



Neonatal drug development

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ABSTRACT

Drug development is crucial to improving the care given to neonates through new and existing medicines. Pressure from regulatory agencies has improved the way in which pharmaceutical companies work with neonates. This provides new opportunities for the neonatal community. This paper describes the issues that arise during the development of new drugs and considers how the contemporary approach to new drugs can inform research on existing drugs.

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1. Introduction

This article will describe a systematic approach to neonatal drug development (NDD). We start by outlining the need for a systematic approach to NDD before considering individual elements of the process [1]. Given the importance of new drugs we will focus on new drugs. However, a lot of existing medicines are used with inadequate information. We will examine how formal NDD benefits the evaluation of existing drugs.

2. Key guidelines

- A systematic approach to drug development will increase the probability that new treatments will be adopted rapidly and will maximise the value of existing medicines.
- Co-ordinated work by a range of professionals and parents is needed to develop new or existing medicines.

3. Research directions

Neonatal drug development requires background research about issues that are central to the design of clinical trials. These include patient pathways, the frequency of use of rescue medications and robust work to validate and qualify biomarkers in neonates.

4. The need for systematic neonatal drug development

Some health care professionals appear to think that if we have been using a medicine for years then we know enough about the medicine to use it effectively, and no further research is needed. There are many aspects of neonatal medicine where this point of

view is not tenable. The management of patent ductus arteriosus with nonsteroidal anti-inflammatory agents [2] and systemic hypotension with inotropes [3] are examples of prescriptions that are not supported by evidence of efficacy or by evidence about a range of other key issues. Efficacy (knowing which medicines work under well-controlled conditions) is only one aspect of good prescribing. Good prescribing also involves assurance that the medicine being administered is of sufficient pharmaceutical quality (including an age-appropriate formulation that minimises risks), that an appropriate dose is being used and that there is sufficient information about safety and the risks of the medicine for a clinician to make a reasonable judgement about the benefit–risk balance for the medicine in particular baby. Large, pragmatic trials of medicines are necessary but not sufficient to develop rational policies for medicine use in neonates. Evidence about efficacy needs to be underpinned by information about pharmaceutical quality, dosage and safety.

Doctors often take the pharmaceutical quality of medicines for granted. However, before the medicine appears on the ward there has been a long and complex supply chain to prepare the medicine for use. Quality issues include all the contents of medicines – including excipients, and assurance about the supply of medicines – including the source of all components of medicines in the light of worldwide concerns about counterfeiting, consistency of manufacturing issues and accountability through the supply chain. All of these aspects have to be in place and supported by an evidence base before a medicine can be marketed.

A medicine will not work if you give the wrong dose. The dosage regimens of very few of the medicines used in neonates have been rigorously evaluated so that we may be giving the wrong dose [4,5]. The consequences of giving the wrong dose are that medicines may be ineffective or we may be exposing babies to unnecessary side effects. Evidence-based dosage regimens may differ from conventional dosage regimens. For example, Suyagh et al. evaluated the pharmacokinetics of metronidazole in neonates using dried blood spots and developed a neonatal dosage regimen. Their results are summarised in

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Table 1[6], including a comparison between the dosage regimen in the BNFC and the dosage regimen derived from their data. It is irrational to conduct large pragmatic trials of a drug if the dosage regimen for that drug is based on guesswork.

Each aspect of the drug needs to be considered before large-scale studies can be done. The approach developed by the European Medicines Agency (EMA) for PIPs is shown in Table 2[7]. This type of systematic approach is not an empty box-ticking exercise. It is ethically necessary to ensure that later stage research has a high chance of success as possible. We have a responsibility to optimise the chances of success for each trial that we do. We have this responsibility towards each baby we recruit but also to the funders. Each trial represents an opportunity cost for other trials. PIPs are designed to ensure that NDD is conducted rigorously.

5. The need for high quality NDD

The need for high quality NDD arises from the need to complete research as quickly as possible so that treatments that work can be used and so that treatments that don't work can be abandoned. All research involves risk. In the case of NDD those risks can be reduced by careful planning and aiming for quality at every step [8].

