

Use

Maternal treatment with betamethasone accelerates surfactant production by the fetal lung reducing the incidence of neonatal respiratory distress, a property it shares with dexamethasone (q.v.).

Pharmacology

The pharmacology of betamethasone and dexamethasone are very similar. See the web commentary for increasingly strong evidence that, antenatally, betamethasone is much safer than dexamethasone.

Indications for antenatal use

The seminal paper that first identified a strategy for preventing, rather than curing, surfactant deficiency was published more than 30 years ago. The first clue came from the observation that experimental lambs delivered prematurely failed to develop the respiratory problems seen in control animals if exposed to corticosteroids before delivery. A randomised placebo-controlled trial, that eventually recruited more than a thousand mothers from New Zealand, soon confirmed that two 12 mg IM doses of betamethasone caused a significant reduction in the incidence of respiratory distress in babies born more than eight weeks early, and a fall in neonatal mortality in all babies born more than three weeks early. Doubling this dose brought about no further improvement in outcome. No study has ever looked to see if a smaller dose might be equally effective.

It took 20 years for this strategy to gain general acceptance and, in the interim, a further eleven trials were done to replicate the original findings. Eventually a Cochrane review of all the trials in 1989 showed that antenatal treatment with 24 mg of betamethasone or dexamethasone was associated with a 40–60% reduction in the risk of neonatal respiratory distress, independent of gender, and that benefit 'appears to apply to babies born at all gestational ages at which respiratory distress syndrome may occur'. Indeed another, recently completed, trial has shown that prophylaxis also reduces the risk of respiratory distress in babies delivered by elective section at 37–38 weeks gestation. While most benefit is seen in babies delivered more than 24 hours but less than 7 days after prophylaxis is started, babies born before or after the optimum period also appear to benefit. The reduction in the risk of respiratory distress is accompanied by a reduction in periventricular haemorrhage and (probably) in necrotising enterocolitis, and this, in turn, results in a reduced mortality rate, and in a reduction in the cost and duration of neonatal care. A further trial published in 2006 has now shown that, in women not delivered within seven days, further weekly treatment also reduces the number of babies troubled by respiratory problems after birth. However, while a review of the health of the children recruited into the first trial in New Zealand found no adverse late consequence of exposure to a single course of betamethasone 30 years later, we will not know if this is true after repeated exposure until 2007.

Women with hypertension, fetal growth retardation, and rhesus isoimmunisation were excluded from most of the early trials, it now seems clear that treatment benefits these babies too. The 1972 study suggested that steroids might increase the risk of stillbirth in severe pre-eclampsia, but even here we now know that treatment is beneficial as long as this does not conflict with the need for urgent delivery. Use (under prophylactic antibiotic cover) is also beneficial where there has been prelabour rupture of membranes, but use in mothers with diabetes remains less well established, since treatment could affect diabetic control.

Maternal prophylaxis

First course of treatment: Give 12 mg of betamethasone *base* as a deep IM injection, and a second dose after 24 hours if the baby is still undelivered. (A 6 mg dose twice a day by mouth for two days is also quite effective). While prophylaxis is of no proven benefit when delivery threatens before 24 weeks gestation, it should not be denied to those at risk of delivering at 23 weeks if they request it.

Repeat treatment: Give another 12 mg IM dose once every 7 days if the mother remains undelivered, and the baby is still at substantial risk of respiratory problems (generally only true before 30 weeks gestation).

Supply

Celastone[®], a product that contains both betamethasone sodium phosphate and the more long acting ester betamethasone acetate, was used in all the more important perinatal trials, but this product is still not on sale in the UK. Indeed, the only formulation routinely available in the UK is a 1 ml ampoule containing 5.3 mg of betamethasone sodium phosphate (4 mg of betamethasone *base*) costing £1.20, and the ampoules provided by some manufacturers contain sodium metabisulphite. 500 microgram (5p) tablets are also available.

References

See also the relevant Cochrane reviews

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BREAST MILK FORTIFIERS

Use

Powdered products are now commercially available for modifying the nutritional content of human breast milk when this is used to feed the very preterm baby. However the benefits have been modest to date, because the variability of expressed breast milk makes 'tailored' supplementation very difficult.

Immunological factors

Human milk is the ideal food for almost every baby. Although the various artificial products available seem to meet all the key nutritional needs of the term and preterm baby (as outlined in the monograph on milk formulas) feeding with unpasteurised human milk still confers a number of unique, if poorly understood, immunological advantages. While it is now recommended that all 'donor' milk should be pasteurised before use, the mother's own milk can be used without pasteurisation. Milk collected in the home is safe for 8 days if kept at 4°C, and is best *not* frozen. Cells are damaged by storage and by freezing, but the immunoprotective constituents remain stable when stored at 0–4°C for 3 days, when frozen at –20°C for 12 months, or when pasteurised at 56°C for 30 minutes. Use thawed milk at once.

