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Is ketoprofen safe to use when breastfeeding?

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Abstract

The NSAIDS is one of the most prescribed drugs during breastfeeding. It is mainly used for pain or inflammatory diseases. Some recent data suggest that ibuprofen is compatible with prolonged breastfeeding. Some women will however need a "stronger" treatment. Drugs such as codeine, tramadol or morphine are not recommended for breastfeeding women, especially during the early post-partum stage. Thus, Ketoprofen could be interesting. Due to a lack of pharmacologic information on the drug's transfer in mature milk, breast-feeding is being contraindicated. As a result the mother is "under treated". The present study was undertaken in order to quantify ketoprofen's transfer in mature breast milk. 13 patients gave their written informed consent to participate and completed the study. After the first week following the delivery, women received ketoprofen in order to treat pain or inflammatory disorders. Each patient received a dose of 176mg/day (+/-56). One milk sample and 2 blood samples at different stage of the treatment were collected. Ketoprofen milk concentrations were determined by using high-performance liquid chromatography. The mean ketoprofen milk concentration was 3.3mg/l [range 12.2 to 76]. The mean fat milk content was 3.9g/100mL range 1.7 to 6.5] and mean milk protein content 1g/100mL [range 0.8 to1.6]. Our first results showed a ketoprofen TID of 0,16mg/kg/day [range 0,02 to 0,37] and a relative infant dose RID of 0,037% [range 0,009 to 0,138] of the weight-adjusted maternal daily dose. Ketoprofen was not found into breast milk. Due to its hydrophilic properties, the drug could not cross blood milk barrier. In conclusion, the use of ketoprofen is compatible with prolonged breastfeeding, after the early post-partum stage.

Keywords: Ketoprofen, Mature breast milk, Breastfeeding, Therapeutic drug monitoring, NSAID, HPLC

Abbreviations: NSAID: Non Steroidal Anti Inflammatory drug; HPLC: High Performance Liquid Chromatography; LOQ: Limit Of Quantification; LOD: Limit of Detection; HMA: Human Milk Analyzer; MIRSA: Mid Infrared Spectral Analysis; DHM: Donor's Human Milk

Introduction

Breastfeeding rates varies depending on the mother's age, marital status, education, birthplace, BMI and smoking status during pregnancy [1]. Medication exposure is the second cause of stopping breastfeeding. The number one cause is a lack of supportive practices [2]. During the post-partum period, every women will receive in average 3,3 medications [2]. Analgesics /AINS, antibiotics and anti hypertensive drugs appear in first place. Medical network data confirm that these medications are also prescribed at a late stage of breastfeeding. One of the most given treatments during this period is analgesics (22% according the Medic-Al network; (Table 1). For example after a C-section, breastfeeding women were given up to 400 mg of ibuprofen. No measurable amounts of ibuprofen were found by Gas-liquid chromatography assay methodology in the samples of breast milk [3]. A recent study of our team on pharmacologic data of ibuprofen in mature milk concluded that ibuprofen is safe even for prolonged breastfeeding [4]. However, women might sometimes need a stronger painkiller. In 2006, Gideon Koren et al. [5] demonstrated that codeine, initially approved by the AAP to be compatible during breastfeeding, was responsible for a breastfed neonate death. Later other authors concluded that opioid and codeine are hazardous to breastfeed infants [6-8]. Furthermore our team had published a retrospective diagnosis of an adverse drug reaction in a breastfed neonate with dextropopoxyphene [9]. A clinical study including 26 breastfeeding women showed that the concentration of ketoprofen transferred into colostrum was very low [10]. In 2014 a French team reviewed epidemiological

data about ADR in breastfed children. It showed that ketoprofen prescribed to the mothers had gastrointestinal effect [11]. They have highlighted the need of pharmacokinetic study in order to prove the link between ADR and ketoprofen maternal use. Therefore, the aim of the present study was to quantify the transfer of ketoprofen in mure milk and to discuss whether nursing mothers could receive ketoprofen on a long period. Furthermore we compared these concentrations with the age of lactation, milk's fat and protein content.

Table 1: Medic-Al network statistics from April 2011- 2012.