The characteristics of high quality NDD are:

- Explicit information about each stage of the drug development process. When feasible each step needs to be understood before a new step is started. When this is not feasible there need to be a clear process for making explicit judgments about when to proceed in the presence of uncertainty
- A balance between benefit and risk before moving on the next step with independent, proportionate review.
- Care with biomarkers and feasibility to make sure the results can be interpreted and the patients can be recruited.
- Flexibility. If an early phase study shows results that are unexpected the developmental programme will need to change so that later phase studies reflect the lessons learnt.
- A strategy to frame hypothesis-driven studies. Some elements of NDD are best thought of as descriptive studies. Other elements are based on hypotheses. Some studies based on hypotheses will not test the hypotheses directly but will be pilot or feasibility studies.

6. Parents

Parents need to be involved in the design of research in a way that respects their opinions and the pressure on their time. The experience of the English National Institute for Health Research Medicines for Children Research Network (NIHR MCRN) is that parent input to studies is invaluable. This needs to include opportunities to comment on the

Table 1
Comparison between dosage regimen in BNFC 2011 and dosage regimen suggested by PK modelling.

| BNFC 2011 | Dosage regimen | Status of BNFC dose compared to dosage suggested by PK modelling |
|--------------------|---|--|
| | 15 mg/kg as a single loading dose and 7.5 mg/kg every 12 h thereafter | |
| Suyagh et al. 2011 | | |
| 24–25 weeks | 7.5 mg/kg 24 h | Overdose |
| 26–27 weeks | 10 mg/kg 24 h | Partial underdose |
| 28–33 weeks | 7.5 mg/kg 12 h | Similar dose |
| 34–37 weeks: | 10 mg/kg 12 h | Underdose |

With regard to potential overdosage in the most preterm infants, it may be important to note that in older age groups metronidazole is associated with peripheral neuropathy.

Table 2

Key components of an application for a Paediatric Investigation Plan. Each component needs to be addressed. Inclusion or exclusion of studies needs to be explicitly justified. From EMA website and document to summarise how PIPs are evaluated. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91#. Last accessed 3rd August 2011. Aspects which a neonatologist could contribute to are in bold. All other aspects are more appropriately dealt with by other professionals.

| | |
|---|---|
| Part A – Procedure for the assessment of the application | |
| A.1 | Details of the medicinal product and overview of the application |
| A.2 | Regulatory information on clinical trials related to the condition and to the development for the paediatric population |
| A.3 | Regulatory status of the product |
| A.3.1 | Marketing authorisation status inside the community |
| A.3.2 | Marketing authorisation status outside the community |
| A.4 | Regulatory advice on the development of the product |
| A.4.1 | Advices from any regulatory authority relevant to the development in the paediatrics population |
| A.4.2 | Relevant guidelines |
| Part B – Overall development of the medicinal product including information on the target diseases/conditions | |
| B.1.1 | Similarities and differences of the disease/condition between populations |
| B.1.2 | Pharmacological rationale and explanation |
| B.2 | Current methods of diagnosis, prevention or treatment in paediatric populations |
| B.3 | Significant therapeutic benefit/fulfilment of therapeutic needs |
| Part C – Applications for product-specific waivers | |
| C.1 | Overview waiver request(s) |
| C.2 | Grounds for a product-specific waiver |
| C.2.1 | Grounds based on lack of efficacy or safety |
| C.2.2 | Grounds based on the disease or condition not occurring in the specified paediatric subset(s) |
| C.2.3 | Grounds based on lack of significant therapeutic benefit |
| Part D – Paediatric investigation plan | |
| D.1 | Purpose of and existing data for the proposed paediatric development |
| D.1.1 | Paediatric Investigation Plan indication |
| D.1.2 | Selected paediatric subset(s) |
| D.1.3 | Outline of the existing quality, non-clinical and <i>clinical data</i> |
| D.2 | Quality aspects |
| D.2.1 | Strategy in relation to quality aspects |
| D.2.2 | Outline of each of the planned and/or ongoing, studies and steps in the pharmaceutical development |
| D.3 | Non-clinical aspects |
| D.3.2 | Strategy in relation to non-clinical aspects |
| D.3.2 | Overall summary table of all planned and/or ongoing non-clinical studies |
| D.3.3 | Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies |
| D.4 | Clinical aspects |
| D.4.1 | Strategy in relation to clinical aspects |
| D.4.2 | Overall summary table of all planned and/or ongoing clinical studies |
| D.4.3 | Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies |
| D.5 | Timelines of measures in the paediatric investigation plan |

impact of study schedules on families as well as the prioritisation of studies. Research governance must include the perspective of families.

