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Quantification of infant exposure to celecoxib through breast milk

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Aims
To determine the milk-to-plasma (M/P) concentration ratio of celecoxib, and estimate likely infant exposure.

Methods
Blood and milk were sampled for 48 h after oral administration of celecoxib 200 mg to six lactating volunteers. The M/P ratio was derived from the area under the concentration–time curves (0–∞) and the infant 'dose' estimated from celecoxib concentrations in milk.

Results
The median (range) M/P ratio was 0.18 (0.15–0.26). The median (range) infant 'dose' was 0.23% (0.17–0.30%) of the maternal dose, adjusted for weight.

Conclusion
The relative 'dose' of celecoxib to which infants are exposed via milk is very low, suggesting that breastfeeding during routine dosing would pose minimal risk.

Introduction

Prescribing in pregnant or lactating women is often difficult. Studies documenting pregnancy outcomes or quantifying transfer into human milk are often sparse for older agents, and inevitably lacking for new drugs. Many breastfeeding women have painful inflammatory conditions and nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to relieve symptoms. Conventional NSAIDs such as ibuprofen are used in lactation and are believed to be safe for the infant because of low transfer into milk [1, 2]. Use of selective COX-2 inhibitors during breastfeeding has been limited by insufficient data confirming safety, although recent studies suggest celecoxib [3, 4] and rofecoxib [5] pose minimal risk.

An initial case [3] and a subsequent study of five subjects [4] used variable methodology to quantify risk to suckling infants during maternal use of celecoxib. In the first report [3], celecoxib was assayed in milk only and breastfeeding temporarily withheld. In the larger study [4], three women taking celecoxib 200 mg daily regularly provided milk across a dosing interval at steady-state. In addition, two subjects temporarily abstained from breastfeeding and provided blood and

milk samples for 8 h after a single 200-mg dose. The mean milk to plasma (M/P) ratio based on the respective area under the concentration–time curves ($AUC_{0–8}$) in these two subjects was 0.23. Limited assay sensitivity (limit of quantification 25 μg l^{-1}) meant that celecoxib could not be measured in milk beyond 8 h postdose [4] (the assay sensitivity in the case report was not disclosed [3]). The data from these two studies suggest that babies ingest less than 0.5% of the maternal celecoxib dose, corrected for weight. This low 'dose' is consistent with conventional NSAIDs and is likely to result from physicochemical factors that limit transfer into milk such as high plasma protein binding (>97%).

There is worldwide concern about the cardiovascular safety of selective COX-2 inhibitors, as highlighted by the voluntary withdrawal of rofecoxib (Vioxx™) in September 2004 [6]. As this class is subject to increased scrutiny, it is imperative that there are adequate studies quantifying risk in specific clinical situations such as lactation. We have conducted a rigorous study of celecoxib transfer into human milk using a sensitive assay and full area under the concentration–time curve (0–∞) analysis in plasma and milk to estimate infant exposure.

Methods

Subjects and protocol

Six lactating women in the final stage of weaning were enrolled on the basis that they would cease breastfeeding after celecoxib administration. Subjects were excluded if they had contraindications to celecoxib or medical conditions that might compromise the study. The study was conducted in a research centre at Christchurch Hospital and in the subjects' own homes. A single celecoxib 200-mg capsule (Celebrex™; Pfizer, Auckland, New Zealand) was administered orally at approximately 08.30 h on the study day and the exact time was recorded.

Venous blood (~5 ml, heparinized) was collected via an intravenous catheter or by venepuncture at approximately 0 (predose), 1, 2, 4, 8, 12, 24 and 48 h postdose. The exact time of sampling was recorded. The samples were centrifuged at 3000 *g* for 10 min and the plasma stored at −80 °C until analysis. Milk was collected at 0 h (predose) and at the following intervals 0–2 h, 2–4 h, 4–8 h, 8–12 h, 12–24 h, 24–28 h, 28–32 h, 32–36 h and 36–48 h postdose (the time point in the middle of these expression intervals was used in subsequent analyses). At each expression both breasts were emptied of milk by hand or breast pump and the exact time of starting and finishing the expression documented. The milk at each expression was mixed, the volume recorded and an aliquot stored at −80 °C prior to analysis. Any excess milk was discarded.

The study was approved by the Canterbury Ethics Committee, Christchurch, New Zealand. Informed written consent was obtained from all participants.