Medic-Al network, clinical cases from april 2011-2012	N=590
Analgesics+NSAID	N=130 (22%)
Ibuprofen	N=48(8%)
Ketoprofen	26(4%)

Materials And Methods

Study Design

The present study ANTALAIT PHRC AOR 10127 was funded by the French Ministry of Health and approved by the institutional ethical review board (Comite de protection des personnes (CPP) 12506, CPP Ile de France 01 Hotel Dieu Paris). The study included 13 breastfeeding mothers. All treated orally by one or two 100 mg tablets of ketoprofen for uncontrolled pain (post chirurgical pain, back pain, dental treatment) with standard treatments on the 7th day after the delivery. Ketoprofen half life (t1/2) is previously documented in the literature between 90 and 120 minutes/ Steady state concentrations are achieved when ketoprofen is administered at a constant rate (5 x t1/2 ~ 10 hours), at a minimum of one tablet/day of 100 mg ketoprofen. Women included in our study were among those who contacting the Medic-Al network. They were asking for information on the compatibility of ketoprofen with breastfeeding. Women below 18 years of age and/or treated by naproxen and/or who have not given their informed written consent were not included in the study. This study took place from the 1st of January 2011 till the 30th of September 2012.

Sample Collection

The samples from breast milk were taken sub sequentially between 1 hour and a half and 8 hours from the breast pump following the third ketoprofen dose. Each woman provided a sample of 20 mL breast milk. Two maternal blood tests were obtained as well, the first sample between 30 minutes and 2 hours following the ketoprofen intake and the second sample between 4 and 8 hours. The milk samples were obtained between 1 day and a half and 8 hours after the third ketoprofen dosage (Figure 1). The samples were then analyzed, in order to determine ketoprofen's concentrations. All of these measures were made at the Toulouse pharmacokinetic and clinical toxicology laboratory Purpan Hospital.

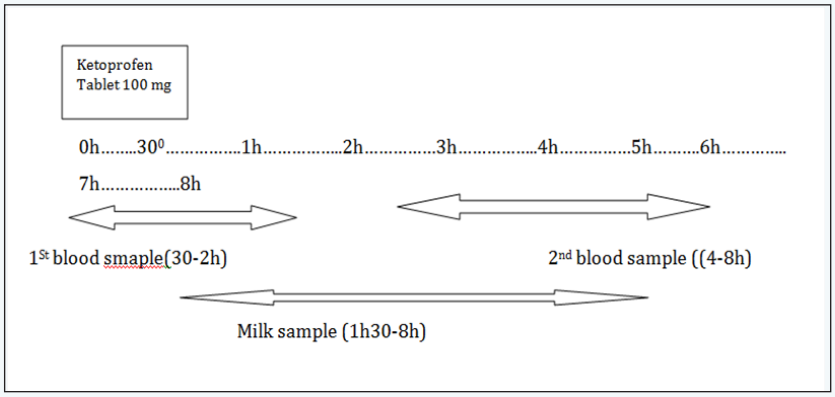

Figure 1: Methods, Blood and milk samples.

Ketoprofen in Blood and Milk Samples

Milk was then frozen at -18°C and defrosted before analysis. As for the blood samples, they were stored at +4°C. A stability test was made for concentration of ketoprofen in milk and plasma. This test was made to make sure the blood could be stored at +4°C then frozen and defrosted. Ketoprofen concentrations in milk and blood samples were measured by using a high performance liquid chromatography (HPLC) with ultraviolet (UV-DAD) detection. For blood samples, 200 µL of serum was spike with 40 µL internal standard and a liquid-liquid extraction with dichloromethane at an acid pH was used. For analyzing the milk samples, we eliminated the high hydrophobic compounds (lipids) with dichloromethane at an alkaline pH followed by an acidification of the aqueous phase