There is a growing recognition of the importance of patient reported outcome measures in clinical trials of efficacy and effectiveness. Parent and child reported outcomes will have a place in NDD. However, these are not easy to define [9]. The role of PROMs in neonatal research has not been established.

7. Planning NDD

The first step is to define an indication. This is a crucial step because all the studies need to recruit babies who meet the indication. The indication needs to be feasible: there need to be enough babies available for study and enough babies with the condition to justify marketing the medicine. Assessment of the indication needs to be reliable (see comments on Biomarkers). In some therapeutic areas within neonatology work is needed to define a feasible indication.

A clinical indication may not be the same as the indication included in a Marketing Authorisation. For example there is a difference between the clinical indications for antibiotics in neonates and the indication associated with a Marketing Authorisation.

The preferred “regulatory” indication is proven bacterial infection. The clinical indication is suspected infection. The clinical indication is common but is an unsafe basis for recruitment to trials that aim to evaluate the efficacy of antibiotics. Antibiotics do no good to babies without an inflammatory response. It is very difficult to assess the effect of antibiotics in babies with culture negative sepsis.

Neonates are a vulnerable group and we need to avoid doing unnecessary research on them. If a medicine works in older age-groups and there is good reason to think it will work in neonates then it is not necessary to do efficacy studies in neonates. There is a framework for making judgments about when to extrapolate information from older age-groups to neonates and children. This framework is summarised in Fig. 1. For many indications, PK studies in neonates and a safety registry may be all that is needed. However, there are some indications specific to neonates that will require a full drug development programme. These include surfactant deficiency, chronic lung disease of prematurity, necrotizing enterocolitis, haemodynamics of

adaptation – including patent ductus arteriosus (PDA), retinopathy of prematurity and hypoxic–ischaemic encephalopathy.

A particular feature of neonatal drug development is the need to tailor medicines to the context in which they will be used. For example, some of the currently available formulations of medicines used in neonates require manipulations before they are used, or, large volumes of fluid to administer them. Given the effort required to assure the pharmaceutical quality of medicines it is important that the optimal formulation and presentation are decided before clinical trials are done on a medicine. This requires input from a range of professionals. Formulations need to take account of practical issues with administration across Europe. Formulations need to be decided before animal and dosing studies since different formulations may have different pharmacokinetic and safety profiles.

European regulators value information from animal work, which are included in “pre-clinical studies” [7]. Juvenile animals provide a unique opportunity to scope out what the safety issues may be. There is enough similarity between mammal species to allow some judgments about safety issues in humans. This may be particularly important for long-term outcomes in neonatal studies. Species such as rodents have much shorter life-spans so that gross safety problems

