Neonatal Formulary 5

Drug Use in Pregnancy and the First Year of Life

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Companion website: www.neonatalformulary.com
All substances are toxic; only the dose makes a thing not a poison.

— Paracelsus (1493–1541)
Introduction

NNF5 has been designed to answer the growing need for compact and up to date, referenced, advice on the prescribing of drugs, and their safe and accurate nursing administration, during pregnancy, labour and the first year of life. While the book’s main focus is on the baby, many drugs that are given to women during pregnancy are given with the baby’s welfare in mind as much as the mother’s. To exclude a drug simply because it is mostly given before birth rather than after birth would be to create an entirely artificial divide, so both receive attention in this compendium. Only limited information is provided, however, when the indications for use during pregnancy are essentially the same as at any other time in adult life in order to conserve space, because this information is readily available in many other texts, including the British National Formulary (BNF).

The number of drugs used in late pregnancy and the first few weeks of life continues to rise rapidly, even though the manufacturers have not yet, in many cases, sought market authorisation to recommend neonatal use. One recent study in the UK found that more than 80% of neonatal prescriptions were for a product, or for a dose, formulation or purpose, that lacked licensed endorsement from the manufacturer. The situation in the rest of Europe is not dissimilar. While a lot of general information on these drugs is given in the manufacturer’s summary of product characteristics (SPC), advice on use in young children is often non-existent. Since advice in the SPC is all that has been seen and approved by the UK Committee on Safety of Medicines, and since the BNF normally limits itself, as a matter of policy, to summarising information that has been so validated, much drug use in the neonate occurs in a dangerous information vacuum. Much the same goes for the use of many drugs during pregnancy and lactation. All this makes it increasingly important for midwives and nurses, as well as pharmacists and doctors, to be able to put their hands on a pocket-sized reference text that summarises the scattered but extensive therapeutic and pharmacokinetic information that is available on the safe and appropriate use of these products. A number of other drugs that have a well authenticated, if limited, therapeutic role are also reviewed, even though no commercial product is currently available. Caffeine remains the most notable, but by no means the only, drug to fall into this category in the UK.

Information on placental transfer and teratogenicity, and on the extent to which each drug appears in human milk (and the extent to which this matters) is provided for each drug. Where the text merely says that treatment during lactation is safe it can be taken that the dose ingested by the baby is likely to be less than 5% of the dose taken by the mother on a weight-for-weight basis, and that no reports have appeared suggesting that the baby could be clinically affected. Special attention has been paid to the rapid changes that occur in the renal and hepatic handling of some drugs in the first few weeks of life, and the impact of illness and severe prematurity on drug metabolism and drug elimination. The symptoms associated with overtreatment are summarised, and the management of toxicity is outlined. Information is also included on the best way to use the few drugs so far known to be of therapeutic benefit to the fetus.

NNF5 provides information on the main drugs used to modify the diet of babies with congenital enzyme deficiencies (‘inborn errors of metabolism’), a short monograph on breast milk fortifiers, and a monograph on the artificial milks (‘formula’ milks) most commonly used in the UK. However, no attempt has been made to list other dietary products — a need that was very comprehensively covered in Medicines for Children, published by the Royal College of Paediatrics and Child Health in London, and is also covered, rather more briefly, by its successor BNF for Children.

While the text reflects, in the main, practice in the UK, medicine is increasingly international in its scope. Every section of the text has been revised with this in mind by a wide range of local, national and overseas collaborators. A comprehensive range of journals have been searched in order to make the advice given in the latest revision as comprehensive and up to date as possible, and all relevant Cochrane reviews consulted. Input has also been sought from colleagues with a range of professional expertise in an attempt to ensure that the text reflects a distillation of current opinion. However, in deciding what should eventually find its way into print, it was the advice of those who could provide evidence to support their approach that carried most weight. A consensus driven text could, all too easily, merely reflect what most people are doing.
rather than what they ought to be doing! The references cited below each entry should make it easier for readers to make up their own minds on such issues.

The first part of the book contains important general information on drug storage, drug licensing, and drug prescribing, with advice on drug administration, the care and use of intravascular (IV) lines and the recognition, drug management in renal failure and the management and reporting of adverse reactions. The information given on individual drugs in the second section needs to be interpreted in the light of this general advice. Readers skip this at their peril.