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and an extraction of ketoprofen with hexane. Separation was realized at 25°C on Protonsil 120-5-C18-ACE-EPS (5,0 µm ; 125 mm x 4,6 mm; Bischoff). The mobile phase consisted of a gradient of acetonitril (35%), methanol (15%) and ammonium formate buffer pH 3 (50 %) to acetonitril / methanol / ammonium formate buffer pH 3 (40%/15%/45%) during acquisition of 13 min at a flow rate of 1 mL/min. For both serum and breast milk, ketoprofen was detected at 256 nm. Assay performance was validated through determination of linearity, specificity, recovery, limit of quantification (LOQ), limit of detection (LOD), repeatability and reproducibility over five days. Retention times were 6,70 min for ketoprofen and 7,74 min for the IS. Linear responses in analyte/IS peak area ratios were observed for ketoprofen concentrations ranging from 0,1 to 25 mg/L in plasma and 10 to 200 µg/L in breast milk, using a weighted (1/C) linear regression and a regression coefficient of > 0.999 (for all samples). The average extraction recovery for both ketoprofen and IS was 79 % in serum and 51 % in breast milk with an imprecision (coefficient of variation; CV %) of less than 20 %. For serum and breast milk, the LOQ was 0,1 mg/L and 10 µg/L respectively, LOD was 0,03 mg/L and 4 µg/L respectively. For serum and breast milk, maximum imprecision and inaccuracy were respectively 5,66 and -8,34 % for within-day variability and 4,67 and -10,57 % for between-day variability.

Determining the protein and fat concentrations of breast milk

By using the Miris Human Milk Analyzer (HMA) device at the human milk bank Ile de France Necker Hospital Paris we analyzed the components of human breast milk, such as the protein and fat milk concentration using a mid infrared spectral analysis (MIRSA) (4 specific filter instruments). This device from the Miris HMA (Beldico Villeurbanne France SAS) was designed to study the nutritional quality of small samples of unprocessed or homogenized human milk. Our team and others have validated MIRSA, for mother's milk and donor's human milk (DHM). HMA reproducibility: Specification of MIRSA gave a reproducibility of the measure < 0.5% for fat and protein. The intra-assay variation of the MIRSA for fat and protein was 1.8% (SD 0.04%) and 2.4% (SD 0.07%) respectively. The protein composition of a milk sample was determined by monitoring the intensity of specific wavelengths of mid-infrared radiation absorbed by the organic substances present in the sample. Absorbed radiation was transformed into molecular vibration energy. This difference in intensity between the incidental shelves and the outgoing shelves at specific wavelengths decreases according to the concentration of various substances in the samples, such as fats and proteins. By applying the Beer-Lambert law and by following the technical protocol of the manufacturer, we were able to determine the fat and protein concentration within the milk samples. Our milk samples of 2 mL were frozen at -20°C, then thawed, heated at 40°C and mixed thoroughly before analysis.

Data Analysis

Data analysis was performed according to the guidelines for studies on the transfer of drugs into breast milk. For samples with undetectable concentrations, a lower limit of quantification for ketoprofen of 10µg/L was used for calculation. For each compound

- The mean and maximum milk concentrations over the period of collection were determined;
- The mean and maximum doses that the infant would ingest, assuming an ingestion volume of 150 mL/kg/day, expressed in absolute amounts per kg and day; and
- The relative infant dose (RID, expressed in percentage), by dividing the mean dose that the infant would ingest and the maternal dose related to body weight (expressed in mg/kg/day). The results were expressed as mean ± standard deviation. Estimated serum concentrations of ketoprofen (concentrations corresponding to the milk sampling time) were determined from the serum concentration measured in the first blood sample by using Microsoft Excel and the formula

$$C(T)=A*e(-0.0061xT)$$

Ketoprofen stability in blood and milk was evaluated at +4°C, -20C and room temperature corresponding to storage condition for the study.

Statistical Analyses

We used a polynomial regression analysis of quadratic type, with a regression line and data at the log10 scale (Minitab Inc. USA V.14 2010 software). The polynomial regression method allows modeling the curve of the relation between the RID (Y) response variable and each (X) predictor variable: protein concentration, lipid concentration, duration of lactation, by extension of the simple linear regression model and including the square predictor variable (X^2).