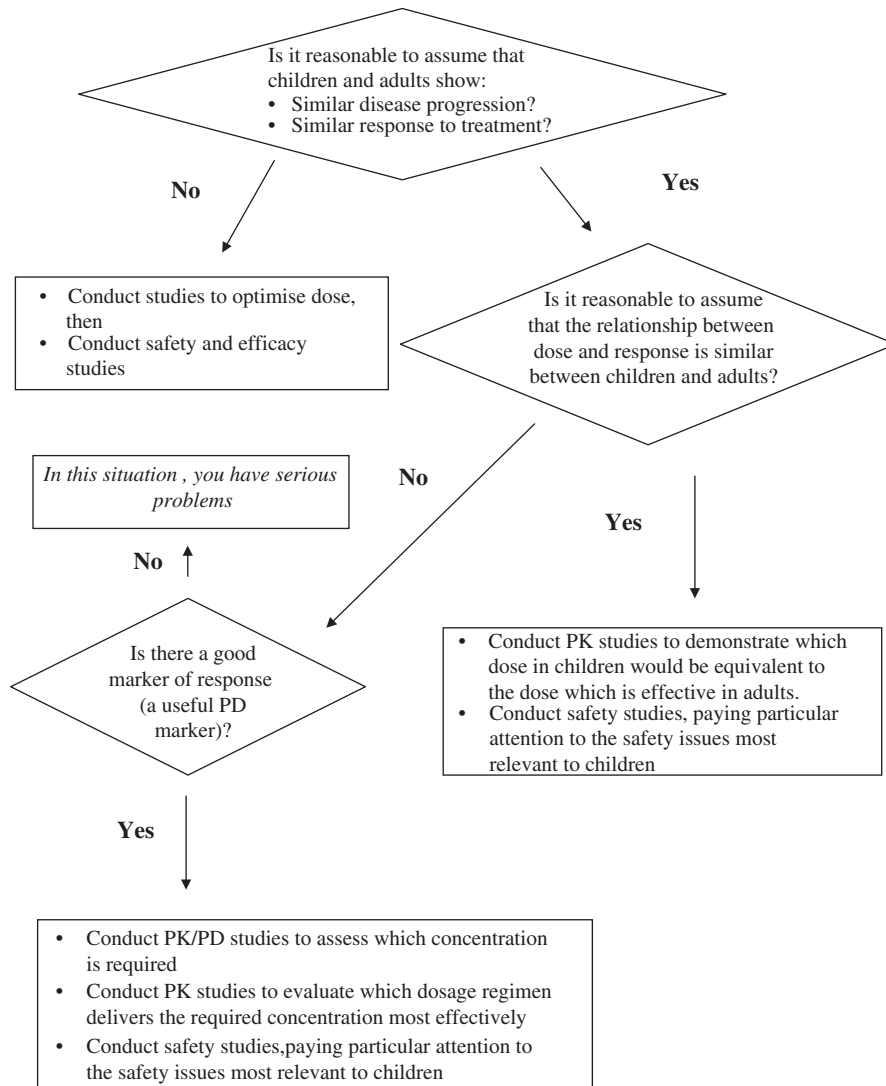


Fig. 1. Decision tree about which trials are needed to develop medicines in children. This is based on the “FDA Pediatric Study Decision Tree” PK: pharmacokinetics, what does the body do to the drug, how does the body handle the drug. PD: pharmacodynamics, what does the drug do to the body.

relating to problems in later life may be identified using animal models long before they would be identified in humans. Pre-clinical juvenile animal studies may not be required for an established medicine.

7.1. Biomarkers

Biomarkers are often used to define inclusion criteria for trials. A useful biomarker (or clinical characteristic or risk factor) needs to be validated and qualified [10]. Validation can be summed up as “does the biomarker consistently measure what you think it measures”. It is important to be sure about this because if the biomarker is imprecise or inconsistent the trials will not capture the right babies and studies may need to be much larger. Qualification can be summed up as “does the biomarker predict the outcome you are worried about”. In neonatal practice, systemic hypotension is a poorly qualified biomarker for long-term neurodevelopmental outcome. That is why the use of inotropes is so controversial. A useful biomarker for inclusion in a trial is one that is consistently measured and which predicts the outcome. Good NDD will use a biomarker that has been demonstrated to have these properties. Relatively few biomarkers used in neonates have been validated and qualified. This reduces the likelihood of successful drug development. A drive to encourage the appropriate use of medicines through NDD will require significant background work to define appropriate biomarkers. Consensus statements about indications and outcomes may allow studies to proceed. However, unless the indications and outcomes are validated and qualified there is a significant risk of misclassification errors during studies. Study feasibility requires validated estimates of patient numbers at all stages of the trial. Using consensus statements that have not been subject to feasibility assessments may allow unfeasible studies to open [11]. Future research needs to capture information that informs drug development (such as patient flow, numbers of babies needing rescue medication, numbers of babies lost to follow-up).

7.2. Tolerability and dosage

Tolerability refers to the demonstration that there are no gross problems that would prevent a medicine from being used in a population. This is always a concern when a medicine is first given to humans. In neonates, there are relatively few medicines for which the first in neonate study is also the first in human. There may be age-specific tolerance issues. Local tolerance during intravenous infusion is a particular issue for many medicines used in neonates.

Rational medicine usage in neonates depends on the establishment of evidence-based dosage regimens. These require pharmacokinetic studies. Contemporary methodologies such as dried blood spots and population pharmacokinetic models render these studies relatively simple to design. The rate limiting step is parental tolerance of the study. It is relatively easy to recruit babies to a PK study about a medicine the baby would be getting anyway. It is more difficult to recruit babies to a study about a medicine the babies would not be getting anyway.

7.3. Mechanism and feasibility

The preparation of large scale clinical studies is often hindered by a range of uncertainties. Good NDD will minimise the risks posed by those uncertainties by conducting at least one relatively small study of the population that will later be studied in a large study. The aims and design of the relatively small study will vary between drugs and populations, depending on the uncertainties that are present. These studies can be called Phase 2b or Therapeutic Exploratory studies [12]. They can involve randomisation, but not always. They can include an assessment of feasibility, or they may be formal pilot studies. These studies are informed by a list of uncertainties relating

to the drug in question and aim to minimise the uncertainties that hinder drug development.

