Milk transfer of phenoxymethylpenicillin during puerperal mastitis

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1   The milk excretion of phenoxymethylpenicillin (PMP) was studied from both breasts in patients with mastitis ($n = 12$) and healthy volunteers (controls, $n = 4$) to investigate the hypothesis that milk transfer of PMP is higher in mastitic than in non-mastitic breasts.

2   Patients were included according to clinical symptoms of mastitis. Milk (and serum from controls) were sampled 0, 1, 2, 3, 4, 6 and 8 h after a single oral dose of 1320 mg PMP. Penicillin concentrations in milk and serum were measured by an agar diffusion technique.

3   Maximum milk concentrations (C_{max}) of PMP in patients were higher ($P < 0.05$) in mastitic than in non-mastitic breasts. The latter concentrations were higher ($P < 0.05$) than those in breast milk from healthy controls. In milk from the mastitis patients (both breasts) the C_{max} was reached after 2 h with a subsequent rapid decline in concentration. In milk from the healthy controls the PMP concentration reached a plateau after 4 h. The area under the milk concentration *vs* time curve (AUC_{0-8h}) was not different for mastitic *vs* non-mastitic breast milk in patients nor for mastitic *vs* control breast milk. This can be explained by higher rates of appearance and disappearance of PMP in the breast milk of mastitis patients compared with healthy controls.

In mastitic breast milk there was a moderate ($P < 0.01$) increase in sodium and albumin compared with non-mastitic milk. However, milk potassium, glucose and lactose values were within normal limits.

4   The average infant dose of PMP ingested during the first day of PMP therapy was estimated to be 0.06, 0.05 and 0.04 mg kg^{-1}, respectively, if nursing from mastitic, non-mastitic and control breast milk. This corresponds to 0.14, 0.11 and 0.09% of the maternal dose per kg body weight.

5   The present findings suggest an elevated rate of milk transfer of PMP to both breasts during the early stage of unilateral mastitis. The consequent infant dose of PMP ingested from breast milk was very low and would justify breast-feeding during maternal penicillin treatment, unless the infant is hypersensitive to penicillin.

Keywords   phenoxymethylpenicillin   oxytocin   milk sodium   human serum
milk albumin   breast milk   mastitis

Introduction

Today epidemic mastitis is seldom seen in the maternity wards, whereas sporadic mastitis after discharge is relatively frequent (Niebyl *et al.*, 1978; Marshall *et al.*, 1975) with an incidence of 2–3% per month in breast-feeding women (Matheson *et al.*, 1986; Prentice *et al.*, 1985). A

precise diagnosis based on the cardinal clinical symptoms of inflammation remains difficult, however. Thus recent studies suggest that nursing women with such symptoms of the breast may suffer from milk stasis, non-infectious as well as infectious mastitis (Thomsen *et al.*, 1984).

Phenoxymethylpenicillin, penicillin V, (PMP) is often used to treat infectious mastitis caused by penicillin-susceptible strains. Whereas parenteral use of benzylpenicillin (penicillin G) in healthy mothers has been shown to give only small amounts in breast milk (Greene *et al.*, 1946; Rozansky & Brzezinsky, 1949; Matsuda, 1984), no such reports have been found for PMP. In milk from mastitic udders in cows, however, the concentrations of benzylpenicillin were 2–3 times higher than those in non-infected udders (Ziv, 1980). An opening of the paracellular pathway (Neville *et al.*, 1983; Prentice *et al.*, 1985), an increase in breast milk pH as shown in cows (Schalm, 1977) and an increased leakage of drug binding proteins to mastitic milk may lead to an enhanced transfer of penicillin to milk during human mastitis.

The present study was performed to investigate whether this is also relevant to PMP.

Methods

Subjects

Nine lactating women with unilateral mastitis and one woman with bilateral mastitis were included according to clinical symptoms. Redness, tenderness, heat and swelling of the breast were scored from 0–3 in increasing severity, and a total score of symptoms was calculated. Two women who had been treated for mastitis for a period of 4 and 10 days were also included. A control group of four lactating women without mastitis volunteered for the study. One had a throat infection and three were healthy. Informed consent was obtained from all mothers. The study protocol was reviewed by the Norwegian Medicines Control Authority.