Model was defined as follows:

$Y = b0+b1X+b11X^2$

$Y = RID$

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X = predictor

b0 = intercept

b1, b11 = coefficients

Results

13 women who were treated with ketoprofen. For each of them we evaluated the transfer of ketoprofen into breast milk. Results were expressed as mean ± standard deviation. Inclusion's clinical information's are resumed in Table 2. The mean age of the nursing women included in this study was 31 years old [range 27 to 37], parity was 2,3 [range 1 to 4], gestity 2,4 [range 1 to 4]. Four of the deliveries were premature (under 37 SA) and the over at term (above 37 SA). The average delivery term was 38.5SA [range 28+6SA to 41SA]. The stability test proved than blood can be stored more than 18 days at +4°C and 3 days for milk and respectively frozen at -18°C more than 53 days and 4 month then defrosted before analysis ketoprofen concentration (Table 3). Out of the 13 patients included, 2 of them received acetaminophen as well as ketoprofen in order to treat pain. The mean ketoprofen dose taken by the mothers was 176mg/day +/-56, milk concentration was 31,3 mg/l+/-17,4 [range 11,3 to 76], TID 0,16 µg/kg/day [range 0,02 to 0,37], RID 0,037 [range 0,009 to 0,138], milk/blood rate 0,027 [range 0,007 to 0,1]. Individual data for ketoprofen are presented in Table 4. Ketoprofen was detected in all plasma and milk samples. Maternal residual ketoprofen blood concentration at T0 was 40,24 mg/L [range 18,04 to 62,44]. The mean ketoprofen milk concentrations at Tmax was 34 mg/L [range 16 to 76].The mean TID of ketoprofen is 0,16µg/kg/day [range 0,15 to 0,37]. The mean fat content in milk sample was 3,23g/100mL ± 1,15 and mean protein content 0,87g/100mL ± 0,27 (Table 5). Then RID in function of lactation age, fat content and protein content in milk sample was illustrate in (Figures 2-4).

Table 2: Inclusion's clinical information.

N	Age	Parity	Gestity	Birth weight	Week of	Dose/day	Child's weight	Mother's
(g)	amenorrhea	(mg)	during the	weight at the				
(WA)	study (Kg)	inclusion (Kg)						
1	35	3	3	4900	39+3	100	4.7	72
2	32	2	2	1500	28+6	100	1390	55
3	31	2	2	2975	39	150	8.5	47
4	33	1	1	3670	40	100	9	74
5	27	1	1	3350	39+4	150	8.5	47
6	36	4	4	2295	36	200	6	62
7	37	2	2	3500	38	150	6	78
8	34	2	2	3820	40	100	10.6	76
9	28	4	4	2190	35	100	9.2	40
10	31	3	3	4390	41	100	8	75
11	31	1	1	3280	39	100	3.24	56
12	31	3	3	3180	36	100	3.4	67
13	27	2	4	3300	41	100	4.3	101

Table 3: Stability data of ketoprofen in blood and milk sample.

Temperature	Stability in milk	Stability in blood
Room temperature	24 hours	No data
+4°C	3 days	> 18 days
20°		
C	4 months	> 53 days
Freeze and defrosting	3 cycles	No data

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Table 4: Results, ketoprofen milk and blood concentration measured.

N	Ketoprofen concentrations in milk sample(µg/L)	Time of milk sample (minutes)	Ketoprofen concentrations in Blood sample 1 (mg/L)	Time of blood sample 1(minutes)	Ketoprofen concentrations in Blood sample 2 (mg/L)	Time of blood sample 2 (minutes)
1	17.31	260	0.44	40	0.55	455
2	16.09	175	2.28	165	4.14	265
3	50.97	120	4.95	73	2.42	313
4	76.25	130	8.13	60	1.71	300
5	38.5	270	10.1	60	2.26	360
6	29.64	110	2.17	60	1.76	255
7	34.01	340	4.1	95	0.7	400
8	29.13	105	2.91	75	1.76	245
9	19.6	120	2.22	65	1.27	390
10	29.05	310	9.28	45	0.15	495
11	37.82	330	6.49	120	0.57	435
12	16.89	120	1.31	100	0.96	315
13	12.29	110	1.71	100	0.85	285

Table 5: Protein and fat content according to the RID.

