cology and Obstetrics, *15*, 501, 1978. – Nelson M. M., Forfar J. O.: *British Medical Journal*, *1*, 523, 1971. – Nishimura H., Tanimura T.: *Clinical Aspects of the Teratogenicity of Drugs*, p. 3 and 84. Excerpta Medica, Amsterdam, 1976. – Robinson G. C., Brummit J. R., Miller J. R.: *Pediatrics*, *32*, 115, 1963. – Robinson G. C., Cambon K. G.: *New England Journal of Medicine*, *271*, 949, 1964. – Royal College of General Practitioners: *Journal of the Royal College of General Practitioners*, *25*, 631, 1975. – Smithells R. W.: "The demonstration of teratogenic effects of drugs in human". In: *Drugs and Pregnancy*, D. F. Hawkins (Ed.), p. 22, Churchill Livingstone, Edinburgh, 1983. – Smithells R. W.: *British Medical Bulletin*, *32*, 27, 1976. – Smithells R. W., Sheppard S., Schorach C. J., Seller M. J., Nevin N. C., Harris R., Read A. P., Fielding D. W.: *Lancet*, *1*, 339, 1980. – Snider D. E. jr., Layde P. M., Johnson M. W., Lyle M. A.: *Treatment of tuberculosis during pregnancy. American Review of Respiratory Diseases*, *122,* 65-79, 1980. – Storey E.: *Drugs*, *6*, 321, 1973. – Thiersch J. B.: *American Journal ob Obstetrics and Gynecology*, *63*, 1298-1304, 1952. – Ullberg S., Lindquist N. G., Sjöstrand S. E.: *Nature*, *227*, 1257-58, 1970. – Varpela E.: *Acta Tuberculosis Scandinavica*, *45*, 53, 1964. – Varpela E., Mietalahti J., Aro M. J. T.: *Scandinavian Journal of Respiratory Diseases*, *50*, 101, 1969. – Wallman I. S., Hilton H. B.: *Lancet*, *1*, 827-829, 1962. – Wilson J. G.: *Teratology*, *7*, 3, 1973.

ANTIBIOTICS AND BREAST FEEDING

PETER J. LEWIS

INTRODUCTION

Breast feeding is now so much encouraged that it has become the norm rather than the exception. The puerperium is the most frequently medicated stage of pregnancy and a significant proportion of breast feeding women receive drugs. Concern is frequently expressed about potential adverse effects on the breast feeding infant of treating lactating women with drugs (Arena, 1980). The question is often raised about antibiotics, which following analgesics and sedatives, are the drugs most frequently prescribed to lactating women. Concern about the safety of antibiotics is natural but in the majority of cases adverse effects are likely to be extremely uncommon (Lewis, 1983; Wilson *et al.*, 1980).

WHAT ANTIBIOTICS COULD BE TOXIC TO THE NEONATE?

The neonate, in addition to being susceptible to the usual adverse effects of antibiotics, such as ototoxicity from the aminoglycosides, nephrotoxicity from cephalosporins and allergic reactions to penicillin, shows particularly susceptibility to certain antibiotics which are thus usually avoided in paediatric practice (Schwarz and Cronublehome, 1980).

A number of drugs therefore are generally avoided in neonates, it might be supposed that they should automatically be excluded from treatment of the breast

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XIII, n. 3-4, 1986

feeding mother. However, as we shall see, treatment of the lactating mother with any of these drugs is rather unlikely to pose a significant risk to the suckling infant because only small amounts of each drug would be ingested and absorbed from the milk by the infant.

WHAT ANTIBIOTICS COULD BE ABSORBED FROM MILK?

Many antibiotics are not orally active as they are not absorbed by the gut. This is the case for example with the aminoglycosides such as gentamicin or streptomycin. Vancomycin is another antibiotic which is not orally absorbed. Thus even if large amounts of these drugs were present in breast milk, the infant would not absorb them.

Tetracycline is poorly absorbed by the infant simply because milk inhibits its absorption from the gut. It can be anticipated that only a small proportion of any tetracycline present in breast milk would be absorbed by the infant and this has been shown to be the case (Hendeles and Trask, 1983).

HOW MUCH OF AN ANTIBIOTIC WOULD REACH BREAST MILK?

Almost all antibiotics are present in breast milk of women receiving therapeutic doses. However, in most cases, the amounts are extremely small. The principles of transfer of drugs to breast milk are now quite well understood (Rasmussen, 1966). With the possible rare exceptions of certain antithyroid drugs and iodine, drugs gain access to breast milk by simple diffusion: they are not actively secreted into milk. Equilibration is apparently very rapid and the concentration of drug in breast milk is, at any time point, a certain fixed multiple of the plasma concentration. This ratio between milk and plasma concentration of the drug is characteristic of the drug and can vary from less than 0.01 up to about 4.

