exposed solutions was $\leqslant 42$ °C, therefore these minor differences in spectra were mainly due to the ultraviolet irradiation from sunlight.

The effect of UV irradiation is similar to that recorded for the sunlight exposure (Fig. 2). The temperature recorded in the cells of UV-irradiated amodiaquine was 38 °C.

Unlike chloroquine which showed the "spectral shift" phenomenon at concentrations $\leqslant 50$ μg/ml (Sams and Carroll, 1966; Owoyale, 1989) when exposed to sunlight or UV light, amodiaquine did not show any appreciable "spectral shift" even at 10 μg/ml, hence 1 μg/ml solution was used in this study. This suggests that amodiaquine was more stable than chloroquine in these buffer solutions since the lower the concentration the more pronounced is the "spectral shift". There was no noticeable change in colour of the amodiaquine solutions on irradiation with UV light and there was no fluorescence unlike what was reported for chloroquine (Owoyale and Elmarakby, 1982; Owoyale, 1989).

Though there were some increases in absorbance in the 230–320 nm range (a prerequisite for those compounds that undergo photochemical reactions) (Storck, 1965), amodiaquine did not appear to readily undergo photochemical reactions like chloroquine. The absence of fluorescence and colour changes appeared to support the above observation since compounds that are photoallergic and/or photosensitive usually undergo fluorescence, "spectral shift" phenomenon and colouration (Storck, 1965). Chloroquine exhibited fluorescence, "spectral shift" phenomenon and pink colouration (Owoyale, 1989) which was not the case with amodiaquine.

Some studies on 4-aminoquinoline (Kovi et al., 1972) and chloroquine (Schulman and Young, 1974) indicated that at pH 10, the fluorescence of chloroquine was quenched, vanishing completely at pH 14. This phenomenon was attributed to proton abstraction from the 4-amino group of chloroquine and 4-aminoquinoline in the fluorescence state beyond pH 10. Chloroquine does not fluoresce at low pH (Sams and Carroll, 1966; Owoyale and Elmarakby, 1982). One may thus suggest that the presence in amodiaquine of a phenolic group whose proton can be abstracted above pH 7 even at the ground state might be responsible for the absence of fluorescence, and therefore the absence of both the "spectral shift" phenomenon and the development of colouration which are all indicative of the greater stability of amodiaquine compared to chloroquine in phosphate buffer solutions.

References

Kovi, P.J., Capomacchia, A.C. and Schulman, S.G., Electronic spectra of 4-aminoquinoline and 4-aminoquinaldine. Evidence for the cyclic amidine structure of singly protonated cations. *Anal Chem.*, 44 (1972) 1611–1615.

Owoyale, J.A., Decomposition profile of ultraviolet irradiated chloroquine. *Int. J Pharm.*, 52 (1989) 179–181.

Owoyale, J.A. and Elmarakby, Z., On the ultraviolet "spectral shift" phenomenon of chloroquine. *Int. J. Pharm.*, 12 (1982) 265–269.

Owoyale, J.A. and Elmarakby, Z.S., Effect of sunlight, ultraviolet irradiation and heat on proguanil. *Int. J. Pharm.*, 50 (1989) 219–221.

Sams, W.M. and Carroll, N.V., The "spectral shift" phenomenon of chloroquine. *Arch. Dermatol.*, 93 (1966) 123–128.

Schulman, G.S. and Young, J.F., A modified fluorimetric determination of chloroquine in biological samples. *Anal. Chim. Acta*, 70 (1974) 229–232.

Spencer, H.C., Oloo, A.J., Watkins, W.W., Sixsmith, D.G., Churchill, F.C. and Koech, D.K., Amodiaquine more effective than chloroquine against *Plasmodium falciparum* malaria on Kenya Coast. *Lancet*, i (1984) 956–957.

Storck, H., Photoallergy and photosensitivity. *Arch. Dermatol.*, 91 (1965) 469–482.

Watkins, W.M., Sixsmith, D.G., Spencer, H.C., Boriga, D.A., Kariuki, D.A., Kipingor, T. and Koech, D.K., Effectiveness of amodiaquine as treatment for chloroquine resistant *Plasmodium falciparum* infections in Kenya. *Lancet*, i (1984) 357–359.