Study design

Information about this study was supplied to all women discharged from maternity wards in Oslo during the first half of 1986. If symptoms of mastitis occurred the woman was asked to consult one of ten general practitioners enrolled for the purpose. Treatment with 2640 mg (= 4 Mu) PMP daily for 7 days was given if clinical symptoms were indicative of mastitis. Oxytocin 40 u ml^{-1} as nasal spray was provided to facilitate emptying of the breast. The patients were instructed to continue breast-feeding during treatment. If bacteriological examination of the patient's milk showed penicillin resistant bacteria, an alternative antibiotic was prescribed. Paracetamol was allowed when needed for pain relief. The patients received an initial dose of two tablets followed by a daily regimen of one + one + two tablets (660 mg PMP each) at 8 h intervals.

The healthy mothers (controls) pumped their breasts, but did not breast-feed their infants during the 8 h experiment. Milk was sampled from both breasts (patients and controls) 0, 1, 2, 3, 4, 6 and 8 h after oral intake of 1320 mg (= 2 Mu) PMP. Sampling took place after the first dose in the patients' home, whereas the controls stayed in the laboratory during the single dose experiment.

In the patients concomitant samples of milk and capillary blood from the tip of the finger were taken approximately 24 h after the first dose (8 h after the third dose). Milk (4 ml) was expressed by a breast pump which was thoroughly cleaned and dried between each sample. In the healthy volunteers venous blood (10 ml) was drawn concomitantly with the milk samples. Milk and serum were stored at 4°C and analysed for PMP within 28 h after the first sample was taken. The milk was frozen at −20°C before compositional analysis.

Urine from two of the infants was collected in a urinary bag after they were breast-fed by mothers who had taken PMP for 4 days because of mastitis.

Diagnosis and tests

A non-contaminated milk specimen from the inflamed breast was taken for bacteriological culturing and sensitivity testing. More than 10^3 pathogenic bacteria ml^{-1} milk was considered compatible with infectious mastitis (Thomsen *et al.*, 1983). Leucocyte counts ($> 10^5$ ml^{-1} milk) were intended to confirm the diagnosis (Thomsen *et al.*, 1983) but proved not to be feasible.

Sodium, potassium, lactose, glucose and albumin (HSA) in milk samples were analysed at the Dunn Nutrition Unit, Cambridge. Sodium and potassium were measured by flame photometry (Instrumentation Laboratory, model 243). Glucose was determined using an enzymatic method (Boehringer) adapted for use on a centrifuge analyser. Lactose was cleaved by β-galactosidase to generate glucose, which was phosphorylated using hexokinase and NADP. The NADPH formed was quantitated spectrophotometrically. HSA was measured using a sandwich ELISA technique (Hudson & Hay, 1980) specific for human

albumin which utilizes commercially available antisera, conjugates and standards (Behring, Dakopatts, Sigma).

The mothers were asked to report any unexpected reactions from the infant's gut and skin during penicillin therapy.

Microbiological assay

The concentration of PMP in milk, serum and urine was determined by an agar diffusion method. The assays were performed in Petri-dishes (diameter 140 mm) filled with 60 ml PDM Antibiotic Sensitivity Medium (AB Biodisk). *Micrococcus luteus* ATCC 9341 was used as reference strain and the inoculum contained approx. 10^6 cells ml^{-1} to yield semiconfluent colonies on the agar. After inoculation cylindric holes (diameter 5 mm) were made in the agar and each well filled with exactly 0.05 ml of sample/standard solution. In case of PMP concentrations below 0.0625 mg l^{-1} the diameter of the wells was increased to 10 mm and each well filled with exactly 0.250 ml. After 30 min prediffusion at room temperature the test plates were incubated at 37°C for 24 h. Inhibition zones were measured to an accuracy of 0.2 mm by an antibiotic zone reader. Each assay was done in triplicate.

Standard curves were made for solutions of PMP in pooled breast milk (0.0625 – 2.5 mg l^{-1}), in serum (0.0625 – 10 mg l^{-1}) and in infant urine (0.125 – 1 mg l^{-1}). The serial dilutions of PMP in milk were prepared with and without oxytocin 0.22 mg l^{-1} and the solutions were assayed as newly made, 1-day-old stored at 4° C and 14-days-old stored at −70° C. The standard curves obtained by linear regression were all similar and corresponded to the equation $y = 0.136x + 0.15$. The coefficient of variation was 2.9 and 14.8% respectively, for the highest (2.5 mg l^{-1}) and lowest (0.0625 mg l^{-1}) concentration of PMP in breast milk.