Composition per 100 ml of human milk after fortification.

	Protein	Fat	Carbo- hydrate	Energy	Na	Ca	P	Fe	Zn	Vit D
	g	g	g	kcal	mmol	mmol	mmol	mg	mg	µg
Mature human breast milk Widdowson (1977)	1.3	4.2	7.4	70	0.7	0.9	0.5	0.1	0.4	<0.1
Cow & Gate <i>Nutriprem fortifier</i> ® 2 sachets (3 g) per 100 ml	2.5	4.0	9.0	80	1.5	2.1	1.7	0.1	0.7	≥5
Mead Johnson <i>Enfamil</i> ® 4 sachets (4 g) per 100 ml	2.0	4.2	9.7	83	1.0	3.1	1.9	0.1	1.6	5.3
Milupa <i>Eoprotin</i> ® 3 scoops (3 g) per 100 ml	1.9	4.2	9.5	81	1.3	1.9	1.3	0.1	0.4	<0.1
SMA <i>Breast milk fortifier</i> ® 2 sachets (4 g) per 100 ml	2.3	4.4	9.8	85	1.4	3.1	2.0	0.1	0.6	7.6

Nutritional factors

All these products are designed to enhance the nutritional value of human milk. Don't insist on an arbitrary upper limit to oral intake – some preterm babies do very well on a daily intake of 220 ml/kg when two or three weeks old. The milk of a mother delivering a preterm baby usually has a relatively high protein content in the first couple of weeks of life, and too high a protein intake could, theoretically, be hazardous. Fortification is best not started, therefore, until about two weeks after delivery and seldom needs to be continued once breastfeeding is established, or the baby weighs 2 kg.

All the products listed enhance the protein and calorie content of the milk. They also provide minerals to improve bone growth (an important requirement for all babies of less than 30 weeks gestation, as discussed in the monograph on phosphate). Human milk contains relatively little protein, and a plasma urea of less than 1.6 mmol/l may be a sign of suboptimal protein intake. Some preterm babies fed on fortified breast milk may benefit from additional sodium (either as sodium chloride (q.v.), or as some other salt) in the first few weeks of life, until their obligatory renal sodium loss decreases. Babies on Eoprotin may benefit from a further vitamin D supplement (q.v.), as may babies on Enfamil. Only the Nutriprem and Enfamil fortifiers provide added folate. Breastfed babies should get additional vitamin K (q.v.) to prevent late vitamin K deficiency bleeding, unless they are given a total 'depot' supply of 1 mg IM shortly after birth. Preterm breastfed babies may need additional iron (q.v.). A few need zinc (q.v.).

Supply

Enfamil has been widely used in the USA, but it is not commercially available in the UK. The SMA product is not yet on general release, but is available in boxes containing 50 × 2 g sachets to units stocking and using SMA low birth weight formula milk. Eoprotin is supplied in 200 g tins costing £15 each and Nutriprem fortifier in boxes containing 50 × 1.5 g sachets costing £10. The powder is best added just before the baby is fed. Do not use these products to further fortify artificial formula milks.

References

See also the relevant Cochrane reviews

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Use

Sustained treatment with erythropoietin stimulates red blood cell production, but its impact on the need for blood transfusion is negligible in the neonate if steps are taken to eliminate unnecessary blood sampling.

Pharmacology

Erythropoietin is a natural glycoprotein produced primarily in the kidneys which stimulates red blood cell production, particularly when there is relative tissue anoxia. During fetal life it is mostly produced in the liver (which is presumably why babies with renal agenesis are not anaemic). Two commercial versions (epoetin alfa and epoetin beta), both synthesised using recombinant DNA technology, became available in 1986. They have identical amino acid sequences, but different glycosylation patterns. Epoetin alfa is the product most widely used in America, but epoetin beta is the product the manufacturer has been authorised to recommend for use in infancy in Europe. Progressive hypertension and severe red cell aplasia are the most serious adverse effect seen in adults, but they have not been reported in neonates to date. The platelet count may rise. Erythropoietin does not seem to cross the human placenta, and the amount absorbed from breast milk is not enough to affect haemopoiesis (although it could enhance gut maturity) so women should not be denied treatment just because they are pregnant or breastfeeding.

