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Excretion of hydroxychloroquine in human milk

Hydroxychloroquine is a 4-aminoquinoline compound that possesses antimalarial activity and it also exerts a beneficial effect in lupus erythematosus and rheumatoid arthritis. The drug is potentially very toxic and may have adverse effects on the eyes, skin, heart, nervous system, blood, ears and gastrointestinal tract (Tester-Dalderup, 1980).

Most drugs can be expected to be excreted into breast milk to some extent and consumed by a suckling infant (Wilson *et al.*, 1980). Although there are no data on the excretion of hydroxychloroquine into human milk, the advisability of mothers breast feeding their infants while receiving antimalarial drugs has been questioned (Wilson *et al.*, 1980). Two reports that the closely related antimalarial chloroquine was not detected in milk have been cited (O'Brien, 1974). However, both these reports used chemical assay methods which were less sensitive and specific than those currently available. Chloroquine is a relatively small molecule (molecular weight 320), it is a base (pK_as 8.37 and 10.76) which is only approximately 60–65% bound in plasma (Walker *et al.*, 1983) and the pH of milk is generally slightly lower than that of blood (Wilson *et al.*, 1980). Therefore on theoretical grounds chloroquine would be expected to be excreted in milk.

We have been able to perform a study on the extent to which hydroxychloroquine is excreted into human milk. Studies on drug excretion in breast milk are usually opportunistic in nature (Wilson *et al.*, 1980) and this was the case in the present investigation. As a result, the number of milk and blood samples collected and their timing were less than ideal, and recognised limitations exist in the pharmacokinetic analysis of the data. The results of our study are reported in this communication.

The subject was a 27 year old mother who had been breast feeding her infant for 9 months. At the time of the study, the mother weighed 52 kg and the infant 10 kg; the mother had been regularly taking a nightly dose of 400 mg hydroxychloroquine sulphate (Plaquenil tablets, Winthrop Laboratories; equivalent to 310 mg hydroxychloroquine base) for a period of 6 weeks to control an exacerbation of systemic lupus erythematosus. The subject collected four milk samples by manual expression during two consecutive dosage intervals; sampling times were 2, 9.5 and 14 h after the first dose and 17.7 h after the second dose. A heparinized blood sample was collected 15.5 h after the first dose.

Hydroxychloroquine (base) concentrations in milk, whole blood and plasma were determined by high-performance liquid chromatography (h.p.l.c.). Briefly, an aliquot (1 ml) of biological fluid was placed in a silanized glass centrifuge tube and chloroquine (equivalent to 1.8 μg, 3 μg or 0.6 μg chloroquine base for milk, whole blood or plasma, respectively) was added as internal standard. The samples were alkalinized by the addition of sodium hydroxide (0.45 M, 0.2 ml) and then extracted by vigorous shaking for 5 min with dichloromethane (10 ml). After centrifugation, the aqueous layer was discarded and 8 ml of the organic phase was transferred to a silanized glass tube and evaporated at 50°C under a stream of nitrogen. The residue was dissolved in 200 μl of h.p.l.c. mobile phase and 80 μl of the resulting solution was injected onto the h.p.l.c. column. The mobile phase was acetonitrile: phosphate buffer (45 mM potassium dihydrogen phosphate adjusted to pH 3 with phosphoric acid) in the proportions 15:85 and it was pumped at 2 ml/min through a 30 cm × 4 mm i.d. μBondapak C_{18} column (Waters Associates, Milford, MA). The column effluent was monitored by an ultraviolet detector set at 330 nm. Hydroxychloroquine and chloroquine had retention times of 3.8 min and 4.7 min, respectively, and they were separated from endogenous compounds. Standard curves for milk (over the range 0.5–4 mg/l), whole blood (0.5–4 mg/l) and plasma (0.1–0.5 mg/l) were run with the subject's samples and the lower limit of sensitivity of the assay was 0.05

mg/l for milk and blood and 0.01 mg/l for plasma. The coefficients of variation for replicate analyses (n = 5) of milk (performed at 1 mg/l), whole blood (1 mg/l) and plasma (0.15 mg/l) were 5.4%, 4.4% and 5.5%, respectively.

The concentrations of hydroxychloroquine in the four milk samples were 1.46, 1.09, 1.09 and 0.85 mg/l at the sequential sampling times. There was considerably less than two-fold variation in the milk concentrations during the many hours after drug administration, as might be expected for a drug with a half-life of 5–7 days (Mackenzie & Scherbel, 1980). In this opportunistic study four milk samples were collected during two consecutive dosage intervals. The resulting milk drug concentration-time data were insufficient to allow pharmacokinetic calculation of the mean milk concentration of hydroxychloroquine during a dosage interval. However, the arithmetic mean drug concentration for the four milk samples was calculated and was 1.1 mg/l. The whole blood and plasma hydroxychloroquine concentrations were 1.76 and 0.20 mg/l, respectively, indicating that the drug distributes extensively into blood cells, as does chloroquine (Walker *et al.*, 1982). Using the 14 h milk sample and the 15.5 h blood sample, the milk to plasma concentration ratio was approximately 5.5 while the milk to whole blood ratio was approximately 0.6.

In discussing drugs contraindicated in breast feeding mothers, Wilson *et al.* (1980) have suggested that special concern should be given to those drugs which have a milk to plasma concentration ratio of greater than or equal to unity. The milk to plasma ratio found in the present study for hydroxychloroquine was some 5.5 times greater than that value. However, analysis of the results indicates that the dose of hydroxychloroqine received by the infant was relatively small. Assuming that steady state conditions were obtained (as would be expected after 6 weeks treatment) and a daily milk consumption of 1 l for a 9 month old infant (Rattigan *et al.*, 1981), the daily dose of hydroxychloroquine (base) received by the infant via breast feeding would be about 1.1 mg. This dose is 0.35% of the daily maternal dose of 310 mg. After correction for body weight, the maternal and infant doses correspond to 5.96 and 0.11 mg/kg, respectively. That is, on a body weight basis, the infant dose would be about 2% of the maternal dose.

In conclusion, we have demonstrated that hydroxychloroquine is excreted in human milk. However, in the absence of information on the pharmacokinetics and pharmacodynamics of hydroxychloroquine in infants, the clinical significance of this finding remains speculative.

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Received August 10, 1983,
accepted November 4, 1983

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Facial flushing induced by vasopressin-like peptides lacking pressor activity

Facial flushing sometimes occurs when I-desamino-8-D-arginine vasopressin (DDAVP) is given intravenously (0.4 μg/kg over 15 to 20 min) to man (Mannucci *et al.*, 1977; Ockelford *et al.*, 1980). It is unexplained. DDAVP has negligible pressor effects hence the flushing is paradoxical,