Two main characteristics of the drug determine this ratio, protein binding and the basic or acidic nature of the drug (Lewis, 1983). Milk is slightly acidic, pH 6.9, and this effects the distribution of drug between plasma, pH 7.4, and milk. Drugs which are weak bases tend to attain higher concentrations in milk than in plasma and drugs which are weak acids tend to attain a lower concentration in milk than in plasma (Rasmussen, 1966).

Many drugs are bound to plasma proteins. Milk has a lower protein content than plasma and milk protein binds drug less avidly than plasma protein. Hence, drugs which are highly protein bound do not achieve high milk concentrations; the classic case is warfarin which is 99% protein bound. Almost no warfarin is present in breast milk. Most antibiotics are about 50 to 80% protein bound.

While all these considerations are of great theoretical interest to the pharmacokineticist, they obscure a most important fact about drug transfer into breast milk. Even a drug with a very high milk plasma ratio may have a low total dose of drug in the milk. This is because most drugs have a low plasma concentration in comparison to dose. Most of the drug is distributed in the body tissues and is

not circulating in the blood. Since plasma concentrations of many drugs taken in the 100-200 mg dose range are in the ng/ml range their milk concentration will only amount to a few ng/ml and the infant dose per day will not exceed a few milligrams. The milk intake by a baby varies widely but in the neonate it averages 500 ml/day, i.e. 150 to 200 ml/kg.

The milk/plasma ratio for a drug is therefore less important than the neonatal dose to maternal dose ratio. For example, for labetalol, a beta blocker with a milk plasma ratio of 2, the dose ratio is still 1 to 40, that is the neonatal dose per unit body weight is less than 3% maternal therapeutic dose. This concept is not generally appreciated.

DOSES OF ANTIBIOTICS IN BREAST MILK

Few quantitative studies on breast milk drug concentrations have been published for antibiotics, but most of these drugs have relatively low milk concentrations.

There is quite an extensive literature on the passage of various cephalosphorins into milk. In general these drugs have extremely low milk plasma ratios and low total doses in milk. Cefoxitin has a very low milk plasma ratio of 0.1 and the neonate will receive less than 1% of the maternal dose (Dresse *et al.*, 1983; Dubois *et al.*, 1981). Similar figures can be quoted from cefazedone (Von Kobyletski *et al.*, 1979), ceftazidime (Blanco *et al.*, 1983) and cefotaxime (Novick, 1982). Breast milk concentrations of these cephalosporins are around the 1 mg/l level, whereas therapeutic dose is measured in grams or about 50 mg/kg. Furthermore, many of the cephalosphorins are parenteral drugs with poor absorption from the gut.

The situation with penicillin is rather similar. Amoxycillin has a low milk to plasma ratio, about 0.05 and hence only a very small amount will reach the breast feeding infant (Kaferzis *et al.*, 1981). This is because amoxycillin, like the cephalosporins is a weak acid and is protein bound. Ticarcillin is present in milk after a therapeutic dose of 15 g/day at a very low concentration of 2.5 mg/l (Von Kobyletski *et al.*, 1983). Mezlocillin is undetectable in milk (Singlas, 1982).

The milk plasma ratio for chloramphenicol is about 0.5 (Havelka *et al.*, 1968). The milk dose is thus relatively high compared to penicillin and as chloramphenicol is a potentially toxic drug it is best avoided in the breast feeding mother.

Another antibiotic with potential toxicity to the suckling infant is clindamycin. In a recent study of breast milk concentrations of clindamycin it was shown that the drug could achieve concentrations in milk several times those in plasma (Steen and Rane, 1982). In view of the particular tendency of clindamycin to provoke pseudomembranous colitis, the syndrome due to selection of *Clostridium difficile*, clindamycin represents a potential hazard. There is in fact one case report of bloody diarrhoea in a nursing baby whose mother was treated with clindamycin, but *C. difficile* was not detected (Mann, 1980).

The potential hazard of sulphonamide treatment is that kernicterus might be induced in the infant especially as unconjugated hyperbilirubinanaemia is more common in breast feeding infants than in bottle fed infants. However, several

TABLE 1. — *Antibiotics best avoided in breast feeding women because of potential for toxicity in the infant.*

Clindamycin	(pseudomembraneous colitis)
Metronidazole	(mutagenicity)
Dapsone	(haemolytic anaemia)
Tetracycline	(theoretical risk of tooth staining)
Chloramphenicol	(pancytopaenia)
Novobiocin	(jaundice)

studies show very low concentrations of sulphonamide in breast milk, and this potential hazard (Azad Khan and Truelove, 1979). Sulphonamides do occasionally induce haemolytic anaemia in neonates as does dapsone and both of these drugs are probably best avoided in breast feeding women (Sanders *et al.*, 1982).

