REVIEW ARTICLE

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Use of Antibiotic and Analgesic Drugs during Lactation

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Abstract

During lactation, multiple situations can arise that require maternal pharmacological treatment. Because of the many health advantages of human milk to infants, breast feeding should be interrupted only when the needed drug might be harmful to the nursing child and exposure via the breast milk will be sufficient to pose a risk. Since the majority of drugs have not been shown to cause adverse

effects when used during lactation, and even temporary interruption of breast feeding can be difficult for the nursing dyad, decisions regarding maternal medication use during breast feeding should be based on accurate and up-to-date information. This article reviews available data on the most commonly used antibiotics and analgesics.

The use of most antibiotics is considered compatible with breast feeding. Penicillins, aminopenicillins, clavulanic acid, cephalosporins, macrolides and metronidazole at dosages at the low end of the recommended dosage range are considered appropriate for use for lactating women. Fluoroquinolones should not be administered as first-line treatment, but if they are indicated, breast feeding should not be interrupted because the risk of adverse effects is low and the risks are justified.

Paracetamol (acetaminophen), low-dose aspirin (acetylsalicylic acid) [up to 100 mg/day] and short-term treatment with NSAIDs, codeine, morphine and propoxyphene are considered compatible with breast feeding.

Safer alternatives should be considered instead of dipyrone, aspirin at a dosage >100 mg/day and pethidine (meperidine).

In the light of the many safe alternatives for pain control, breast-feeding mothers should not be allowed to experience pain or be made to feel that they must choose between analgesia and breast feeding.

Because of its myriad benefits to mothers and babies, breast feeding is the gold standard of infant nutrition.[1-8] Exclusive breast feeding for 6 months followed by continued breast feeding with the addition of complementary iron-enriched solid foods is recommended by the American Academy of Pediatrics (AAP) and WHO as the ideal nutrition. Breast feeding can continue as long as mutually desired by mother and infant.[1,9] During this time, multiple situations can arise necessitating drug therapy of the mother.

There is much confusion among medical professionals about the management of drug therapy in breast feeding mothers.

The AAP published a revised statement of drug use during lactation in 1994[10] and an update in 2001.[11] However, these statements do not discuss the supporting data and do not include a number of drugs that are frequently prescribed. This article aims to review relevant clinical studies, give recommendations from major health organisations where available and present our opinion on drugs for which formal statements do not exist. Because questions about the use of antibiotics and analgesics during lactation were the most frequently asked of our teratogen information centre, we restricted this review to these two drug classes. From these two classes we chose the most commonly prescribed medications to be included in our review. A Medline search using the terms 'milk', 'breast milk', 'breast feeding' and 'lactation' was performed for all the medications included in this review, namely: penicillins, clavulinic acid, cephalosporins, metronidazole, fluoroquinolones, macrolides, cotrimoxazole (trimethoprim/sulfamethoxazole), paracetamol (acetaminophen), dipyrone (metamizole), aspirin (acetylsalicylic acid), NSAIDs, codeine, morphine, pethidine (mepridine) and propoxyphene. Previously published review articles and major reference books were scanned as well to identity and retrieve additional papers.

The goal of this review is to provide up-to-date information to allow clinicians to prescribe most commonly needed antibiotic and analgesic medications without inappropriate interruption of breast feeding, bearing in mind that most of the information is based on single-dose and short-term studies. For some of the drugs only single or few case reports

are available, and the ability to assess the possible adverse drug reactions in neonates and infants is limited.

1. Pharmacokinetics of Drugs in Breast Milk

1.1 Factors Influencing the Excretion of Drugs Into Milk

Transfer of substances, including drugs, into breast milk can occur by passive diffusion or active transport. The physicochemical characteristics of the drug determine how much drug is excreted into breast milk. The most important factors are plasma protein binding, ionisation characteristics, lipophilicity and molecular size.[12,13]

High plasma protein binding decreases the amount of drug excreted into breast milk, whereas high milk protein binding results in sustained presence of the drug in milk. The degree of drug ionisation, determined by the drug pKa (ionisation constant) and the pH of the plasma and the milk, plays a role in determining the amount of drug excreted in the milk in a process called 'ion or drug trapping'. High lipophilicity of the drug favours its accumulation in milk. Drugs with high molecular weight are transferred less easily into breast milk than those with lower molecular weight.