The second (and largest) part contains whole page monographs on 229 of the drugs most often used during labour and the first few months of life listed in alphabetical order. Information on a number of blood products and vaccines is included. Each monograph lists the drug’s main uses, and the most appropriate dose to give, both in the term and the preterm baby. The neonatal half life is noted where known, and a note made of those with an unusually large volume of distribution ($V_d > 1 \text{l/kg}$). A brief summary of the drug’s discovery and development is usually included. Advice is also provided on how to measure accurately the small volumes frequently required, and how to administer bolus and IV infusions safely. The advice given can, in general, be used to guide management throughout the first year of life. Significant interactions between drugs included in the main section of the compendium are outlined. Adverse effects commonly encountered in infancy, and their management, receive attention, but the SPC should be consulted in respect of other, less common, adverse effects. All the major multicentre clinical drug trials under development, or in progress, in the UK when the book went to press get a mention. Information under the heading ‘supply’ refers to the formulation most widely used in the UK. It is important to realise that other strengths and formulations may exist, and essential to check the label on the container before giving medicine to any patient. The stated cost is the basic net price (normally quoted in the BNF) when the book went to press, rounded to two significant figures. This information has been included in order to make clinicians more cost conscious, but should not be interpreted as representing the pricing policy of any particular hospital. Every monograph concludes with one or more recent key references to the obstetric, perinatal or neonatal literature (from which it is usually possible to identify other key reports).

The third part contains brief notes on a further 141 drugs, or groups of drugs, that are not infrequently taken by mothers during pregnancy, labour or the puerperium. The drugs mentioned include all the more commonly used products thought to affect the baby either because of placental transfer or because of excretion in human milk. Illicit drug use and legitimate self-medication both receive attention. Entries are almost always linked to two key references that can be used to access additional original studies and reports.

The index at the back of the compendium includes all the UK and US synonyms by which some drugs are occasionally known, and serves to identify more than 50 other drugs only referred to, in passing, within another drug monograph. Various common contractions are also spelt out.

A website was launched in January 2001 (www.neonatalformulary.com). New drugs continue to come onto the market at regular intervals, and further information relating to the use of many of the drugs already contained in the book continues to appear almost monthly. As a result, the text remains under semi-continuous review. The website also provides longer, more fully referenced, commentaries on some important products, direct access to abstracts of all relevant Cochrane reviews and link access to the UK Government’s current vaccination policy guidelines. It also contains monographs on a number of drugs that were included in earlier editions of this book, but which do not appear in the present print version (although their existence can still be traced using the index) because they are no longer used as often as they once were. While the publishers plan to continue producing new editions of the book approximately once every three years, the existence of a website makes it possible to alert readers to all the more important changes that get made to the text as soon as they are issued.
Important advisory statement

While every effort has been made to check the veracity of the information in this compendium, those responsible for its compilation cannot accept responsibility for the consequences of any remaining inaccuracy.

The drugs included are, for the most part, those in current use in the neonatal units in the UK, but the most recent updates have increasingly attempted to reflect international practice. Omission cannot be taken as implying criticism of a particular drug’s usefulness, but neither is inclusion necessarily a recommendation. Indeed, a number of products are mentioned specifically to alert clinicians to some of the uncertainties or limitations associated with use in infancy. Personal preference and past experience must inevitably influence prescribing practice, and in neonatal practice, more than any other branch of medicine, it is better to use a limited number of carefully evaluated and widely used drugs knowledgeably than to use drugs with which the prescriber is not fully familiar. It is also dangerous to go uncritically for the latest product to reach the market: too many drugs of proven value in adult medicine have been widely and indiscriminately used in pregnancy and in the neonatal period over a number of years before the potential hazards associated with their use became apparent. If diethylstilbestrol had been tested for efficacy before being given to millions of women in an effort to prevent miscarriage and premature delivery, many children would have been saved from genital tract deformity, and several hundred from developing vaginal cancer. If the pharmacokinetics of chloramphenicol and the sulphonamides had been established before these drugs were first widely used in the neonatal period some fifty years ago, many hundreds of deaths could have been avoided. Hexachlorophene baths and vitamin K injections also killed several hundred babies before anyone realised what was happening.

Neither are such inadvertent drug tragedies merely a thing of the past. Within the last eight years evidence has emerged that acetazolamide for post-haemorrhagic hydrocephalus can do more harm than good, and that the amount of aluminium often infused during parenteral nutrition can cause permanent neurological damage. The harm that was being done to these patients only finally came to light when these forms of treatment were exposed to controlled trial scrutiny. Cisapride was widely used for ten years before it became clear that it was of very little use and that overenthusiastic use could trigger a cardiac arrhythmia. Concern has now surfaced regarding the safety of sustained ante- or post-natal steroid use. Because early trials focused on short term outcomes and did not look at the child’s later development, we still do not know whether a drug that has now been in widespread use for more than twenty years actually does more harm than good when high dose treatment is given for more than a few days.