Numerous randomised and blinded, or placebo controlled, trials have now shown that early and sustained treatment with erythropoietin can stimulate red cell production in the very preterm baby, as long as supplemental iron is also given. However large doses have to be given because clearance, and the volume of distribution, are both 3–4 times as high as in adult life. Treatment certainly has a place in the early care of vulnerable babies born to families who are reluctant to sanction blood transfusion on religious grounds. Nevertheless, although treatment reduces the need for replacement transfusion, especially in the smallest babies, it seldom eliminates it, and no response to treatment is generally seen for 1–2 weeks. In two recent well conducted controlled trials involving 391 babies weighing 1 kg or less at birth, high dose treatment only marginally reduced the number of transfusions given (1.86 vs 2.66 in one study). Attention to reducing loss into the placenta and loss from unnecessary blood sampling, together with a more structured approach to transfusion policy can be at least as effective as treatment with erythropoietin in reducing the need for blood transfusion. As long as the safety of donor blood can be assured, and care is taken to minimise the number of donors used using the strategies outlined in the monograph on blood (q.v.), cost reduction is limited. Since treatment has to be started early to be effective, and since it is difficult to predict within a few days of birth which babies will later become anaemic, all high risk babies need treating, further limiting the drug's cost effectiveness.

Treatment

Give 400 units/kg by subcutaneous injection into the thigh 3 times a week for at least 3 weeks (treatment was continued for 6 weeks in many of the clinical trials).

Supplementary iron

Erythropoietin will fail to stimulate sustained red cell production if iron deficiency develops. A minimum of 3 mg/kg of elemental iron a day seems to be necessary in the neonatal period, which is more than in any UK formula milk (q.v.). It is common practice to give twice as much as this. For very low birthweight babies supplementation can conveniently be achieved by giving 1 ml of oral sodium ferredetate (5.5 mg of elemental iron) once a day, as outlined in the monograph on iron (q.v.).

Compatibility

Erythropoietin seems equally effective given as a continuous (but not as a bolus) infusion in parenteral nutrition (q.v.), together with 1 mg/kg a day of parenteral iron if oral iron can not be given.

Supply

500 unit and 1000 unit prefilled syringes of recombinant human erythropoietin (epoetin beta) cost £3.90 and £7.80 respectively. The large multidose vials, which require water for reconstitution, should not be used when treating babies because they contain benzyl alcohol. Supplies should be stored at 4°C.

References

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Use

Platelet concentrates are used in the management of severe thrombocytopenia with bleeding.

Pathophysiology

The risk of serious internal haemorrhage increases significantly when the platelet count falls below $30 \times 10^9/l$, and the risk of intracranial haemorrhage may be particularly high in the preterm baby shortly after birth. Always check first that the 'thrombocytopenia' is not due to clots in the sample.

A number of inherited conditions, and syndromes (such as thrombocytopenia absent radius [TAR] syndrome) are associated with thrombocytopenia. These seldom call for active treatment. Ill babies can have sepsis or a consumption coagulopathy (disseminated intravascular coagulation, or DIC): the main need here is usually to treat the underlying condition. Platelets can pool in the spleen in conditions causing hypersplenism (such as rhesus isoimmunisation), and exchange transfusion can further exacerbate thrombocytopenia. A low count may point to focal infection or to thrombus formation on a long line. Marrow disorders will reduce platelet production, but the results of a full blood count and examination of a blood film will usually provide a diagnostic clue in these situations. Heparin therapy (q.v.) occasionally causes a dangerous thrombocytopenia that is made worse if platelets are given.

Platelet antibodies cause most cases of severe *isolated* neonatal thrombocytopenia. Platelet transfusions are of little value in *autoimmune* thrombocytopenia because the maternal antiplatelet antibodies also attack any transfused platelets. Most of these mothers will have idiopathic thrombocytopenia (ITP) or systemic lupus erythematosus (SLE). *Alloimmune* thrombocytopenia is more hazardous. Here maternal antibodies, produced as a result of transplacental sensitisation, attack fetal platelets (in a process analogous to the red cell destruction that occurs in rhesus haemolytic disease): treatment with immunoglobulin (q.v.) may be appropriate, and fully compatible platelets are required (i.e. they must lack the antigen against which the antibodies are directed). The transfusion service can usually provide platelets that are both HPA-1a and HPA-5b negative (the antibodies responsible for 95% of all problems). These will almost always be suitable, and can be used if the situation is urgent before platelet grouping and any formal confirmation of the diagnosis is possible. Maternal washed and irradiated platelets can be used on those rare occasions when the blood transfusion service finds itself unable to provide suitable donor platelets.