1.2 Milk-to-Plasma Ratio

The amount of drug transferred into milk is often presented as a ratio between the drug concentration in the milk and maternal plasma (the M/P ratio) and is usually derived from experimental data. This ratio can vary over time depending on the dose and the time interval between drug intake and sampling time, since the milk concentration-time curve usually lags behind the plasma concentration-time curve. The ratio yields an estimate of the amount of drug to which the nursing infant is exposed, but does not account for clearance or bioavailability in the infant. The M/P ratio can be predicted by using the model described by Begg et al.,[14] using pKa, plasma protein binding and octanol-water partition coefficient. From this ratio one can calculate or estimate the relative daily dose to the suckling infant, expressed per kilogram bodyweight as a percentage of the maternal dose per kilogram bodyweight (infants' adjusted dose), and compare the ingested dose with the relevant infant therapeutic dose for that drug.

1.3 Infant Drug Exposure

The actual exposure of an infant to a drug while breast feeding is influenced by some additional factors other than M/P ratio, namely the dose and the dose interval, the elimination half-life of the drug, and the infant's suckling pattern (number of feeds, amount of milk ingested, and relationship of feeding to the time of maternal drug administration). Drug exposure in a breast-fed infant may differ from that in an adult because of different drug absorption, metabolism and excretion. These differences should be taken into consideration when estimating exposure. For instance, a drug with a low M/P ratio may result in a high level of exposure in the breast-fed infant because of decreased clearance rate and resultant accumulation.

2. Excretion of Antibiotics in Breast Milk

2.1 Penicillins

Two aminopenicillins, amoxicillin and ampicillin, have been approved by the AAP to be compatible for use during breast feeding,[11] but the other drugs in this class are not mentioned. Penicillins penetrate into breast milk in small concentrations. After an intramuscular dose of benzylpenicillin 100 000IU the M/P ratio varied between 0.03 and 0.13. The safe use of penicillins during lactation has been well established.[15,16] The milk penetration after oral administration of the penicillinase-resistant penicillins cloxacillin and dicloxacillin has been shown to be very low.[15,17]

Nafcillin and methicillin are used only parenterally, because of minimal gastrointestinal absorption of the former and extreme instability at gastric pH of the latter. Although no reports of their milk concentration have been published, presumably penetration is low as for other penicillins. Furthermore, drug

absorption in an infant exposed via the oral route from its mother's milk would be minimal.

Of the antipseudomonal penicillins, only ticarcillin is approved by the AAP to be used in breast-feeding mothers.[11] Because of poor oral absorption, ticarcillin is used only parenterally. Therefore, infants' gastrointestinal absorption is limited.[15] No data about milk transfer are available for mezlocillin. As with other parenteral antibiotics, concentrations of piperacillin secreted into milk are believed to be extremely low and absorption by infants from milk is presumed to be minimal.[15,17]

In summary, breast feeding should not be considered contraindicated while taking any of the penicillins.

2.2 Clavulanic Acid

Clavulanic acid is generally used in combination with amoxicillin to increase the efficacy of the latter drug against β-lactamase-producing bacteria. The drug is well absorbed orally and undergoes transfer to milk;[15] however, no harmful effects have been reported. We therefore consider this medication compatible with breast feeding.

2.3 Cephalosporins

Similar to penicillins, cephalosporins appear minimally in breast milk.[18] The pharmacodynamics of a large number of drugs in this group have been studied, and their use in breast-feeding mothers is considered to be appropriate.[18-25]

2.3.1 First-Generation Cephalosporins

First-generation cephalosporins administered orally or parenterally have been shown to be poorly transferred to milk. For example, cefazolin and cefalothin plasma levels in infants were undetectable.[18,19,24] The AAP has approved first-generation cephalosporins for use during breast feeding.[11]

2.3.2 Second-Generation Cephalosporins

Although cefuroxime and cefaclor are widely used, no data about milk secretion in humans are available. However, no adverse effects in infants of breast-feeding mothers taking these medications have been reported.[17,24] We thus consider this group of drugs compatible with breast feeding.