Significant inhibition zones before the addition of PMP were noted in one batch of pooled breast milk which then was discarded. Inhibition zones were also present in the 0 h sample from one volunteer and from two patients. In order to destroy the unspecific antimicrobial activity samples and standards were heated to 80° C for 10 min. However, these subjects were not included in the mean calculations because the PMP concentrations after heating remain uncertain.

Pharmacokinetic and statistical calculations

Pharmacokinetic estimates were carried out by the computer programme AUTOAN 2/NONLIN (Wagner, 1975). This program performs curve fitting after automatic model selection and input of proper start parameters. The one-compartment open model was employed to analyse the milk half-life ($t_{1/2}$) of PMP and the area under the milk curve (AUC$_{0-8h}$) for the first dose interval. The coefficient of correlation (r) was calculated between the fitted curve and the values observed. Because of too few values in the elimination phase, biological half-life was not calculated for subjects 17 and 19. The maximal concentration (C_{max}) and the time to peak (t_{max}) were derived from values observed.

Calculation of the dose to the breast-fed infant was based on the average PMP concentration $\left(\frac{AUC_{0-8h}}{8}\right)$ obtained multiplied by the daily milk intake for infants, 0.15 l kg^{-1}. A relative dose in milk was calculated by dividing this dose with the maternal daily dose (2640 mg : 60 kg).

Statistical significance at the 5% level was assessed by Student's *t*-test for paired and unpaired samples as appropriate. Values for control breast milk were means of right and left breast milk. When several tests are performed the chance of getting a random significant difference is higher. A one-sided test was used to test the main hypothesis that C_{max} was higher and t_{max} shorter in mastitic *vs* non-mastitic milk.

Results

PMP concentrations

Clinical characteristics are shown for all subjects (patients and controls) included in the study (Table 1). Subjects were divided into three groups; (1) those with mastitic symptoms in one breast, excluding two patients (no. 4 and 5) with milk factors interfering with the bioassay ($n = 7$), (2) subjects with bilateral mastitis, cured mastitis treated with repeated doses of PMP and those with confounding factors in milk ($n = 5$), (3) controls who were healthy volunteers including one with throat infection ($n = 4$). The time course of PMP concentration in milk after the first dose (Figure 1) show that the peak concentration of PMP was higher in mastitic milk than in control breast milk, but only slightly higher than in milk from the non-mastitic contralateral breast. Only patients with unilateral mastitis are included in the mean calculation for mastitic and non-mastitic milk. No difference was observed between the right and left breast in the control mothers.

Urinary concentrations of PMP were determined in two infants in whom urine was collected for 2 h after a breast-feed. In one infant the concentration was 0.52 mg l^{-1} and in the other PMP was not detectable.

Table 1 Characteristics of 16 subjects included in the study

Diagnosis (symptom score)*	Subject number	Days between partus and consultation	Fever $> 38.5°\,C$	Bacterial counts ml^{-1}
Group 1				
Unilateral mastitis (5,0)	1	10	Yes	Staph. aur. $> 10^3$
Unilateral mastitis (6,0)	8	15	No	Staph. aur. $> 10^5$
Unilateral mastitis (6,0)	9	12	Yes	Micrococc. $> 10^3$
Unilateral mastitis (7,0)	10	131	No	Micrococc. $< 10^3$
Unilateral mastitis (8,0)	13	10	Yes	—
Unilateral mastitis (4,0)	14	10	Yes	Micrococc. $> 10^4$ Streptococc. $> 10^3$
Unilateral mastitis (11,0)	15	68	Yes	Micrococc. $> 10^4$
Group 2				
Bilateral mastitis (4,2)	2	13	—	Streptococc. $< 10^3$ Micrococc. $< 10^3$
Unilateral mastitis (4,0)	4	18	No	Staph. aur. PR $> 10^3$
Unilateral mastitis (8,0)	5	16	No	Staph. aur. PR $> 10^5$
Mastitis, 10 days PMP therapy	6	12		
Mastitis, 4 days PMP therapy	17	90		
Group 3				
Throat infection	7	—		
Healthy, volunteer	18	21		
Healthy, volunteer	19	180		
Healthy, volunteer	20	330		

* Sum of score (0–3) for redness, tenderness, heat and swelling of each breast (mastitic, nonmastitic).