CONCLUSIONS

In general toxic effects of drugs are dependent on dose and the theoretical risks of harmful effects in breast feeding infants can be dismissed if it can be shown that the amount of drug transferred in milk is low. It is likely that breast milk drug transfer is not a great hazard to the neonate and this impression is strenghthened by the paucity in the literature of documented cases of adverse effects.

The example of the potential hazard of tetracycline may be taken. This is stressed in repeated review articles on the subject (George and O'Toole, 1983), but a thorough search of the literature fails to produce a single case where tooth staining has occurred as a result of mother breast feeding while taking tetracycline (Hendeles and Trask, 1983). Little tetracycline is present in breast milk, still less is absorbed and most breast feeding infants are under 3 months of age and therefore are not at risk for toothstaining.

These considerations all suggest a very low level of risk. But on the other hand, the infant may derive a low level of benefit from continuing to breast feed when the mother is taking tetracycline. It must not be forgotten that although breast milk is an ideal food, it can easily be substituted, and prudence will suggest that breast feeding be interrupted if any drug is taken with a least risk of toxicity to the infant.

In this regard, a short list of antibiotics is suggested as best avoided (table 1). Almost all the risks described are theoretical rather than fully documented. By contrast a second list of drugs unlikely to produce any specific toxicity in the breast feeding infant is given in table 2.

There are many other antibiotics not mentioned in either of these two tables. This is in general because there is no specific information on them in the literature. However, consideration of the principles should enable a clinician to take the appro-

TABLE 2. — *Antibiotics apparently safe for use in breast feeding women. No particular toxicity to the breast feeding infant.*

Penicillin
Cephalosporins
Erythromycin
Aminoglycosides
Vancomycin

priate decision. If the infant is not normally harmed by the antibiotic, there is probably no hazard. Many antibiotics are poorly absorbed by the infant's gut and most of them are present in milk only in extremely small amounts.

REFERENCES

Arena J. M.: *Pediatric Annals, 9,* 452, 1980. – Azad Khan A. K., Truelove S. C.: *British Medical Journal, 2,* 1553, 1979. – Blanco J. D., Jörgensen J. H., Castaneda Y. S., Crawford S. A.: *Antimicrobial Agents and Chemotherapy, 23,* 479, 1983. – Dresse A., Lambotte R., Dubois M., Delapierre D., Kramp R.: *Journal of Clinical Pharmocology, 23,* 438, 1983. – Dubois M., Delapierre D., Chanteux L., Demonty J., Lambotte R., Kramp R., Dresse A.: *Journal of Clinical Pharmacology, 21,* 477, 1981. – George D. I. jr., O'Toole T. J.: *Journal of American Dental Association, 106,* 204, 1983. – Havelka J., Hejzlar M., Popov V., Viktorinova D., Prochazka J.: *Chemotherapy, 13,* 204, 1968. – Hendeles L., Trask P. A.: *Journal of American Dental Association, 107,* 12, 1983. – Kafetzis D. A., Siafas C. A., Georgakopoulos P. A., Papadatos C. J.: *Acta Paediatrica Scandinavica, 70,* 285, 1981. – Kafetzis D. A., Brater D. C., Fanourgakis J. E., Voyatzis J., Georgakopoulos P.: *Antimicrobial Agents and Chemotherapy, 23,* 870, 1983. – von Kobyletzki D., Sas M., Dingeldein E., Wahling H., Wiemann H.: *Arzneimittel-förschung, 29,* 1763, 1979. – von Kobyletzki D., Dalhoff A., Lindemeyer H., Primavesi C. A.: *Infection, 11,* 144, 1983. – Lewis P. J.: "Drugs and breast feeding". In: *Clinical Pharmacology in Obstetrics,* p. 366, P. J. Lewis (Ed.), Wright Publishers, London, 1983. – Mann C. F.: *Pediatrics, 66,* 1030, 1980. – Novick W. J. jr.: *Reviews of Infectious Diseases, 4,* S346, 1982. – Rasmussen F.: "Studies on the mammary excretion and absorption of drugs", Carl F. Mortensen, Copenhagen, 1966. – Sanders S. W., Zone J. J., Foltz R. L., Tolman K. G., Rollins D. E.: *Annals of Internal Medicine, 96,* 465, 1982. – Schwarz R. H., Crombleholme W. R.: *Progress in Clinical Biological Research,* 44, 1980. – Singlas E.: *La Nouvelle Presse Medicale, 11,* 373, 1982. – Steen B., Rane A.: *British Journal of Clinical Pharmacy, 13,* 661, 1982. – Wilson J. T., Don Brown R., Cherek D. R., Dailey J. W., Hilman B., Jobe P. C., Manno B. R., Manno J. E., Redetzki H. M., Stewart J. J.: "Drug excretion in human breast milk: principles, pharmacokinetics and projectd consequences". In: *Clinical Pharmacokinetics,* vol. 5, p. 1, ADIS Press, Australasia Pty Ltd., 1980.