2.3.3 Third-Generation Cephalosporins

Compared with that of cephalosporins of the first and second generations, oral bioavailability of the third-generation drugs is significantly lower.[24] Cefixime was undetectable in milk 1–6 hours after a 100mg oral dose. Ceftibuten is poorly absorbed with meals, but small to moderate amounts may penetrate into milk.[17] The M/P ratio at 3 hours from a 1000mg dose of cefotaxime was 0.16.[18] After parenteral administration of ceftazidime 1–2g, concentrations in milk peaked at 5 hours, with an approximate milk penetration of 4.4%.[22] Of the parenteral third-generation drugs, cefotaxime, ceftazidime and ceftriaxone have been approved by the AAP for use in breast-feeding mothers.[11] We believe that all members of this group of drugs are compatible with breast feeding.

2.4 Metronidazole

Metronidazole has been implicated in carcinogenesis in rodents, but has not been proved to have any similar effect in humans.[26,27] The drug is not approved by the US FDA for use in infants, although in practice it is often used for the treatment of giardiasis. The AAP considers its effect on nursing infants as unknown but may be of concern. It is not absolutely contraindicated during lactation.[11] No harmful effects attributable to breast feeding have been reported. In one study, average infant intake was estimated to be 3 mg/kg/500mL milk after a maternal oral dose of 200mg three times daily,[28] which is much less than the 15–30 mg/kg/day recommended therapeutic dose for infants.[17,29] Erickson and colleagues[30] estimated that after a single maternal 2g oral dose about 25mg is passed to the infant by normal breast feeding during the following 48 hours. Passamore et. al.[31] reported a group of 12 mothers who received metronidazole 400mg three times daily while breast feeding their babies; no adverse reactions were recorded in any of the babies. Vaginal gel applications produce about 2% of the plasma levels reported after a 500mg oral administration, and milk levels are presumed to be minimal.

Even lower systemic absorption was reported for use of a topical skin preparation.[17] The AAP recommends to discontinue breast feeding for 12–24 hours after single-dose therapy given to the mother.[11] However, according to the above-mentioned reports, we argue that short-term use of metronidazole therapy or a low-dose regimen should not interrupt breast feeding.

2.5 Fluoroquinolones

This group of antibiotics has been reported to cause arthropathy in young animals.[32,33] Based on this information, fluoroquinolones have not been approved by the FDA for use in infants and children. Recently, a number of studies have reassessed their safety in the paediatric population. Incidence and severity of adverse effects seem to be similar to those reported in adults.[34-36]

Ciprofloxacin has been implicated as a causative factor of arthropathy in newborn animals. Phototoxicity after exposure to ultraviolet light has been reported.[37] Green teeth on eruption have been reported after treatment with ciprofloxacin in two neonates.[38] One case of severe pseudomembranous colitis was reported in an infant of a breast-feeding mother who had been on self-medication with ciprofloxacin for 6 days.[39] In one study, drug concentrations were evaluated after three oral doses of 750mg, and the milk-to-serum ratio varied between 0.85 and 2.14, with the maximum values at 4 hours. Milk concentrations were highest after 2 hours with 3.79 mg/L and declined to 0.02 mg/L at 24 hours.[36] In another case report, the distribution of ciprofloxacin (500mg once daily for 10 days) from the mother to the breast-feeding infant has been evaluated. The concentration in maternal serum was 0.21 mg/L, that in breast milk was 0.98 mg/L, and that in the infant serum was not detectable.[40] Reported peak serum concentration ranges following ciprofloxacin 250mg, 500mg and 750mg were 0.94–1.53 mg/L, 2–2.9 mg/L and 2.6–3.4 mg/L, respectively.[41] These data imply that the amount of drug transferred to the suckling infant would be low or negligible. Based on this, we believe that ciprofloxacin can be used, but it should be the last alternative of the quinolones for use in breast-feeding women.

Among quinolones, ofloxacin, norfloxacin or levofloxacin might be preferred in breast-feeding mothers, because of their lower milk concentrations.[17,42] Norfloxacin is reported by the manufacturer not to be found in the breast milk of mothers ingesting the drug.[32] The AAP considers ciprofloxacin and ofloxacin as compatible with breast feeding.[11]

In summary, quinolones should not be first-line therapy in lactating women. However, if quinolones are the only option, breast feeding need not be interrupted.