	RID	Fat g/100ml	Protein g/100ml	Lactation duration (d)
1	0,009	3.9	1.1	9
2	0,42	1.7	1.3	8
3	0,04	3.7	0.8	180
4	0,138	NC	NC	281
5	0,028	4.3	0.4	300
6	0,05	4.6	1.2	391
7	0,01	NC	NC	99
8	0,025	NC	NC	356
9	0,011	6.1	1	487
10	0,015	NC	NC	244
11	0,032	2.3	0.9	
12	0,036	4	1.6	23
13	0,048	0.7	0.8	77
Mean	0,037	3.9	1	185
Sd	0,033			

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Discussion

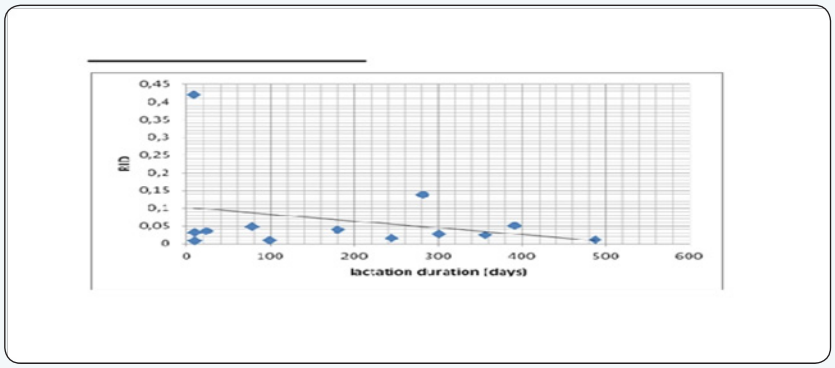

Figure 2: RID according the age of lactation.

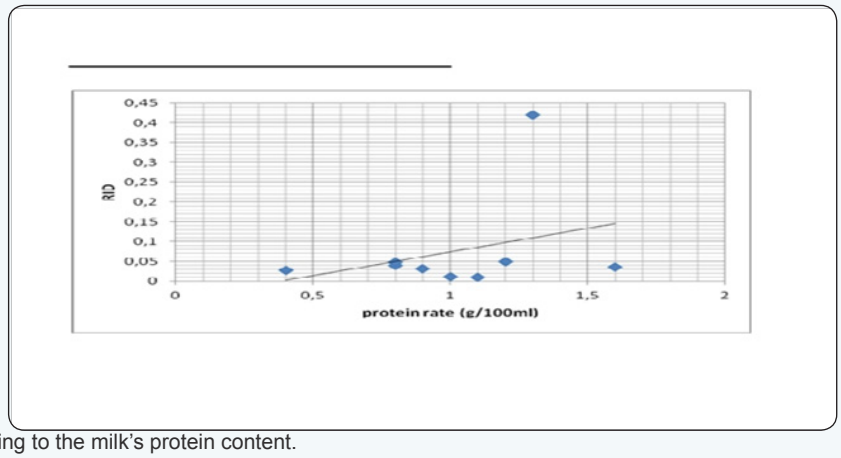

Figure 3: RID in according to the milk's protein content.

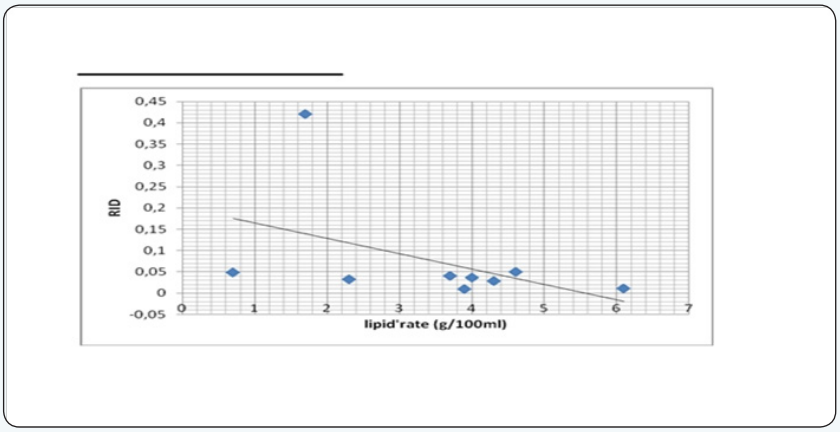

Figure 4: RID according to the fat content.