Administration

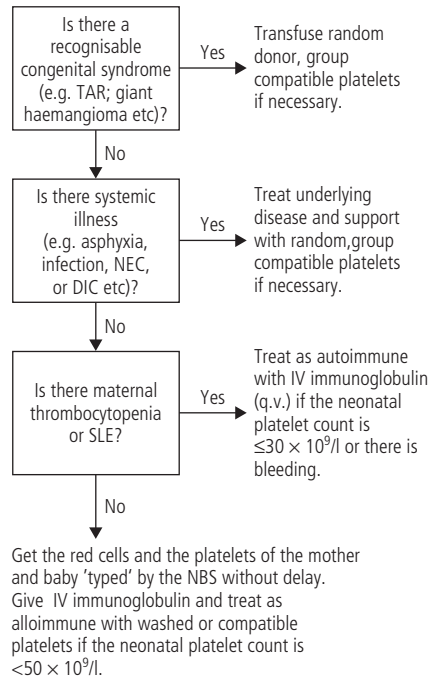
10 ml/kg of platelets from a single ABO and Rh compatible CMV-negative donor will usually suffice unless there is alloimmune thrombocytopenia. Here more is given, and a higher minimum count aimed for, because platelet function is poorer. To minimise loss, draw the contents of the pack into a 50 ml syringe through a special platelet or blood transfusion set with a 170–200 μ m filter and then infuse over 30 minutes, using a narrow bore extension set linked (near the patient) to an IV line primed with 0.9% sodium chloride. **Always confirm compatibility by checking that the patient's name is on the pack.**

Supply

Leucodepleted 50 ml single-unit packs containing 60×10^9 platelets are available from hospital blood banks. They cost about £70 to prepare and dispense. Packs for intrauterine use are irradiated and further concentrated before issue. Platelets need to be stored under special conditions, kept at room temperature, and used *promptly* on receipt. They quickly lose their therapeutic power if this is not done, and bacterial contamination also becomes increasingly likely. Send 2 ml of blood for grouping.

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Use

Polio vaccine gives lasting immunity to the three polio viruses.

Poliomyelitis

Poliomyelitis is a notifiable infectious illness that has now been eradicated from most of the world, but cases were still being recorded in Afghanistan, Chad, Ethiopia, north India, Indonesia, Pakistan, Nigeria and the Yemen in 2005. The WHO launched a global 15-year plan to rid the world of this disease in 1988 and one country (northern Nigeria) now accounts for almost half of all the new cases being reported across the world each year. Infection may not be clinically apparent, but may also produce aseptic meningitis and severe lasting paralysis. An injectable formaldehyde-inactivated triple-strain (Salk) vaccine first became available in 1958, and a live, attenuated, triple-strain oral (Sabin) vaccine was introduced in 1962. The Salk vaccine is now being used again with increasing frequency in most parts of Europe, and is currently the only product used in North America. However, the Sabin vaccine was, until September 2004, still used to provide lasting immunity to paralytic poliomyelitis in the UK. These two products have, between them, made the eventual global eradication of polio a realistic aim. Polio (and measles) could, with commitment and good management, soon go the same way as smallpox did in 1980.

Indications

Inactivated parenteral vaccine (IPV): With the arrival of a combined, injectable, vaccine that also offers protection from diphtheria, tetanus, whooping cough and haemophilus (Hib) infection, this is now becoming the product of choice worldwide. Give 3 doses IM at monthly intervals, starting 2 months after birth. Because the live and inactivated products are interchangeable, there is nothing to stop the inactivated vaccine being used to complete a course of treatment started using the live, oral vaccine.

Live oral vaccine (OPV): Give 3 doses by mouth at monthly intervals (as with the inactivated vaccine). Remember however that children excrete the live virus in their stools for up to 6 weeks after immunisation, putting other unimmunised and immunocompromised patients and family contacts at risk. This product should never, therefore, be used in a maternity hospital setting. There is also a one in a million chance of the live, attenuated vaccine itself causing paralytic disease.

Contra-indications

Early pregnancy, immunodeficiency, immunosuppression, reticuloendothelial malignancy and high dose corticosteroid treatment (the equivalent of more than 1 mg/kg prednisolone a day, or 2 mg/kg for more than one week in the last 6 weeks) are contra-indications to the use of any live vaccine (but **not** for the inactivated Salk [IPV] vaccine). Children should not be immunised while febrile, or given the oral vaccine while suffering from diarrhoea or vomiting. For anaphylaxis (rare even with the IM product), see under immunisation.