2.6 Macrolides

Erythromycin is the oldest drug in the macrolide class. It is secreted into milk, with a maximum milk concentration ranging between 0.4 mg/L and 1.6 mg/L after a maternal oral dose of 400mg three times daily and between 1.6 mg/L and 3.2 mg/L after a maternal oral dose of 2 g/day.[43] There was one report of pyloric stenosis associated with ingestion by an infant of erythromycin via breast milk,[44] but despite this, erythromycin is considered by the AAP to be compatible with breast feeding.[11]

Clarithromycin, like other macrolides, is a weak base and could therefore be concentrated in milk by ion trapping. In one study reporting the passage of the drug into breast milk, mean peak concentration of clarithromycin in breast milk was 25% of the corresponding maternal serum concentration. The mean peak concentration of its metabolite was 75% of the corresponding maternal serum concentration.[45]

Azithromycin has an extremely long half-life in tissues and is accumulated to a certain extent in milk. There has been one published case report of a nursing mother receiving azithromycin 1g followed by two doses of 500mg once daily. Milk concentrations were 0.64–2.8 mg/L after the last dose. The investigators concluded that azithromycin seemed to demonstrate a time-dependent versus time-accumulation profile in breast milk.[46] Therapeutic paediatric doses of this drug are 5–10 mg/kg/day.[17,46] Our

centre interviewed ten women who received azithromycin 500 mg/day for 3 days for suspected pneumonia and continued breast feeding. The ten exposed infants had no symptoms, no diarrhoea, no vomiting and no rash or any other adverse effects.

When macrolides are needed to treat a breast-feeding woman, erythromycin should be the preferred drug. However, the evidence about the other macrolides does not support the interruption of breast feeding should they be needed.

2.7 Cotrimoxazole (Trimethoprim/Sulfamethoxazole)

Sulfamethoxazole is secreted into milk in small amounts. It has a very long elimination half-life, ranging from 8 hours in infants to 36 hours in neonates. Care should be taken with use of this drug in neonates with hyperbilirubinaemia.[47] Current FDA labelling states that cotrimoxazole is contraindicated during lactation for the first 2 months because of possible development of kernicterus.[48] There is no evidence of or references cited for this contraindication.[48] The AAP approves cotrimoxazole for use in lactating women.[11]

3. Excretion of Analgesics in Breast Milk

3.1 Paracetamol (Acetaminophen)

Only 0.04–0.23% of the maternal dose of paracetamol is excreted in breast milk. The peak level is found 1–2 hours after ingestion.[49,50] The half-life in milk is comparable to that in plasma, being 1.35–3.5 (mean 2.7) hours.[49-51] The estimated maximum dose in a feed is 1.3–4.8% from the bodyweight-adjusted maternal dose.[49-52] The maximum relative daily dose to the suckling infant is estimated to be about 1.5% from the maternal dose.[50] There have been no reports of adverse effects in the infants of mothers who took paracetamol, except for one case where the infant developed a rash that ceased 24 hours after maternal ingestion and reappeared 2 weeks later when the mother took another dose.[53] The AAP considers the use of paracetamol as compatible with breast feeding.[11] Similar recommendations were published by the WHO.[54]

3.2 Dipyrone (Metamizole)

Although not available in the US because of serious adverse effects (agranulocytosis), dipyrone is widely used in other countries. In some of them, its use during pregnancy and postpartum even exceeds the use of paracetamol.[55] Its metabolites appear in the breast milk in concentrations similar to those in the maternal serum. All the metabolites disappear from the milk within 48 hours of the last dose.[56] In one study the drug concentration in the maternal serum was 3.3 mg/L and in breast milk at the same time was 4.3 mg/L. The urine level in the breast-fed infant was 3.2 mg/L and the infant's serum level was 3.74 mg/L.[57]

Reports on the use of this drug in lactation are limited. There are no reports of any adverse effects on infants of mothers who were treated with dipyrone, except for one infant exposed to dipyrone via his mother's breast milk, who had a cyanotic episode that was related to the drug.[57] Dipyrone is not included in the AAP survey of drugs in lactation, as it is not marketed in the US.

Current labelling of the Aventis dipyrone product Novalgina®[1] states that breast feeding should be withheld for 48 hours after use. We believe that short-term dipyrone use is not a contraindication to breast feeding, but one should consider using a safer alternative.

