NADOLOL IN HUMAN SERUM AND BREAST MILK

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1 Simultaneous serum and milk samples were collected over a 10-day period from twelve normotensive, lactating subjects who ingested 80 mg nadolol once daily for a period of 5 days. For comparative purposes, serum samples were also collected from seven patients with a history of mild essential hypertension who ingested the same dose of nadolol for a period of 13 days.

2 In lactating subjects, steady-state serum concentrations of nadolol were attained in 3 days. Milk concentrations of nadolol were much higher than serum concentrations starting on Day 3 and throughout the remainder of the study. The mean ($\pm$ s.e. mean) steady-state levels of nadolol in milk (356.9 ± 40.4 ng/ml) were 4.6 times higher than the mean steady-state levels in serum (77.3 ± 6.9 ng/ml).

3 In hypertensive patients, the mean serum concentration of nadolol 24 h after the twelfth dose was 40.3 ± 8.2 ng/ml as compared to a mean serum concentration in lactating subjects of 40.7 ± 3.4 ng/ml, 24 h after the fifth dose. Mean serum concentrations in hypertensive patients at 1 and 4 h after the final daily dose were not significantly different from those in lactating subjects.

4 It can be estimated that a 5 kg nursing infant would consume about 2–7% of the daily adult therapeutic dose of nadolol. The data suggest that caution should be exercised in the use of nadolol in lactating patients.

Introduction

The medical literature on the subject of drugs in breast milk is often difficult to interpret. Relatively insensitive biochemical assays have led to reports that detectable levels of drugs were not found in milk. However, it is now known that virtually any substance in maternal blood is capable of passing into milk (Anderson, 1977). Many of the published reports in this field have been anecdotal and describe data obtained from so few subjects that extrapolation of results to the general patient population is scientifically precarious. Moreover, very few studies have been designed to take into account the pharmacokinetic behaviour of drugs. Knowledge and application of parameters such as elimination half-life ($T_{1/2}$), peak drug concentration (C_{max}), time to peak drug concentration (T_{max}) and mean steady-state serum levels are extremely helpful, perhaps indispensable requisites, for a useful study design.

In this report, we describe steady-state serum and milk levels of the new β -adrenergic receptor blocking agent, nadolol. The pharmacokinetics of nadolol in serum have been described previously (Dreyfuss *et al.*, 1979). Nadolol has a relatively long elimination half-life (14–24 h) that allows for once daily dosing in the treatment of both angina pectoris and hyper-

tension. Steady-state serum levels are achieved in 3–5 days. Thus, in the present study, twelve lactating normotensive subjects ingested 80 mg of nadolol once daily for 5 consecutive days. Simultaneous serum and milk samples were obtained before, during and after nadolol administration. In addition, sequential serum levels of nadolol were obtained from seven hypertensive patients who received 80 mg nadolol once daily for 13 days.

Methods

Drug

Nadolol is a new β -adrenergic receptor blocking agent useful in the treatment of hypertension and angina. It is designated chemically as *cis*-5-[(3-[1,1-dimethylethyl]amino) -2-hydroxypropoxyl] -1,2,3,4-tetra-hydro-2, 3-naphthalenediol.

Normotensive lactating subjects

Twelve healthy, normotensive, lactating volunteers were enrolled in this study. Each subject had been

nursing her infant for at least 1 month and had already weaned her child, or had agreed to refrain from nursing her infant for a period of 10 days, i.e. for 5 days of nadolol administration followed by 5 days of washout. Mean age for all participants was 27 years (range 18–35 years). No subject received concomitant medication during the study. Each subject agreed not to consume alcohol or caffeine-containing beverages for 12 h before and throughout the remainder of the study. Informed written consent was obtained from each subject before the study was initiated.

Each of twelve lactating subjects was administered an 80 mg nadolol tablet once a day for a period of 5 days. Samples of venous blood were collected immediately prior to the first administration of nadolol (0 h on Day 1) and 3, 51, 96, 97, 98, 99, 100, 102, 104, 120, 168 and 216 h after the first administration of nadolol. Simultaneous milk samples were obtained by means of an Egnell breast pump. Where possible, alternate breasts were employed at each milk collection. Milk samples (5–12 ml) were collected at each time point.

Hypertensive patients

Seven patients with a history of mild essential hypertension (mean duration, 6.8 ± 2.2 years, mean standing blood pressure, $149 \pm 6/99 \pm 3$ mm Hg) were enrolled in this study. Two of the patients were female and five were male. Mean age for all patients was 48.4 years (range 33–63 years).

Each hypertensive patient received an 80 mg nadolol tablet once a day for 13 days. Samples of venous blood were collected immediately prior to the final dose of nadolol and at hourly intervals for the first 4 h after the final nadolol administration.