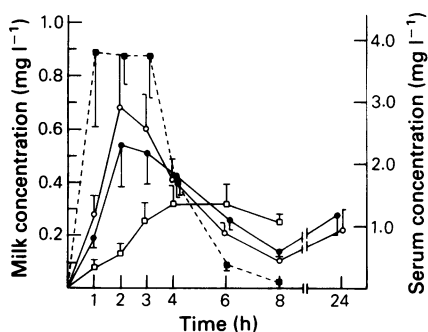| PR	= Penicillin resistant.
—	= Not done, not known.
Staph. aur.	= *Staphylococcus aureus*.
Streptococc.	= *Streptococcus* species.
Micrococc.	= *Micrococcus* species, including coagulase-negative *Staphylococcus*.

Figure 1 Concentrations (mean ± 1 s.e. mean) of PMP in mastitic (○, *n* = 7), non-mastitic (●, *n* = 7), control (left and right) (□, *n* = 4), breast milk and in serum (■) from controls, *n* = 4, followed for 0–8 h after a single dose of 1320 mg PMP p.o. 24 h corresponds to approximately 8 h after a dose of 660 mg PMP.

Pharmacokinetic variables after a single dose of PMP were compared for mastitic, non-mastitic and control breast milk (Table 2). The correlation coefficient between fitted and observed points varied between 0.94 and 1.00. Significant differences were observed between maximum milk concentration in mastitic *vs* non-mastitic ($P < 0.05$), and non-mastitic *vs* control ($P < 0.05$) breast milk, and between time to maximum milk concentration in mastitic *vs* control ($P < 0.025$) breast milk. The penicillin dose ingested the first day by a breast-fed baby was estimated to vary between 20 and 90 μg kg^{-1}, assuming that breasts of all subjects provided the same milk yield.

Due to confounding clinical and methodological factors, five subjects are reported separately. Subject 2 had bilateral mastitis and C_{max} was 1.3 mg l^{-1} in each breast. Subjects 4 and 5 had penicillinase producing *Staphylococcus aureus* in the mastitic milk, C_{max} only reached 0.15 and 0.08 mg l^{-1} in their mastitic breasts compared with 0.26 and 1.30 mg l^{-1} in their non-mastitic breasts. Subjects 6 and 17 had been treated for 4 and 10 days for their mastitis, but had no clinical symptoms when studied. C_{max} was 1.20, 1.00, 0.22 and 0.28 mg l^{-1} in milk (right, left breast) of

Table 2 Pharmacokinetics in mastitic, non-mastitic and control breast milk. Mean (s.d.) and range are shown for C_{max}, t_{max}, biological $t_{1/2}$, AUC_{0-8h}, average milk concentration during 0–8 h (C_{milk}) and daily dose to the infant (D_i)

	Mastitic milk (n = 7)	Non-mastitic milk (n = 7)	Control milk (n = 4)
C_{max} (mg l^{-1})	0·72* (0.50) (0.21–1.55)	0.58 (0.37) (0.30–1.25)	0.30* (0.16) (0.28–0.50)
t_{max} (h)	2.6 (0.7) (2–4)	2.7 (1.1) (2–5)	5.4* (1.8) (4–8)
$t_{1/2}$ (h)	1.8 (0.6) (1.0–2.6)	2.4 (0.9) (1.3–3.8)	(3.1†–7.8)
$AUC_{0-8\,h}$ (mg l^{-1} h)	3.0 (1.5) (1.5–4.8)	2.7 (1.2) (1.2–4.1)	2.1 (0.4) (1.5–2.4)
C_{milk} (mg l^{-1})	0.37 (0.19) (0.19–0.60)	0.34 (0.15) (0.15–0.51)	0.26 (0.05) (0.19–0.3)
D_i (mg kg^{-1})	0.06 (0.03) (0.03–0.09)	0.05 (0.02) (0.02–0.08)	0.04 (0.008) (0.03–0.05)

* Significant differences *vs* non-mastitic milk ($P < 0.05$, one-sided).
† Half-life was calculable in two subjects.

subjects 6 and 17, respectively. $AUC_{0-8\,h}$ calculated for right and left breast was 5.17 and 4.72 mg l^{-1} h for the former and 1.37 and 1.78 mg l^{-1} h for the latter subject. Trough milk concentrations observed at 8 h in these two subjects were somewhat higher than those in mastitis patients (after the first dose), but in the same range as those in the control subjects.