Analytical methods

High-performance liquid chromatography (HPLC) was used to determine celecoxib concentrations in plasma and milk. The method has been described elsewhere [7]. All plasma and milk standard curves were linear ($r^2 > 0.99$) over the range 10–2000 μg l^{-1}. The intra- and interday coefficients of variation of the assay were <10% at the concentrations of 20, 200 and 2000 μg l^{-1} and the limit of quantification was 10 μg l^{-1} for both plasma and milk. All samples were analysed in triplicate and the mean of the three concentrations taken.

Pharmacokinetic analysis and calculations

The log-linear trapezoidal rule was used to calculate the plasma and milk $AUC_{0–\infty}$ using TOPFIT (Version 2.0; Gustav Fischer, Stuttgart, Germany). An estimation of the terminal elimination rate constant (k_{el}) was made using linear regression of the visually determined post-absorptive elimination phase. This enabled extrapolation of the AUC from the last measurable point (C_{last}) to infinity (i.e. C_{last}/k_{el}). The time to peak concentration (T_{max}) and the maximum concentration (C_{max}) were read directly from the data.

The total amount of celecoxib excreted into milk was calculated as the sum of concentration × volume of milk at each expression. The absolute infant dose (mg kg^{-1} day^{-1}) was the product of the mean milk concentration ($AUC_{0–\infty}$ divided by 12 h) and the estimated infant milk ingestion of 0.15 l kg^{-1} day^{-1} [1]. For this calculation, it was assumed that the $AUC_{0–\infty}$ after a single 200-mg dose would be equal to the $AUC_{0–12}$ for a steady-state dosing schedule of 200 mg twice daily. The absolute dose (mg kg^{-1} day^{-1}) was expressed as a percentage of the maternal dose (mg kg^{-1} day^{-1}).

Results

The median age and weight of the six volunteers was 33 years (range 29–39) and 60 kg (range 54–89), respectively. Additional drug therapy was taken by subject 2 (metformin 1.5 g; folic acid 5 mg; flaxseed oil 1000 mg daily) and subject 3 (ethynodiol diacetate 0.5 mg daily; propranolol 10 mg when required). The median age and weight of the infants was 11 months (range 6.5–15) and 9.3 kg (range 8–10.5), respectively.

The results for celecoxib in plasma and milk are shown in Table 1. Plasma and milk concentration pro-

Table 1
Celecoxib concentrations in maternal plasma and milk, M/P_{AUC} ratio, and infant 'dose'

Subject	Maternal dose mg kg^{-1}	Plasma $AUC_{0-\infty}$ (mg l^{-1})·h	Plasma C_{max} mg l^{-1}	Plasma T_{max} h	Plasma Half-life h	Milk $AUC_{0-\infty}$ (mg l^{-1})·h	Milk C_{max}[1] mg l^{-1}	M/P_{AUC}	Estimated infant dose Absolute mg kg^{-1} day^{-1}	Estimated infant dose Relative[2] %
1	3.23	7.11	1.21	2.2	5.1	1.35	0.30	0.19	0.017	0.26
2	2.25	5.31	0.96	2.2	12.6	0.90	0.21	0.17	0.011	0.24
3	3.70	5.54	0.72	2.2	6.1	1.07	0.07	0.19	0.013	0.18
4	3.45	6.24	1.15	1.0	3.8	1.65	0.33	0.26	0.021	0.30
5	2.78	6.57	0.43	4.0	24.0	0.97	0.07	0.15	0.012	0.22
6	3.57	6.85	1.04	2.0	4.6	1.00	0.18	0.15	0.013	0.18
Median	3.3	6.4	1.0	2.2	5.6	1.0	0.20	0.18	0.013	0.23
Range	2.3–3.7	5.3–7.1	0.4–1.2	1.0–4.0	3.8–24.0	0.9–1.7	0.07–0.33	0.15–0.26	0.011–0.21	0.17–0.30

[1]T_{max} in milk is not shown as it occurred at the 2–4 h expression in all subjects. [2]Absolute infant dose (mg kg^{-1} day^{-1}) as a percentage of the maternal dose (mg kg^{-1} day^{-1}), assuming a steady-state regimen of 200 mg twice daily.