Analysis of samples

The fluorometric method for the determination of nadolol in human serum has been described previously (Ivashkiv, 1977). Briefly, serum was saturated with alkaline potassium chloride and extracted with *n*-butyl acetate or ether. After back extraction into 0.1 N HCl, the drug was oxidized with periodic acid. The resulting aldehyde was coupled with *o*-phenylenediamine to produce a fluorescent compound. The method can detect as little as 10 ng nadolol/5 ml serum sample.

Milk samples were treated in a similar fashion except that the samples were centrifuged (12,000 g, for 1 h at 25°C) and the centrifugates recovered for extraction.

Statistics

Comparisons between milk and serum data were carried out using Student's paired *t*-test. Com-

parisons between serum data from hypertensive patients and lactating subjects were carried out using unpaired *t*-tests. Differences were considered significant at *P* levels of 0.05 to 0.001.

Results

Mean concentrations of nadolol in serum and milk over the 10-day period of this study are shown in Figure 1. Milk concentrations of nadolol were much higher than serum concentrations starting on Day 3 and throughout the remainder of the study. Analysis of the serum concentration *v* time curve suggests that steady-state serum levels were achieved by Day 3 of the study. Over the 24 h period after the last dose of nadolol, i.e., 96–120 h into the study, mean milk concentrations of nadolol were 2–8 times higher than mean serum concentrations in lactating subjects.

Various pharmacokinetic and bioavailability parameters derived from the individual time curves of nadolol concentrations in serum and milk are shown in Table 1. Much higher values were found for nadolol in milk as compared to serum during the 24 h period after the final administration of nadolol. The mean $C_{\max}$ for nadolol in milk (442.9 ± 47.1 ng/ml) was 2.7 times higher than the $C_{\max}$ in serum (161.9 ± 16.7 ng/ml, $P < 0.001$). The $C_{\max}$ for nadolol in milk was attained in 6.0 ± 0.9 h ($T_{\max}$) or 2.2 times longer than the $T_{\max}$ for nadolol in serum (2.7 ± 0.4 h, $P < 0.05$). The $AUC_{0 \rightarrow 24 \text{ h}}$ for nadolol in milk (8566 ± 969.2 ng ml⁻¹ h) was 4.6 times higher than the $AUC_{0 \rightarrow 24 \text{ h}}$ for serum (1848 ± 168 ng ml⁻¹ h, $P < 0.001$). The mean steady-state level (derived from the $AUC_{0 \rightarrow 24 \text{ h}}$ of nadolol in milk (356.9 ± 40.4 ng/ml) was 4.6 times higher than the steady-state level in serum (77.3 ± 6.9 ng/ml, $P < 0.001$). The mean half-life of elimination of nadolol from milk (21.8 h) was, however, almost identical to the $T_{1/2}$ in serum (21.7 h).

Discussion

Because the pH of milk is less than that of blood, milk can act as an 'ion trap' for basic compounds (Anderson, 1977). Basic drugs often attain higher levels in milk than in blood. On the other hand, acidic drugs tend to attain lower levels in milk relative to blood. The pKa of the drug is a primary determinant of its ability to pass into milk, with the lipid solubility (octanol/H₂O partition coefficient) being of lesser importance (Hornung, 1975). Nadolol is a weak base and has a pKa of 9.67. It is not very lipid soluble. At most time points after nadolol administration, milk levels of nadolol were 2–8 times higher than serum levels. Average steady-state levels of nadolol in milk were almost 5 times higher than those in serum. The elimination of nadolol from milk was, however,

Figure 1 Mean ($\pm$ s.e. mean) concentrations of nadolol in human serum (Δ) and milk ($\circ$) ($n = 12$).

Table 1 Mean ($\pm$ s.e. mean) pharmacokinetic parameters in serum and milk for twelve normal lactating subjects after the final 80 mg dose of nadolol

Parameter	Units	Serum	Milk	$\frac{\text{Milk}}{\text{serum}}$
$C_{\max}$	(ng/ml)	161.9 ± 16.7	$442.9 \pm 47.1^{**}$	2.7
$T_{\max}$	(h)	2.7 ± 0.4	$6.0 \pm 0.9^*$	2.2
$AUC_{0 \rightarrow 24 \text{ h}}$	(ng ml $^{-1}$ h)	1848.0 ± 168.0	$8566.0 \pm 969.2^{**}$	4.6
$T_{1/2}$	(h)	21.7^a	21.8^a	1.0
c_{ss}^b	(ng/ml)	77.3 ± 6.9	$356.9 \pm 40.3^{**}$	4.6

* Significantly different from value in serum, $P < 0.05$

** Significantly different from value in serum, $P < 0.001$

^a Geometric mean

^b Mean steady-state level (derived from the $AUC_{0 \rightarrow 24 \text{ h}}$)

almost identical to that for serum. The much higher levels of nadolol in milk than in serum may be due to the alkaline character of nadolol, though the process of active transport of the drug into milk cannot be ruled out.