3.3 Aspirin (Acetylsalicylic Acid)

The salicylates, including aspirin, are excreted in breast milk in low quantities, with M/P ratios of 0.03–0.3. Only a small percentage of the maternal dose (4–8%) reaches the nursing infant via the breast milk and the maximum dose in a feed is estimated to be 0.3–8.1% of the bodyweight-adjusted maternal dose.[51,58-60] The peak level in the milk occurs 3–9 hours after ingestion, depending on the dosage taken.[51,59] Drug clearance from the breast milk lags behind that from maternal plasma; thus the

1 Use of tradenames is for product identification only and does not imply endorsement.

M/P ratio 8 hours after ingestion rose to 0.34.[51] The elimination half-life for salicylates has been reported to be considerably longer in neonates than in adults; thus there is a possibility of drug accumulation in their bodies and the appearance of toxic adverse effects.[61]

It has been reported that aspirin taken in late pregnancy can cause haemostatic abnormalities in the fetus and the neonate.[62] Use of low-dose aspirin (<100 mg/day) during late pregnancy was found to be well tolerated and had no adverse effect on platelet function of the neonate.[63,64] There is a theoretical concern that maternal use of high-dose aspirin can cause bleeding in the nursing infant, especially in the gastrointestinal tract, and can adversely affect the infant's clotting factors. Thrombocytopenic purpura has been reported in one infant who was exposed to aspirin via breast milk.[65] Metabolic acidosis was reported in a 16-day-old breast-fed infant whose mother received a high dose of aspirin (3.9 g/day).[66] In a prospective, more recent, study of possible adverse reactions in breast-fed infants of 15 mothers who took aspirin, no negative effects were observed.[67]

The WHO working group on drugs in lactation determined that aspirin is not safe for use in lactation.[54] The AAP recommends caution in using these drugs while breast feeding.[11] In Britain it is recommended that the use of aspirin be avoided while breast feeding because of theoretical concern over the development of Reye's syndrome.[68]

If an analgesic or antipyretic is needed during lactation it is preferable to use other drugs such as paracetamol or other NSAIDs. However, use of low-dose aspirin (up to 100 mg/day) is unlikely to cause adverse effects in the infant. The infant should be observed for any possible adverse effects such as bleeding.

3.4 NSAIDs

The amount of maternal dose found in breast milk is minimal for NSAIDs that have been studied. For ibuprofen and diclofenac it is below the level of detection.[69,70] Naproxen appears minimally in breast milk with an M/P ratio of 0.01,[71] but there is a theoretical concern due to a long half-life.[72,73] One 7-day-old infant developed haematuria, prolonged gastrointestinal bleeding and acute anaemia while his mother was treated with naproxen.[74]

Indomethacin is excreted in breast milk in very small quantities. The median M/P ratio was 0.37 in 7 of 16 women who were treated with daily dosages of 75–300mg.[75] In the other nine women no measurable amounts of the drug were found in the milk or plasma. Plasma samples were obtained from seven infants. Only one of these had a detectable level of indomethacin of 47 μg/L. According to the calculations of this study, a nursing infant is exposed to 0.07–0.98% of the weight-adjusted maternal dose.[75] There are no known negative effects of this drug among infants exposed via breast milk except for one report of a mother who took 200 mg/day and whose infant had seizures. The correlation between the exposure and the convulsion is questionable.[76]

From this class of drugs, the AAP considers ibuprofen, naproxen, diclofenac, indomethacin, ketorolac, piroxicam, mefenamic acid and flufenamic acid as compatible with breast feeding.[11]

Therefore, short-term use of NSAIDs seems to be compatible with breast feeding. For long-term treatment agents without active metabolites, such as ibuprofen, are preferred.