Milk composition

Milk sodium and milk HSA showed significant ($P < 0.01$) differences between mastitic and non-mastitic breasts of the same mothers, whereas milk potassium, lactose and glucose showed no significant differences. There was no variation in milk components within the time period studied, therefore the values from each breast were pooled without regard to sample time (Table 3).

Milk to serum drug ratio

Maximum serum concentrations of PMP in the four control subjects were 6.6, 5.1, 4.2 and 3.0 mg l^{-1} occurring 1–3 h after administration. The mean ratio between concomitant milk and serum concentrations in controls ($n = 4$) varied with time since drug intake. The ratio was 0.06, 0.05, 0.08, 0.21, 0.81 and 1.02 after 1, 2, 3, 4, 6 and 8 h, respectively. The AUC_{0-8h} ratio of milk to serum varied from $0.12 - 0.18$ in the four controls. In patients the mean ratio of concomitant milk and serum concentrations 24 h after the first dose (approximately 8 h after the third dose) was 0.86 and 1.05 for mastitic and non-mastitic milk, respectively.

Observations on the breast-fed infants

Seven of the twelve infants with mastitic mothers behaved as normal, three had looser faecal

Table 3 Composition, mean (s.d.) concentration of sodium, potassium, lactose, glucose and HSA, in mastitic, non-mastitic and control breast milk. Sodium and potassium were measured in samples drawn after 0, 1, 2, 4, 6 and 8 h. Lactose, glucose and HSA were measured in samples drawn after 0 and 2 h

	Sodium (mM)	Potassium (mM)	Lactose (mM)	Glucose (mM)	HSA (g l^{-1})
Mastitic milk ($n = 7$)	13.4** (10.5)	14.8 (2.0)	207 (41)	1.22 (0.72)	0.46** (0.22)
Non-mastitic milk ($n = 7$)	8.2 (4.7)	14.3 (2.2)	219 (20)	1.00 (0.61)	0.33 (0.13)
Control milk ($n = 4$)	4.1** (0.8)	13.6 (2.2)	—	—	0.42 (0.08)

Significant differences *vs* non-mastitic milk; ** $P < 0.01$ (two sided). — Not done.

evacuations, one had a rash on the buttocks on the last day of maternal treatment and one had stains of blood in the stools which also had occurred once, before treatment of the mother. No controls on these observations were available.

Discussion

The agar diffusion technique is frequently used for the determination of antimicrobial activity, because it is sensitive, simple and reproducible. In this assay, the active metabolite *p*-hydroxy-phenoxymethylpenicillin is codetermined. However, it has been shown to represent less than 10% of the serum activity of PMP (Hellstrøm *et al.*, 1974). Because of its hydrophilic character its contribution in milk is probably even less. Furthermore a good correlation ($r = 0.99$) has been shown for quantitation of PMP by h.p.l.c. and the agar diffusion technique (Lindberg *et al.*, 1984). The sensitivity of the microbiological method depends on the reference strain, agar medium and size of cylinder holes. In this study a high sensitivity was obtained with a low sample volume. Assays using h.p.l.c. have reported similar sensitivities when using much larger sample volumes (Lindberg *et al.*, 1984).

Inclusion of patients in the mastitis group was based on clinical symptoms only, although two patients had bacterial counts $< 10^3$ ml^{-1}. The reliability of the bacteriological examination in mastitis has been questioned (Marshall *et al.*, 1975; Niebyl *et al.*, 1978) and was not considered in this study.

Although PMP serum pharmacokinetics usually follows a two compartment open model (Overbosch *et al.*, 1985) the one compartment open model was used as a reasonable approximation in our study. The biological half-life calculated should be interpreted with some caution as it reflects both distribution and elimination of PMP.

In this study small but significant increases in PMP concentration were observed in mastitic milk compared with milk from the contralateral breast. A possible explanation of this difference is that an increase in permeability had occurred in the mastitic breast. Increased permeability during mastitis, characterised by large increases in milk levels of sodium and serum-derived proteins and decreases in lactose concentration, has been described in other studies (Ramadan *et al.*, 1972; Neville *et al.*, 1984; Prentice *et al.*, 1985). In the present study sodium levels were significantly raised in mastitic milk although the magnitude of the increase was relatively small and there was no depression of lactose concentration.

