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COMMUNICATION

SUPPOSITORY FORMULATION OF AMODIAQUINE - IN VITRO RELEASE CHARACTERISTICS

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ABSTRACT

In vitro release characteristics of amodiaquine hydrochloride from suppositories were studied. Results showed that water soluble bases (polyethylene glycol and glycero-gelatin) and water miscible synthetic fatty base (Witepsol W45) are superior to natural fatty bases (theobroma oil and shea butter) in terms of their ability to release amodiaquine hydrochloride.

The in vitro availability of amodiaquine from polyethylene glycol suppository (the suppository which gave the highest rate and extent of release) was compared with its in vitro availability from tablets (Camoquin$^{(R)}$) under the same experimental conditions. Polyethylene glycol suppository was found to be superior to the tablet.

INTRODUCTION

Amodiaquine hydrochloride has generally been considered equal in antimalarial activity to the more widely used chloroquine (1,2). Hepatic biotransformation to desethylamodiaquine seems to result in a considerable first pass effect such that very little of the orally administered amodiaquine escapes unchanged into systemic circulation (3). It has been shown that the antimalarial activity of amodiaquine is greater than that of desethylamodiaquine, the major metabolite (4).

Though pharmacokinetic studies have indicated that amoqiaquine could be administered by slow rate-controlled infusion (1), parenteral admini-

stration of drug is difficult for ambulatory patients. World Health Organisation recently reported that priority for drug development is suppository preparations of chloroquine, amodiaquine and mefloquine (5). The indication is that it is worthwhile to embark on suppository formulation of amodiaquine. It will serve as an alternative to tablet formulation to overcome the problem of first pass effect.

MATERIALS AND METHODS

Amodiaquine hydrochloride was extracted from Camoquin(R) tablets (Parke-Davis, U.K.). The characterization of the extracted product involved melting point determination, thin layer chromatography and U.V. analysis. The values obtained compared favourably to B.P. (1980) values. Polyethylene glycol 4,000 (B.D.H.); polyethylene glycol 1,000; gelatin (Hopkin and Williams, England); Witepsol W45 (Dynamit Nobel, West Germany); glycerol (B.P.); theobroma oil (B.P.) (Halewood chemicals Ltd., England); shea butter (from a local market in Ile-Ife).

Preparation of Amodiaquine Suppositories

All suppositories containing 50mg amodiaquine hydrochloride were prepared by the fusion method. The compositions of the bases are: PEG (polyethylene glycol 1,000 (75% $^{W}/_{W}$) and polyethylene glycol 4,000 (25%$^{W}/_{W}$));Witepsol W45; theobroma oil; shea butter and glycero-gelatin (glycerol 70%$^{W}/_{W}$, gelatin 20%$^{W}/_{W}$ and water 10%$^{W}/_{W}$).

Experimental Design and Statistical Analysis

The factor varied was the suppository base and the design used for this single-factor experiment was randomized complete block design. Five bases were used (treatments) with three replications or blocks. Analysis of variance for a randomized complete block design together with F-test was conducted and comparison among treatment means was carried using the Least Significant Difference test and Duncan's Multiple Range test (6).

Determination of Release Rates

The method used is a modification of the continuous flow bead-bed dissolution apparatus for suppositories earlier described by Roseman et al (7). The release chamber consists of a Gallen Kamp sinta glass No.3 with the suppository enclosed in a bed of glass beads. The chamber was suspended in 500ml 0.1MHCL in a 1000ml beaker. The whole

TABLE I

Results of Duncan's Multiple Range Test for Differences Among the Means of Release Rate Constants and the Means of the Amount Released.

Suppository Base	Release Rate Constants (mg $min^{-\frac{1}{2}}$)	Amount Released (mg)
Polyethlene Glycol	15.45389	27.50
Witepsol W45	6.71667 *	12.63 *
Glycero-Gelatin	5.94926 *	10.50 *
Theobroma Oil	4.24051	7.30
Shea butter	1.00615	1.97

*Bases Not Underscored By The Same Line Are Significantly Different; Bases Underscored By The Same Line Are Not Significantly Different (At 5% Level of Significance).

set-up was placed on a magnetic stireer thermostat hot plate (set at speed No.6) maintained at 37±C. 5ml samples were withdrawn at time intervals and assayed for amodiaquine using U.V. Spectrophotometric method at 340nm.

RESULTS AND DISCUSSION

Straight line relationship was obtained when the amount released was plotted versus square root of time for all the bases with correlation coefficients ranging from 0.97 - 0.99. Similar observations have been reported previously with some suppositories (7). The results of the analysis of variance for the mean release rate constant ($mgmin^{-\frac{1}{2}}$) and the mean of amount released (mg) showed that the five bases exhibited highly statistically significant differences in the in vitro availability of amodiaquine. The block effect was not significant indicating the reproducibility of the suppository preparation and dissolution rate test. To locate the specific differences among the bases, the Least Significant Difference and Duncan s Multiple Range tests were carried out (6) and they gave the same results. Table 1 shows the result of Duncan s Multiple Range test.

The mean release rate constant and the mean of amount released obtained with polyethylene glycol suppositories are statistically significantly different from other suppositories (Table 1). Amodiaquine hydrochloride is a water-soluble drug; its release is favoured by the water soluble base (polyethylene-glycol). Witepsol W45 is an esterified fatty acid with a high hydroxyl value. The high proportion of partial glycerides in Witepsol W45 makes it superior to theobroma oil and shea butter. Witepsol W45 and glycero-gelatin bases show no difference and this can be attributed to the fact that both of them are readily miscible with water.

The desorption of the drug from theobroma oil and shea butter after fusion is slow because they are not readily miscible with the release medium. The difference between theobroma oil and shea butter (Table 1) may reflect the differences in their chemical compositions and their melting points (theobroma oil 36°C and shea butter 37.8°C).

The mean percentage release from Camoquin(R) tablets is 43.96% while that of polyethylene glycol suppositories is 55%. T-test at 5% level of significance shows the difference to be statistically significant.

CONCLUSION

The water-soluble bases andthe synthetic fatty base with high hydroxyl value were found to be superior to the natural fatty bases in terms of their ability to release amodiaquine hydrochloride. The suppository formulations were found to be better than the tablets and this further strengthens the need to pursue formulation of amodiaquine as a suppository.

REFERENCES

1. N.J. White, S. Looareesuwan, G. Edwards, R.E. Phillips, J. Karbwang, D.D. Nicholl, C. Bunch and D.A. Warrell, Br. J. Clin. Pharmac. 23, 127 (1987).

2. W.M. Watkins, D.G. Sixsmith, H.C. Spencer, D.A. Boriga, D.M. Kavinki, T. Kipinger, and D.K. Koeh, Lancet 1, 357 (1984).

3. L.A. Salako and O.R. Idowu, Br. J. Clin. Pharmac. 20, 307 (1985).

4. F.C. Churchill, L.C. Patchen, C.C. Campbell, I.K. Schwartz, D. Nguyen, and C.M. Dickinson, Life Sci. 36, 56 (1985).

5. "Severe and Complicated Malaria" WHO Malaria Action Programme. Transactions of the Royal Society of Tropical Medicine and Hygine, Vol. 80 (Supplement) 1986.

6. R.G.D. Steel and J.H. Torrie "Principle and Procedures of Statistics, a Biometrical Approach" Second Ed. McGraw-Hill International Book Company. (1981).

7. T.J. Roseman, G.R. Derr, K.G. Nelson, B.L. Lieberman and S.S. Butter, J. Pharm. Sci 70, 646 (1981).