The simultaneous use of several drugs increases the risk of harming from drug interaction (furosemide with an aminoglycoside, or erythromycin with carbamazepine). It also increases the risk of erroneous drug prescription or drug administration. Almost all drugs are potentially harmful, and some of the drugs most frequently used in the neonatal period are potentially lethal when given in excess. It has been seriously suggested that every hospital drug cupboard should have the motto ‘Is your prescription really necessary?’ pinned to the door: sadly such a step would probably have little effect because, while doctors are responsible for the original prescriptions, they nearly always leave the hard and responsible work of drug administration to their nursing colleagues!

Many paediatric and neonatal texts provide tabular drug lists and dosage guidelines. They can be a useful aide mémoire, but they encourage the false impression that all you need to know about a drug is how much to give. They should never be used on their own, except by somebody who is already fully familiar with all the drug’s indications and contra-indications, and with all aspects of the drug’s pharmacokinetic behaviour (including its behaviour in the sick preterm baby). Information also becomes dated quite quickly, so any text more than two years old should be used with great caution.
Further reading

A lot of good books about drug use in children now exist, but detailed up to date neonatal information is harder to find. The excellent neonatal reference text published by Roberts in 1984 was never updated, while the slim American reference booklet by Young and Mangum is not widely available in the UK and only covers a limited range of drugs. The paediatric text by Taketomo is very comprehensive, and this is updated annually. *Medicines for Children*, the text that used to be published by the Royal College of Paediatrics and Child Health in the UK, was equally comprehensive. However, even these two books only include limited information on neonatal usage, and neither text is referenced. *Martindale* remains a mine of useful information, and there is more specific information relating to pregnancy and the neonatal period available in the *British National Formulary* (BNF and BNFC) than is generally realised (although the BNFC is the only text to include much information on dosage other than that suggested in the manufacturer’s SPC). The neonatal information in Dollery’s otherwise authoritative text is of very uneven quality. These books and the local Formularies produced by the Hammersmith Hospital in London, by the Hospital for Sick Children in Toronto, and by the Royal Women’s Hospital in Melbourne were all consulted during the preparation of the latest edition of the present text. For books relating to drug use during pregnancy and lactation see p 273.


Guy’s, St Thomas’ and Lewisham Hospitals. *Paediatric formulary*. 7th edn. London: Guy’s Hospital Pharmacy, 2005.


Many drugs in common use have never been shown to achieve what is claimed for them. Others, when subjected to rigorous evaluation in a randomised controlled trial, have eventually been shown to cause unexpected adverse problems. An increasingly complete tally of all such studies and overviews is now available in *The Cochrane Library*, an electronic database published for the international Cochrane Collaboration by John Wiley and Sons Ltd, and updated quarterly. For details contact John Wiley, Journals Fulfillment, 1 Oldlands Way, Bognor Regis, West Sussex, PO22 9SA, UK, (telephone: +44 (0)1243 843397).

A (Cochrane collaboration) symbol has been used to highlight those drugs or topics for which there is at least one review relating to use in pregnancy or the neonatal period, the abstract of which can be viewed on the NNF5 website at www.neonatalformulary.com The symbol identifies those vaccine monographs issued by the Department of Health in the UK that are accessible the same way. For details of how to access the full text of all the Cochrane reviews see p 26.
Part 1

Drug prescribing and
drug administration
Staff should never prescribe or administer any drug without first familiarising themselves with the way it works, the way it is handled by the body, and the problems that can arise as a result of its use. Most of the essential facts relating to use in adults are summarised by the manufacturer in the ‘package insert’ or summary of product characteristics (SPC). Many are also summarised in a range of reference texts, such as the *British National Formulary* (BNF), and the related text *BNF for children*. However manufacturers seldom provide much information about drug handling in infancy, and although *BNFC* now offers more advice on dosage in childhood than can be obtained from the manufacturer’s package insert, it stresses that the use of any unlicensed medicine (or licensed medicine in an unlicensed manner) should only be undertaken by those who have also first consulted ‘other appropriate and up-to-date literature’. The present book aims to summarise, and to provide a referenced guide, to that literature.

While many texts have long offered advice on the best dose to use in infancy – often in tabular form – very few provide much information on the idiosyncrasies associated with neonatal use. Such dosage tables can be a useful aide mémoire, but they should *never* be relied upon, on their own, to help the staff decide what to use when, what works best, or what potential adverse effects are commonly encountered during use in infancy. In addition, lists summarising common side effects and potential drug interactions are seldom of much help in identifying which problems are common or likely to be of clinical importance in the neonate, and access to this more detailed information is as important for the staff responsible for drug administration as it is for those prescribing treatment in the first place.