Interactions

Polio vaccine can be given at the same time as other live and inactivated vaccines. The live, oral (Sabin) vaccine should not, ideally, be given less than three weeks before or three months after any planned injection of normal immunoglobulin.

Administration

Inactivated vaccine: Give 0.5 ml by deep intramuscular injection into any limb not simultaneously being used to give some other vaccine, using a fresh syringe and a 25 mm, 23 gauge, needle.

Oral live vaccine: The normal dose is 3 drops by mouth. Repeat if regurgitated. Older children have, traditionally, been offered the drops on a sugar cube.

Documentation

Inform the district immunisation co-ordinator (see monograph on immunisation) when any UK child is immunised in hospital, and complete the relevant section of the child's own personal health record (red book).

Supply

The combined (DTaP/IPV/Hib) vaccine (Pediacef[®]) made by Aventis Pasteur, is the inactivated polio vaccine (IPV) now used in the UK. Always shake each 0.5 ml vial before use. A monovalent inactivated vaccine is also available on request. The live oral polio vaccine (OPV) remains available in some countries in 10-dose containers (which should be discarded at the end of any session), and in 10 × 1-dose packs. Store all products in the dark at 2–8°C.

References

See also full UK website guidelines

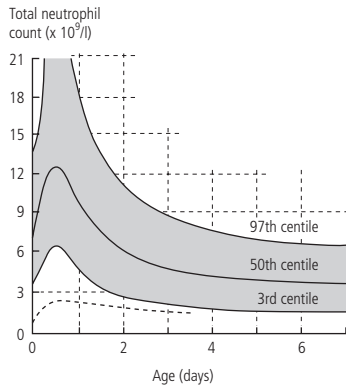
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SARGRAMOSTIM

Use

Sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), and filgrastim (q.v.), a granulocyte colony-stimulating factor (G-CSF) both stimulate the production and release of white blood cells from bone marrow. Whether either can be effective, either prophylactically or therapeutically, in combating neonatal bacterial or fungal infection remains to be established.



Pathophysiology

Neutrophil white cells (so called because they form a thin white line above the red cells when blood is spun, and turn neither red nor blue when stained) engulf and kill bacteria. They usually only remain in circulation for ~ 6 hours after leaving the bone marrow pool before entering other body tissues. Birth causes a transient increase in the number in circulation (see Fig), especially when this is stressful. Neonatal sepsis can rapidly decrease the number in circulation, because production is already close to its peak at birth. This, and functional immaturity, make babies more vulnerable to infection. Babies of <1.5 kg often have very low counts at 2–4 weeks old when the marrow mounts a first response to the growing post-delivery anaemia, as well as earlier (dotted line). Whether they are at more risk of infection is not known.

Pharmacology

Marrow colony-stimulating factors are naturally occurring glycoprotein growth promoters (cytokines) that stimulate the proliferation and

differentiation of red and white blood cell precursors in the bone marrow. A number of these factors – including erythropoietin (q.v.) – have been produced by recombinant DNA technology and brought into clinical use in the last ten years. G-CSF is now widely used to prevent chemotherapy induced neutropenia, and to accelerate neutrophil recovery after bone marrow transplantation. Subcutaneous rather than IV use doubles the elimination half life to about 3 hours, increases therapeutic efficacy, and minimises the risk of toxicity associated with high peak blood levels. Adverse effects, including fever, dyspnoea, nausea and vomiting, seem to have been uncommon with neonatal use. Use during pregnancy is associated with increased fetal death in primates. Use during lactation has not been studied but seems unlikely, on theoretical grounds, to pose any serious risk.

Both G-CSF and GM-CSF have been shown to abolish the postnatal neutropenia, and the sepsis-induced neutropenia, seen in preterm neonates, and to augment neutrophil function. GM-CSF enhances both neutrophil and monocyte production and function, but may have pro-inflammatory side effects. Prophylactic use did not reduce the incidence of later infection in the only neonatal trials completed to date, but did improve survival in one recent small trial in babies with overt infection. The manufacturers have not yet endorsed use in children, but no long term toxicity has yet been identified during ten years of neonatal use. UK trial of prophylactic GM-CSF use (*PROGRAMS*) in babies who are light-for-dates (<10th centile), less than 32 weeks gestation, and less than 72 hours old, continues to recruit. For details contact Dr Modi (email: n.modi@imperial.ac.uk). G-CSF provokes a more rapid rise in the neutrophil count, and a trial of this product in babies who have developed possible sepsis and are neutropenic might serve to test an alternative, focused, treatment strategy (as outlined in the monograph on filgrastim).

