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 hydroxychloroquine 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.

R. L. NATION*, L. P. HACKETT, L. J. DUSCI & K. F. ILETT

Combined Unit in Clinical Pharmacology and Toxicology, The Queen Elizabeth II Medical Centre, Nedlands, W.A. 6009, Australia

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*Present address: School of Pharmacy. The South Australian Institute of Technology, North Terrace, Adelaide, South Australia 5000.

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Facial flushing induced by vasopressin-like peptides lacking pressor activity

Facial flushing sometimes occurs when 1-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,

being *opposite* to the vasoconstrictor action of vasopressin. The vasopressin analogue 8-arginine-9-deglycinamide vasopressin (DGAVP; Org 5667) has negligible pressor and anti-diuretic properties, but retains the behavioural effects of vasopressin in rats. Both peptides are under investigation in man for possible effects on mood and memory. Freeze-dried DGAVP dissolved in saline was given subcutaneously (s.c.) or intramuscularly (1 mg at 08.00 h and 14.00 h, for 10 days) to four healthy male volunteers (20–30 years). The volunteers were resident throughout the study at the Deutsche Klinik für Diagnostik, Wiesbaden, Germany, and observed by Dr W. Hausen and Prof. Dr Med. L. Kuhl. Visible facial flushing and subjective head warmth occurred in all subjects and accompanied 66% of injections. Similar effects were seen after a single dose (1 mg s.c.) in four of five further cases, but not with placebo (saline). The onset of flushing was sometimes immediate or delayed up to 60 min (mean 24 min). Its duration varied from 150 to 120 min (mean 49 min). No other clinical or laboratory variables changed consistently. The frequency of flushing appears greater than that reported for DDAVP, but so was the 1 mg dose ($\times 36$). Flushing has not been reported following intranasal (i.n.) DDAVP, or DGAVP (10 mg i.n.). Parenteral routes might produce higher plasma peaks than those after nasal administration. Intranasal DDAVP takes 4 h to reach its maximum plasma level (Seif *et al.*, 1978).

Two possible hypotheses could explain the flushing. The first involves peripheral mechanisms. Arginine vasopressin (AVP) in physiological concentrations causes vasoconstriction and potentiates the effects of vasoconstrictor agents (Karmazyn *et al.*, 1978). The action probably involves Ca^{2+} dependent (V_1) receptors, whereas the anti-diuretic effects are mediated by adenylate cyclase linked (V_2) receptors (Mitchell *et al.*, 1976). DDAVP can block V_1 receptors (Derckx *et al.*, 1984). It is possible that DGAVP does the same, with competitive inhibition removing AVP tonic control.

The second hypothesis for DGAVP flushing involves opioid mechanisms in the central nervous system. The met-enkephalin analogue FK 33-824 causes a local reaction and facial flushing similar to DGAVP, with a similar time course

(Von Graffenried *et al.*, 1978). The chlorpromamide alcohol flush is thought to involve enkephalins (Medback *et al.*, 1981). Intravenous infusions of morphine to man cause facial flushing and a lasting (35 min) vasodilatation of hand vessels, which can be blocked by naloxone, whereas intra-arterial morphine has no effect on hand vessels, suggesting a central mechanism for the vasodilatation (Cohen & Coffman, 1980). Furthermore, endogenous enkephalins applied to the ventral brain stem cause vasodilatation (Florez & Mediavilla, 1977). DGAVP interacts with opioid mechanisms. In rats tolerance to morphine occurs earlier following DGAVP pre-treatment (Van Ree & de Wied, 1981), as do the withdrawal symptoms that follow a naloxone challenge (Van Ree & de Wied, 1977). It should be noted that tolerance is favoured by the continuous presence of a drug in adequate concentrations (Goldstein *et al.*, 1974). DGAVP also reduces heroin self-administration by rats (Van Ree & de Wied, 1981). Thus it is possible that DGAVP prolongs the action of exogenous and endogenous opioids. According to the experimental paradigm this then results in either earlier tolerance and dependence, or a delayed need for further heroin self-injection. Likewise, vasopressins devoid of pressor effects might cause a flush by *sustaining the central action of endogenous opioids on vasodilatation*. If natural vasopressins also sustain central opioid activity their peripheral vasoconstrictor effects would prevent any flushing.

Further clinical research (measuring skin temperature and conductance) is needed to establish if thermoregulation (also influenced by opioids) is involved in DGAVP flushing. Blockade of the flush by naloxone would indicate an opioid link and central activity. Studies *in vitro* would show if DGAVP blocks peripheral V_1 receptors. The two mechanisms proposed for the flushing need not be mutually exclusive.

R. M. PIGACHE

*Medical Research and Development Unit,
Organon International B.V., P.O. Box 20, 5340
BH Oss, The Netherlands*

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