Similar challenges relate to the safe use of drugs during pregnancy and lactation because standard texts (such as the BNF) offer very little information as to what is, and is not, known about use in these circumstances. Such information is available in a range of specialised reference texts (see p 273) and the Part Three of this compendium summarises what is currently known about the use of most of the more commonly used drugs.

Never use anything except the most recent edition of this or any other reference text. Indeed copies of earlier editions should not be left where they might get used in error.
Terms, symbols, abbreviations and units

Postmenstrual age: The term postmenstrual age, as used in this book, refers to the child’s total age in weeks from the start of the mother’s last menstrual period. Thus a 7 week old baby born at 25 weeks gestation is treated as having a postmenstrual age of 32 weeks. The complaint that, since a baby does not menstruate, it cannot logically have a postmenstrual age is best dismissed for what it is — mere pedantry. The term ‘postconceptional age’ is sometimes used to describe this combination of gestational and postnatal age, although technically, of course, conception occurs about two weeks after the start of the last menstrual period.

Giving intravenous drugs: Intravenous (IV) drugs should always be given slowly, with a few notable exceptions. Because this is such universal good practice the advice is not reiterated in each individual drug monograph. The simplest way of achieving slow administration is described on pages 6 and 7. Where previous dilution or a particularly slow rate of infusion is important this is always specified in the relevant drug monograph, and the reason given. Drugs should also be given separately. Where two different IV drugs have to be given at the same time, the best way to stop them mixing is described on p 14. Intramuscular (IM) drugs should never be mixed, except as described in the individual drug monographs.

Continuous co-infusion: Special problems arise when it is necessary to give more than one drug continuously and vascular access is limited. Here terminal co-infusion (the mixing of two different infusates using a tap or Y connector sited as close to the patient as possible) is sometimes known to be safe. In the most frequently encountered situations where such co-infusion is safe, a comment to that effect occurs in the relevant drug monograph. In all other situations, two different infusion sites will need to be used unless advice to the contrary has been obtained from the local hospital pharmacy. Note, in particular, that the advice in relation to total parenteral nutrition (TPN) only relates to formulations similar to the one described in this compendium.

Drug names: Drugs are, in general, referred to by their non-proprietary (‘generic’) name, following the usage currently adopted by the British National Formulary (BNF). Where, for clarity, a proprietary name has been used, the symbol ® has been appended the first time it is used. Where the British Approved Name (BAN) or the United States Adopted Name (USAN) differ from the International Non-proprietary Name (rINN), these alternatives are also given. All synonyms are indexed.

Symbols and abbreviations: Cross-references between the various monographs are marked by the Latin phrase ‘quod vide’ (contracted to q.v.). Drugs vary widely in the extent to which they are distributed within the body. Some drugs only accumulate in the extracellular tissues. Others are taken up and concentrated in some or all body tissues, the total amount in the body being more than would be presumed from a measure of the amount present in the blood. This property is referred to as the drug’s apparent volume of distribution – a measure summarised by the symbol \(V_D\). References to papers reporting a randomised controlled trial are marked by the symbol [RCT]; those referring to a systematic reviews or meta-analysis are marked [SR]. Drugs for which the Cochrane Collaboration has produced at least one systematic review are marked with the Cochrane logo. Other abbreviations have been kept to a minimum; those used in this book are all explained in the index.

### UNITS

<table>
<thead>
<tr>
<th>Unit</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kilogram (kg)</td>
<td>= 1000 grams</td>
</tr>
<tr>
<td>1 gram (g)</td>
<td>= 1000 milligrams</td>
</tr>
<tr>
<td>1 milligram (mg)</td>
<td>= 1000 micrograms</td>
</tr>
<tr>
<td>1 microgram ((\mu)g) (^\dagger)</td>
<td>= 1000 nanograms</td>
</tr>
<tr>
<td>1 nanogram (ng) (^\dagger)</td>
<td>= 1000 picograms</td>
</tr>
</tbody>
</table>

A 1% weight for volume (w/v) solution contains 1 g of substance in 100 ml of solution.

It follows that:
- a 1:100 (1%) solution contains 10 milligrams in 1 ml
- a 1:1000 (1‰) \(^\dagger\) solution contains 1 milligram in 1 ml
- a 1:10,000 solution contains 100 micrograms in 1 ml

\(^\dagger\) These contractions are best avoided as they can easily be misread when written by hand