Treatment

10 micrograms/kg is usually given subcutaneously once a day for 5 (or 7) days. Inject the cytokine subcutaneously into alternate thighs using a 1 ml syringe and a 26 or 27 French gauge needle.

Supply and administration

Reconstitute a 250 microgram vial with 2.5 ml of water for subcutaneous use, to obtain a preparation containing 100 micrograms/ml. Store vials at 4°C, and use within 6 hours of reconstitution. Sargramostim is marketed in the USA, but it is not generally available in the UK, and the only other product of a similar nature, molgramostim, was withdrawn from the market in 2004.

References

See also the relevant Cochrane reviews



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Introduction

No attempt has been made to review the extensive literature that now exists on the impact of medication during early pregnancy on the growing fetus. However, a summary of what is known about placental transfer, teratogenicity (the propensity to cause a malformation), fetal toxicity, and use in the lactating mother, is included in the section labelled 'Pharmacology' for each drug listed in the main body of this neonatal formulary. Where the text merely says that treatment during lactation is safe it can be taken that the dose ingested by the baby is almost certain to be less than 10% of that being taken by the mother on a weight-for-weight basis, and that no reports have appeared suggesting that the baby could be clinically affected. The purpose of this short addendum is to summarise what is known about the impact on the baby of those drugs that do **not** receive a mention in the main body of this compendium even though they are commonly given to mothers during pregnancy, labour or the puerperium. Information is also given on a range of other drugs that are often taken illicitly. A small number of entries review groups of drugs (such as the anti-histamines) offering a general comment rather than information on one specific drug.

Advice to parents has, in the past, often been too authoritarian. While there are a small number of drugs whose use makes breast feeding extremely unwise, for most drugs it is more a matter of balancing the advantages and the disadvantages, and of being alert to the possibility that the baby might conceivably exhibit a side effect of maternal medication. It is not enough to just say that a particular drug will appear in the mother's milk – that is true of almost every drug ever studied. Mothers will also question why it should be thought unwise to expose their baby to low level of a drug during lactation when no reservation was voiced over much greater exposure during pregnancy. Much of the advice offered to UK clinicians in the *British National Formulary*, and in its paediatric counterpart simply reflects, of necessity, the advice offered by the manufacturer in the summary of product characteristics. Such statements are always cautious, seldom very informative, and often merely designed to meet the minimum requirement laid down by the licensing authority. The same is true of drug use in pregnancy – the arbitrary classification of drugs into one of five 'risk' categories currently used by the Federal Drugs Agency in America is an over-simple approach to a complex issue.

The task of the clinician, in most of these situations, is to provide parents with the information they need to make up their own minds on such issues. To that end each statement in this section is backed by at least one or two published references. In certain cases, readers may also wish to refer to the more comprehensive overviews provided in the books by Bennett, by Briggs, Freeman and Yaffe, by Schaefer, and by Hale (see p 273).

The dose the breastfed baby is likely to receive has been calculated, where this is possible, as a percentage of the maternal dose (both calculated on a mg/kg basis) using the approach recommended in Bennett's authoritative text. Particular caution should be observed when this fraction exceeds 10% because drug elimination will initially be much slower in the baby than in the mother. It would be very useful to have steady-state milk and plasma samples collected for analysis (once any effect of *in utero* exposure has been excluded) for some of the many drugs for which no such published information yet exists. The human milk:plasma (M:P) ratio is also given, where known. This shows the extent to which the drug is concentrated in breast milk. It is not, on its own, an indication of how much drug the baby will receive however, because some drugs achieve a therapeutic effect even when the blood level is very low.

It is often said that risks can be minimised if the mother takes any necessary medication immediately after completing a breastfeed so that the baby avoids being exposed to peak maternal plasma levels. This is something of a counsel of perfection however for any mother feeding frequently and on demand, and the sort of advice usually offered by someone with more theoretical knowledge than practical bedside experience. In many situations:

'the question is not whether a medicated mother should be allowed to nurse, but whether a nursing mother needs to be medicated.'

Sumner Yaffe

Further reading

Many excellent reviews of the issues that need to be considered when prescribing medication to a mother who is pregnant or breastfeeding have been published in the last ten years and these should be turned to for information on drugs not included in this brief, carefully revised, overview. Much high quality epidemiological work has also been done to define the risks of drug use during pregnancy. A lot of information on use during lactation is, by contrast, still anecdotal. Isolated reports recording apparent complications of use during lactation need to be interpreted with caution (especially where these relate to drugs that have been used by large numbers of other mothers uneventfully). Reports published before 1990, in particular, frequently lacked any documentary evidence that significant quantities of the offending drug were actually present in the baby's blood.