Nadolol concentrations in the sera of hypertensive patients were quite similar to those in lactating normotensive subjects. Within 24 h after a dose (on a multiple dosing regimen), nadolol levels in the sera of hypertensive patients and lactating subjects were practically identical. It is therefore reasonable to suggest that hypertensive lactating individuals would have milk levels of nadolol similar to those found in the normotensive lactating subjects reported here. Obviously, the best designed study of this sort would utilize hypertensive lactating patients. In view of the logistical problems in arranging such a study, the design described in this report represents a less desirable but a reasonable alternative.

In the seven hypertensive patients, blood pressure was normalized ($< 140/90$ mm Hg) after 13 days of nadolol administration (80 mg four times daily). The mean serum concentration immediately before the final dose of nadolol on Day 13 of the study was 40.3 ± 8.2 ng/ml. This concentration compares quite well with serum concentrations found in lactating women 24 h after the fourth and fifth doses of nadolol, i.e. 45.0 ± 3.9 and 40.7 ± 3.4 ng/ml. In another recently published study (Dreyfuss *et al.*, 1979) of nadolol concentrations in four hypertensive patients, the average concentration of nadolol found in serum 24 h after the fifth daily dose was 38 ng/ml. Serum concentrations in hypertensive patients at 1, 2, 3 and 4 h after the final dose on Day 13 were 61.9 ± 10.0 , 85.2 ± 22.0 , 92.6 ± 21.4 , and 95.4 ± 22.5 ng/ml, respectively. These values, though somewhat lower, were not significantly different from nadolol concentrations in the sera of lactating women at 1, 2, 3 and 4 h after the final dose, i.e., 94.0 ± 14.3 , 132.8 ± 10.9 , 127.7 ± 19.1 and 139.2 ± 19.5 ng/ml, respectively.

Assuming a large milk production of 1 l/day and a

mean steady-state milk level of 356.9 ng/ml, the total amount of nadolol in the daily maternal milk would be 356.9 μ g/kg of nadolol in a 24 h period. If it is assumed that the dose for children would be equivalent on a weight basis to that for adults, i.e. 1–3 mg $\text{kg}^{-1} \text{ day}^{-1}$, then a 5 kg infant would consume 2–7% of the therapeutic dose for children. However, paediatric dosage of nadolol has not been established and may be lower than adult dosage. Moreover, the accumulative of nadolol might be greater in infants than in adults, since infants have immature kidneys, and nadolol is primarily eliminated via the kidneys.

Nadolol levels in milk were found to be higher than those of some other antihypertensive agents. Propranolol levels in milk were sufficiently low that the nursing infant would consume only 1% of the therapeutic dose for children on a daily basis (Bauer *et al.*, 1979). The levels of guanethidine (Takyl, 1970) and chlorothiazide (Werthmann & Krees, 1972) were probably too small to cause any adverse effects in the nursing infant. Metoprolol, which like nadolol is a weak base, attained levels in breast milk that were on average 3.5 times higher than those in plasma (Sandstrom, 1980). An infant consuming 1 l of breast milk per day would receive about 2% of the normal daily dose of metoprolol for a hypertensive adult. The author felt it unlikely that this amount of metoprolol would induce adverse reactions in the normal breast-fed child.

Since it is not possible to predict the effect of the daily ingestion of up to 7% of the presumed daily paediatric dose of nadolol by the nursing infant, caution should be exercised in the use of nadolol in lactating mothers. Infants of such mothers should be monitored for the possibility of adverse reactions due to β -adrenoceptor blockade.

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References

- ANDERSON, P.O. (1977). Drugs and breast-feeding — a review. *Drug Intelligence Clin. Pharmac.*, **11**, 208–223.
- BAUER, J.H., POPE, B., ZAJICEK, J. & GROSHONG, T. (1979). Propranolol in human plasma and breast milk. *Am J. Cardiol.*, **43**, 860–862.
- DREYFUSS, J., GRIFFITH, D.L., SINGHVI, S.M., SHAW, J.M., ROSS, J.J., VUKOVICH, R.A. & WILLARD, D.A. (1979). Pharmacokinetics of nadolol, A β -receptor antagonist: Administration of therapeutic single and multiple dosage regimen to hypertensive patients. *J. clin. Pharmac.*, **19**, 712–720.
- HORNUNG, M.G. (1975). Identification and quantification of drugs and drug metabolites in human breast milk using GC-MS-COM methods. *Mod. Prob. Pediatr.*, **15**, 73–79.
- IVASHKIV, E. (1977). Fluorometric determination of nadolol in human serum and urine. *J. pharmac. Sci.*, **66**, 1168–1172.
- SANDSTROM, B. (1980). Metoprolol excretion into breast milk. *Br. J. clin. Pharmac.*, **9**, 518–519.
- TAKYI, B.E. (1970). Excretion of drugs in human milk. *J. hosp. Pharmacy*, **28**, 317–326.
- WERTHMANN, M.W. & KREES, S.E. (1972). Excretion of chlorothiazide in human breast milk. *J. Pediatr.*, **81**, 781–783.

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