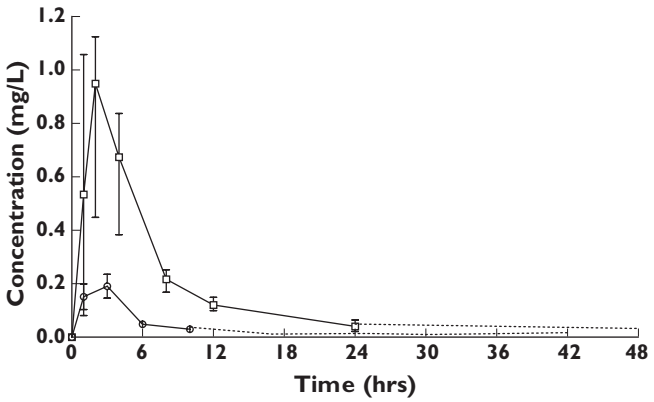

Figure 1
Celecoxib concentration–time profiles for maternal plasma (□) and milk (○) after a single dose of celecoxib 200 mg (median and interquartile range). For plasma, all subjects had quantifiable celecoxib concentrations at 24 h (solid line), but only two (subjects 2 and 5) had quantifiable concentrations at 48 h (dotted line). For milk, all subjects had quantifiable celecoxib concentrations at the 8–12 h expression (solid line), while subjects 5 and 3 still had quantifiable concentrations beyond this time at the 32–36 h and 36–48 h expression, respectively (dotted line)

files are shown in Figure 1 together with intersubject variability. The median (range) AUC for celecoxib in plasma and milk was 6.4 (5.3–7.1) and 1.0 (0.9–1.7) (mg l^{-1})·h, respectively. The median (range) M/P_{AUC} ratio was 0.18 (0.15–0.26). In milk, peak concentrations (0.07–0.33 mg l^{-1}) occurred at the 2–4 h postdose expression in all subjects. All subjects had quantifiable celecoxib at the 8–12 h expression, while two subjects had measurable celecoxib beyond this time. In these subjects, celecoxib could be quantified at the 32–36 h expression, while one also had measurable concentrations at 36–48 h (the final expression). The median (range) total excretion of celecoxib in milk was 0.011 mg (0.004–0.042 mg) or 0.04% (0.01–0.15%) of the maternal single dose (weight adjusted). The median (range) absolute dose in milk was 0.013 (0.011–0.021) mg kg^{-1} day^{-1}, and the relative dose (compared with maternal dose, corrected for body weight) was 0.23% (0.17–0.32).

Discussion

This study shows that celecoxib concentrations in breast milk are low relative to plasma, with a median M/P_{AUC} ratio of 0.18. The absolute infant dose in milk was estimated to be 0.013 mg kg^{-1} day^{-1} on a steady-state maternal dosing regimen of 200 mg twice daily. This is approximately 0.2% of the maternal dose, corrected for weight, and is substantially less than the notional cut-off of 10% that is used to guide the use of wide therapeutic index drugs in mothers feeding healthy term infants [1]. The mean infant dose is 0.2–0.6% of the celecoxib dose of 2.4–6.3 mg kg^{-1} day^{-1} that has been used off label to treat pain and inflammation in children [8]. These findings are consistent with the previous reports that estimated an absolute infant dose of approximately 0.01–0.02 mg kg^{-1} day^{-1} on a maternal dosing regimen of 200 mg daily and a relative dose of 0.3–0.6% [3, 4]. Collectively, the data indicate that infant

exposure to celecoxib in milk is low and unlikely to pose harm.

A limitation of this study is that it was performed in the latter stages of breastfeeding when infants were suckling only once or twice daily. The women produced small volumes of milk (5–47 ml per kg of the infant's body weight per day) which contributed to the very low actual infant 'dose' based on the total excretion of celecoxib into milk (0.04% of the maternal single dose, weight adjusted). The estimated 'dose' based on an assumed infant milk ingestion rate of 150 ml kg^{-1} day^{-1} [1] is also low (0.2% of the maternal dose, weight adjusted) and predicts the 'at worst' exposure scenario during exclusive breastfeeding.

As infants were not exposed to the drug in milk in this study, data on infant drug concentrations could not be obtained. Celecoxib was not detected in two exposed infants in the previous study (limit of detection 10 μg l^{-1}) [4]. However, these infants were older (17 and 22 months) and would be expected to have enhanced ability to clear celecoxib and less reliance on breast milk for sustenance.

Given the very low transfer into milk it is unlikely that significant concentrations of celecoxib would be detected in suckling infants, with the possible exception of situations such as prematurity when clearance may be impaired. As always, consideration of the risks and benefits in each case is essential.

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