Reference texts on drug use during pregnancy and lactation

Ten recent, comprehensively referenced, reviews are:

- Bennett PM, ed. *Drugs and human lactation*. 2nd edn. Amsterdam: Elsevier, 1996.
- Lee, A, Inch S, Finnigan D. *Therapeutics in pregnancy and lactation*. Abingdon: Radcliffe Medical Press, 2000.
- Friedman JM, Polifka JE. *Teratogenic effects of drugs. A resource for clinicians*. 2nd edn. Baltimore: Johns Hopkins University Press, 2000.
- Yankowitz J, Niebyl JR. *Drug therapy in pregnancy*. 3rd edn. Philadelphia: Lippincott, Williams & Wilkins, 2001.
- Schaefer C, ed. *Drugs during pregnancy and lactation. Handbook of prescription drugs and comparative risk assessment*. Amsterdam: Elsevier, 2001.
- Koren G, ed. *Maternal-fetal toxicology. A clinician's guide*. 3rd edn. New York: Marcel Dekker, 2001.
- American Academy of Pediatrics. Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001;**108**:776–89.
- Hale TW. *Medications and mothers' milk*. 11th edn. Amarillo, Texas: Pharmasoft Publishing, 2004.
- Weiner CP, Buhimschi C. *Drugs for pregnant and lactating women*. New York: Churchill Livingstone, 2004. [CD-ROM and PDA versions available]
- Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 7th edn. Philadelphia: Lippincott, Williams & Wilkins, 2005. [CD-ROM and PDA versions available]

The publishers of the book by Briggs update this with a quarterly bulletin, and the book by Hale is updated every 1–2 years. Useful up to date information on drug risk during pregnancy is held electronically by the REPRORISK database which is marketed by Micromedex, 6200 S Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, USA. The UK Breast Feeding Network have a helpline that mothers can ring if they have worries on such issues (telephone: 0239 259 8604). Use the answerphone to leave a phone number saying where you can be contacted during the evening.

Further information

The information given in the *British National Formulary* (BNF), and in the version giving advice on drug use in children, is generally authoritative, but this is *not* always true of the advice it offers on drug use during pregnancy and lactation. Further useful information on safe drug use in **pregnancy** can, however, be obtained in the UK through the local hospital pharmacy, from the Specialist Advisory and Information Service provided by the Northern & Yorkshire Drug & Therapeutics Centre at the Wolfson Unit, 24 Claremont Place, Newcastle upon Tyne, NE2 4HH (telephone: 0191 232 1525). This unit also maintains the UK's main teratology data base. See: www.ncl.ac.uk/pharmsc/entis.htm. More detailed information on drugs in **breast milk** can be obtained, similarly, from the Trent Drug Information Centre, Leicester Royal Infirmary, Leicester LE1 5WW (telephone: 0116 255 5779) or the West Midlands Drug Information Service, Good Hope General Hospital, Sutton Coldfield, B75 7RR (telephone: 0121 311 1974). Details of how to contact other similar advice centres in Europe and North America is provided at the back of the excellent book edited by Christof Schaefer (see above).

Maternal medication and the baby

Acebutolol M:P ratio 9–12 (metabolite ratio 25)

While there is no evidence of teratogenicity, this drug (and other beta blockers) can cause neonatal bradycardia, mild hypotension and transient hypoglycaemia when prescribed to a mother immediately before delivery. No complications have been reported following use during lactation but the drug and its metabolite, diacetolol, accumulate in breast milk, making labetalol or propranolol (q.v.) a better drug to use during lactation, especially if the dose exceeds 400 mg per day.

Rubin: *N Engl J Med* 1981;**305**:132.

Yassen: *Arch Fr Pediatr* 1992;**49**:351.

Acenocoumarol = Nicoumalone (former BAN) M:P ratio <0.01

As for the monograph on warfarin in the central section of this compendium. Breastfeeding is safe.

Pauli: *Dev Brain Dysfunc* 1993;**6**:229.

Barbour: *Obstet Gynaecol Clin North Am* 1997;**24**:499.

Acitretin

Vitamin A, in excess, is a known teratogen and, although this oral vitamin A derivative is rapidly excreted from the body, some is metabolised to etretinate (q.v.) and this can still be detected in the body for 50 months after treatment is stopped. Use is not generally recommended during lactation either, although the baby would only receive weight-for-weight about 2% of the maternal dose when breastfed.

Rollman: *Acta Derm Venereol Stockh* 1990;**70**:487.