The unaltered milk potassium is in concordance with other studies (Neville *et al.*, 1984; Prentice *et al.*, 1985). These findings suggest that in these patients there may have been a modest increase in mammary permeability. An alternative explanation is that mastitis had resulted in a change in milk pH. PMP is a weak acid (pKa $= 2.73$) with moderate lipid solubility (Bergan, 1978). A small rise in milk pH would increase the proportion of PMP in its unionised form and this might promote its transfer from serum into milk. In addition, variations in albumin concentration may have contributed to the different levels of PMP in mastitic and non-mastitic milk as PMP is known to have an affinity for albumin and 65–70% of serum PMP is albumin-bound (Overbosch *et al.*, 1985).

Maximum milk concentrations of PMP were significantly higher and the time-to-peak interval were significantly shorter in both the affected and normal breasts of mastitis patients when compared with control subjects. This suggests that, unlike cows (Ziv, 1980) unilateral mastitis may have general pathophysiological implications for the patient. This could be the result, for example, of elevated serum concentrations of the drug, increased mammary blood flow or other changes in the drug distribution caused by mastitis. No data are available in humans about the possible increase in serum levels of penicillins during infection (Bergan, 1978) nor on the effect of mammary blood flow on drug transfer into milk. It has been shown in goats, however, that antipyrine milk concentrations are affected by mammary blood flow (Rasmussen & Linzell, 1964). On the other hand the use of oxytocin in patients as opposed to controls may influence penetrability of PMP.

Despite differences in PMP transfer between mastitic, non-mastitic and control milk, the area under the milk concentration curve (AUC$_{0-8h}$) was not altered by mastitis. This was due to the fact that in mastitis higher peak concentrations of PMP were accompanied by a faster attainment of the maximum level followed by a more rapid elimination of the drug compared with normal.

We found that the ratio of concomitant milk and serum concentrations for PMP after oral administration varied considerably from 0.05 to 1.02, due to the fact that equilibrium between the two phases was not established. Rasmussen (1966) found a M/S-ratio of 0.1 in cows' milk for benzylpenicillin during continuous infusion. This is similar to the mean ratio of 0.15 calculated from the areas under the milk and serum curve during the first dose interval. However, with the longer half-life of PMP in milk than in serum the

ratio is probably somewhat higher upon repeated doses. The relatively long time to peak in milk from controls is in accordance with that reported for amoxicillin in milk from healthy mothers (Kafetzis *et al.*, 1981).

The measured PMP peak concentrations were usually 10–20 times higher than the minimum inhibitory concentrations (MIC) for penicillin sensitive *Staphylococcus aureus* (Garrod *et al.*, 1981), showing that therapeutic activities are obtained in the mastitic breast milk.

The relative dose of PMP ingested on the first day of therapy by the breast fed baby, as calculated from average milk concentrations in mastitic, non-mastitic and healthy breast milk is very small, corresponding to 0.14, 0.11 and 0.09% of the weight adjusted maternal daily dose. Accumulation of PMP in milk was not observed in the two patients receiving repeated doses for 4 and 10 days. Assuming that maximum milk concentrations after repeated doses equal the maximum milk concentration observed, 1.55 mg l^{-1}, the daily dose of PMP ingested with milk would maximally be 0.23 mg kg^{-1}, corresponding to 0.5% of the weight adjusted maternal daily dose. Less is absorbed by the baby, because the oral absorption of PMP is in general low and further reduced by a milk feed in infants (McCracken *et al.*, 1978). In newborns the elimination half-life of PMP is increased, which may result in higher serum levels, depending on the creatinine clearance (McCracken *et al.*, 1973). Whether the PMP dose transferred to milk could induce antibody formation and sensitize the infant to penicillins is still an open question. However, if sensitized *in utero* the infant is likely to exhibit allergic reactions to very small doses of penicillin (Gavalov *et al.*, 1986).

In conclusion women receiving phenoxymethylpenicillin in the early stage of mastitis have higher penicillin concentrations in milk from both breasts compared with healthy mothers. This is probably due to inflammatory processes. The penicillin dose ingested by the breast-fed infant is very low and no contraindication to breast-feeding seems to exist, unless the infant is hypersensitive to penicillin. More studies are needed to study milk transfer of drugs under pathological conditions to find out if other mechanisms than passive diffusion such as the paracellular pathway, are of importance.

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