Ibuprofen is frequently used to treat pain and inflammatory diseases especially since codeine was proven to be toxic for breastfed infants, but it could be in little situation insufficiency to treat high score [7,12]. Until August 2010, according to the American Academy of Pediatrics policy, NSAIDs are compatible with breast-feeding [13]. The data showing a limited milk transfer, are available only for ibuprofen [3,14]. There is a very low concentration of ibuprofen, detected in breast milk due to hydrophilic properties of NSAID. These results initially only concerned colostrums. But we have also demonstrated that the transfer of ibuprofen into mature breast milk is minimum4. Concerning ketoprofen's transfer into breast milk, data concerning colostrum were published in 2007. In this clinical study (26 breastfeeding women) RID was under 1%10. We decided to confirm these data in mature milk as suggested by epidemiologist study in 2014 [11]. In the present study, the maximum milk concentration was used to calculate the maximum dose of ketoprofen

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that the baby would ingest, by using his personal milk intake. Gas-liquid chromatography assay methodology was used to determine concentrations of ketoprofen in serum and breast milk [15]. Our first results showed a ketoprofen TID of 0,16 µg/kg/day [0,02-0,37] and a relative infant dose RID of 0,037% [0,009-0,138] of the weight-adjusted maternal daily dose. This proves that the amount of ketoprofen ingested by the baby is very small and therefore compatible with breast-feeding. We showed in the present study that, after oral administration of ketoprofen in prolonged breastfeeding (more than one week duration), the amount transferred into mature breast milk and ingested by the nursing baby is negligible. In addition, according to our study, the mother declared no side effects and no infant present adverse reaction. Due to ketoprofen hydrophilic properties and high protein bound [10] we were expecting this low milk transfer. The RID was significantly inferior to 1% and lower than the RID found in colostrum (0,6%). The ketoprofen's transfer into mature breast milk, decreases with the age of lactation. This decrease can be explained by the protein milk content decreases with the age of lactation (Figures 2&3). No correlation was found between the fat content and the relative infant dose (Figure 4). MIRSA offers an accurate method to simultaneously determine protein, fat and even energy concentration of the DHM provided by human milk banks 116. Therefore, MIRSA-based instruments may be useful in the daily practice of milk banks and in the clinical practice of neonatal intensive care units [16]. This experimental study could respond to epidemiological interrogation by Soussan and et al. [11] about ketoprofen into breast milk. Our results have proven that maternal ketoprofen could not be responsible for symptoms found in breastfeed neonates because of no milk transfer. According to our results, breastfeeding may be allowed when ketoprofen is administered to the mother. It can be used to treat any type of pain and infectious diseases after the first postpartum week. However, additional factors should be considered, such as associated therapy, infant's clinical state [17]. Human milk bank would also be questioned about donors who take or want to take ketoprofen. Indeed, infants who receive milk from a donor's milk bank are premature babies. In our study four mothers breastfed their preterm baby (under than 37 weeks gestational age). Their RID was still under 1%. So we could advice that ketoprofen is safe during breastfeeding. It is also approved for women who donate their own milk to their child or even anonymous donors.

Conclusion

No specific data, can be find on painkillers transfer and prolonged breastfeeding. What can we prescribe to breastfeeding women, who are in need of a stronger painkiller? Ketoprofen could be prescribed to breastfeeding mothers even for prolonged period without any side effect for the infant. Our study is the first one about pharmacologic data of ketoprofen in mature milk. There is no passage of ketoprofen in breast milk on the long term and we report no adverse reaction. Our results would participate to promote prolonged breastfeeding, and to accept safely donor human milk [18,19]. As suggested by Soussan et al. [11] pharmacokinetic data on analgesics and NAIDS are needed to understand drug-related adverse events occurring in breastfed children. Further research like this experimental design for other frequent drugs prescribed (neurological, endocrine, psychotropic and antihypertensive drugs) or auto medication (plants) during breastfeeding is necessary to analyse the balance risk-benefit and to promote prolonged breastfeeding [20,21].

Conflict of Interest

We declare no conflict of interest. This study was funded by National funding program AOR 10127.

Acknowledgment

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