Pilkington: *Drugs* 1992;**43**:597.

Alcohol M:P ratio 0.9; Infant dose 4–19%

A high alcohol consumption in pregnancy damages both the physical and mental development of the fetus. Even occasional 'binge' consumption may not be without hazard, and there are some reports suggesting that behavioural problems are commoner in the children born to those women who drink even moderately during pregnancy. The alcohol content of breast milk is over 90% of the mother's simultaneous plasma level. Side effects in the baby are rare, but drowsiness is occasionally seen. For a summary of UK advice see Green Top Guideline No 9 on *Alcohol consumption in pregnancy* issued by the Royal College of Obstetricians and Gynaecologists in 1999 (Accessible from: www.rcog.org.uk)

Little: *N Engl J Med* 1989;**321**:425 (see also **322**:338).

Mennella: *N Engl J Med* 1991;**325**:981.

Alimemazine = Trimeprazine (former BAN)

There is no evidence that this long established antihistamine is hazardous in pregnancy. While use (either as a sedative or to control itching and pruritis) is not now recommended in children less than two years old, use during lactation has not been reported to cause problems. Little appears in animal milk. The content in human milk has not been studied.

O'Brien: *Am J Hosp Pharm* 1974;**31**:844.

Allergic rhinitis

The use of nasal decongestants, of sodium cromoglicate, and of nasal corticosteroids is entirely safe during pregnancy and during lactation. See also the entry on the use of systemic antihistamines.

Amantadine

This antiviral drug used in Parkinsonism is teratogenic in animals and its use is not recommended in pregnancy.

Mothers should probably be advised against breastfeeding, although only a little appears in breast milk.

Nora: *Lancet* 1975;**2**:607 (and 1044).

Rosa: *Reprod Toxicol* 1994;**8**:531.

Amitriptyline M:P ratio 1.5; Infant dose about 1%

There is no good evidence that this tricyclic antidepressant and its metabolite, nortriptyline, are teratogenic. They are excreted in breast milk, but no hazardous neonatal consequences have been documented.

Bader: *Am J Psychiatr* 1980;**137**:855.

Breyer-Pfaff: *Am J Psychiatr* 1995;**152**:812.

Angiotensin-converting enzyme (ACE) inhibitors

All the ACE inhibitors are known to be fetotoxic, causing serious interference with fetal kidney function, growth retardation and an increased risk of stillbirth or neonatal death. There is also increasing evidence that exposure in the first trimester of pregnancy can be teratogenic, causing a modest but significant increase in the number of babies born with at least some (of ten minor) congenital malformation. Captopril (q.v.), cilazapril, enalapril, fosinopril, imidapril, lisinopril, moxetilapril, perindopril, quinapril, ramipril andtrandolapril are among the more commonly used drugs in this class. However, even though babies seem to be exquisitely sensitive to these drugs but, despite this, it is almost certainly safe for mothers to use captopril or enalapril during lactation because the baby will not be exposed to even 1% of the weight-related maternal dose. Whether this is also true of other drugs in this class is not yet clear.

Rush: *Clin Nephrol* 1991;**35**:234.

Copper: *N Engl J Med* 2006;**354**:2443.

Angiotensin-II receptor antagonists

There is accumulating evidence that the recently introduced drugs in this group (including candesartan cilexetil, eprosartan, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan and valsartan) cause the same problems as the more widely studied angiotensin-converting enzyme (ACE) inhibitors (see above). Nothing is known about use during lactation.

Serreau: *Br J Obstet Gynaecol* 2005;**112**:710.

Antidepressants

Most tricyclic antidepressants are safe during both pregnancy and lactation. Blood levels may need monitoring once each trimester if treatment is to be optimised, and neonatal withdrawal symptoms are sometimes seen after birth. Monoamine oxidase inhibitors are often avoided in pregnancy because they can increase the risk of hypertension. Several of the selective serotonin re-uptake inhibitors (SSRIs) have now been subject to careful study and these are listed separately. Use does not seem to cause any long term problems, but all are probably capable, on occasion, of precipitating signs of acute withdrawal with neonatal agitation and irritability shortly after birth. However, while much unnecessary distress can be caused if these symptoms are wrongly interpreted as indicating that the baby has suffered asphyxial stress during delivery, the symptoms are rarely severe and seldom last more than a week. More rarely, there is probably a slightly increased risk that use in pregnancy will result in the baby exhibiting signs of persistent pulmonary hypertension at birth.

Moses-Kolko: *JAMA* 2005;**293**:2372.

Chambers: *N Engl J Med* 2006;**354**:579.