3.5 Opioids

3.5.1 Codeine

Only small amounts of codeine and its metabolites are excreted in breast milk.[51,77-79] Infants are more sensitive to this drug in the neonatal period; there are four reported cases of neonates exposed to codeine via breast milk who had apnoeic episodes. In each of these cases the mothers took high doses – 60mg every 4–6 hours. It should be noted that in all four cases the maternal serum level was undetectable.[80] Therefore, codeine in daily dosages <240mg is considered appropriate for use during lactation.[79] The drug is classified by the AAP as compatible during breast feeding.[11]

3.5.2 Morphine

Morphine is excreted in breast milk in low concentrations.[81-85] In a group of nursing women treated with morphine either via epidural, intravenous or intramuscular routes, the highest level was found in the milk half an hour after giving the drug. The highest level was 0.082mg per litre of milk when administered by the epidural route and 0.5mg per litre of milk when given intravenously or intramuscularly. The mean M/P ratio was 2.45.[81] In a study reporting seven women receiving intravenous patient-controlled analgesia, breast milk samples were obtained from first administration to 48 hours later. In breast milk, opioids were found in only three patients. The M/P ratio was always below 1 for morphine.[82] In a case report where an infant was exposed to morphine via breast milk, the authors calculated that the infant received 0.8–12% of the maternal dose and did not exhibit any symptoms of morphine toxicity.[83] As the bioavailability of this drug when taken orally (as it is by the nursing infant) is very low (26%), it is unlikely that the infant will receive a significant dose of morphine via breast milk. The AAP considers morphine to be compatible with breast feeding.[11]

3.5.3 Pethidine (Meperidine)

Small amounts of pethidine appear in breast milk.[84-88] It undergoes hepatic metabolism to the pharmacologically active metabolite norpethidine (normeperidine). In nine women given a single dose of 50mg the peak breast milk level of the drug was 0.13 μg/mL after 2 hours and 0.02 μg/mL after 24 hours. The M/P ratio was greater than 1.[87] In another study of two nursing women who received a dose of 75mg or 150mg, the breast milk levels 8–12 hours later were 0.209 μg/mL and 0.275 μg/mL, respectively, with an M/P ratio of 0.84–1.59. The level of norpethidine in the breast milk was 8.1 μg/L 56 hours after drug administration, a fact that illustrates the slow clearance time of the metabolite.[88] The long half-lives of pethidine (13 hours) and norpethidine (63 hours) in the neonate can lead over time to high serum levels in the infant. It has been found that infants who were exposed to pethidine via breast milk from their mothers, who received this medication intravenously because of caesarean section, were neurologically and behaviourally depressed in comparison to neonates who were exposed to morphine.[84,85] In a group of infants whose mothers received pethidine in labour, higher levels were found in breast-fed than in formula-fed infants.[85] Pethidine is approved by the AAP for use in breast-feeding mothers.[11] The working group of the WHO claimed that breast feeding after a single dose of pethidine was appropriate, but one should consider the possibility of accumulation of norpethidine in the nursing infant before approving the drug for ongoing use in lactation.[54]

3.5.4 Propoxyphene

This drug is excreted in breast milk in small amounts. It reaches a peak in maternal serum 2 hours after administration. Even when the maximum therapeutic dose is used, the infant receives via breast milk less than 1mg, a completely insignificant amount.[89,90] The active metabolite norpropoxyphene is cleared by renal elimination. However, renal clearance is considerably lower in infants than in adults; thus significant amounts of this compound can be accumulated in the suckling infant during long-term maternal treatment. To date no adverse effects have been reported in infants exposed to the drug via breast milk. This drug is considered to be compatible with breast feeding by the AAP.[11]

4. Conclusions

Breast feeding is the gold standard of infant nutrition. When treatment of a lactating mother with an antibiotic or analgesic drug is considered necessary, one should take into account the potential risk for the breast-fed infant, against the benefits of continuing breast feeding. The lowest effective maternal dose should be given to avoid detrimental effects in the breast-fed infant.

The use of most antibiotics is considered compatible with breast feeding. Penicillins, aminopenicillins, clavulanic acid, cephalosporins, macrolides and metronidazole in low, regular doses are considered appropriate for breast-feeding women. Fluoroquinolones should not be administered as first-line

treatment, but if they are indicated, breast feeding should not be interrupted.

Paracetamol, low-dose aspirin (up to 100 mg/day), short-term treatment with NSAIDs, codeine, morphine and propoxyphene are considered compatible with breast feeding. Safer alternatives should be considered instead of dipyrone, aspirin and pethidine. In the light of the many appropriate alternatives for pain control, breast-feeding mothers should not be allowed to experience unnecessary pain or be made to feel that they need to choose between analgesia and breast feeding.

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