7.4. Efficacy and safety

Conclusive evidence about efficacy requires randomisation and large enough sample sizes to allow for a precise estimate of the treatment effect taking account of the variation seen in the population. These studies are described as Phase 3 or Therapeutic Confirmatory studies. Efficacy studies (does the medicine work under research conditions) require careful attention to biomarker validation and qualification. They benefit from common definitions of key outcomes to support meta-analysis. There are similar issues for safety reporting.

7.5. Effectiveness and clinical strategy

Once efficacy has been established and a picture about safety has been developed then, and only then, it is possible to ask questions about effectiveness (how to use the medicine in real life). For new medicines this is when the manufacturer moves beyond the PIP and the Marketing Authorisation and looks at convincing the people who pay for health care to buy their product. In the UK and many other countries there are explicit mechanisms for doing this. There are other issues about “life-cycle management” which relate to how information about the medicine can be used to develop its use.

It should be noted that European legislation also allows for designation of a drug as an orphan which allows access to incentives for drug development. The most common example in neonatology is Ibuprofen for PDA. The requirements for orphan designation include a prevalence of less than 1:2000 people within Europe at the time of submission of the application for orphan status. Given the low prevalence of many neonatal conditions other neonatal conditions may be suitable for this approach [13].

8. Existing medicines

Most medicines used to treat newborn babies have not been tested appropriately. We may be using the wrong dose. As noted above, there are no technical, ethical or scientific barriers to PK studies about the large numbers of medicines which are used frequently on neonatal units with no evidence about drug disposition in this age group. We may be using ineffective medicines.

When faced with the amount of work involved in NDD, there is a body of opinion among neonatal health care professionals that states (implicitly) we don't need to study off-label medicines in the same detail. The problem with that point of view is that off-label use has costs and risks that may be hidden from the medical and nursing staff but which are borne by others (Pharmacy etc.). Off-label use may be appropriate if supported by PK data [14]. Nevertheless, if it is feasible to obtain a Marketing Authorisation that would be preferable because the holder of the MA then has significantly greater responsibilities that can provide greater assurances to families and staff.

A key step is to work out where the formal drug development process has got up to and what study should be done next. A conceptual approach to this is illustrated in Fig. 2. Radar diagrams can be used to illustrate how much is known about each aspect of the drug in a particular context. Even though we use some medicines in ways that suggest that a large Phase 3 trial has been done, the evidence may suggest that we need to do early Phase 2 work on those medicines before doing any large-scale research. Moving straight to the large efficacy trial is a high risk approach. Most medicine studies in neonates are reported as under-powered studies of efficacy. A more productive way of thinking is to consider them as misinterpreted Phase 2 or therapeutic exploratory studies. As an example, the author's personal assessment of the drug development process with regard to PDA is given in Table 3.

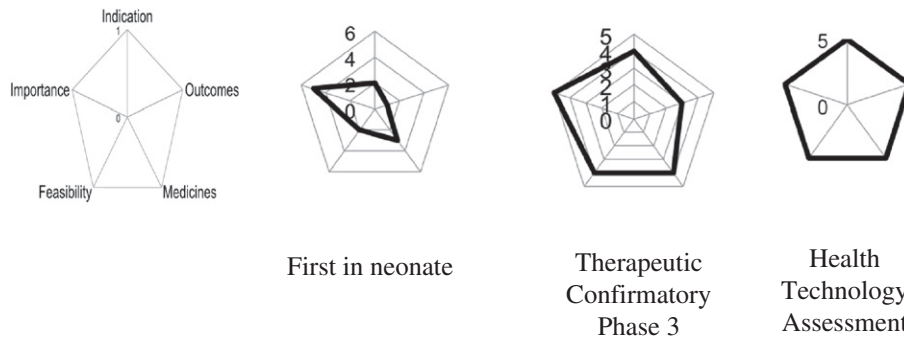


Fig. 2. Radar diagrams to illustrate how the “state of the art” for a series of hypothetical drugs maps onto key stages in drug development.

Trials are difficult and drug development programmes are imperfect. Some evidence gaps need to be fudged and it will be necessary to make judgments. However, some judgments may be a step too far. It is best to make these judgments in a structured, transparent manner [8]. Just as it is good to publish protocols for individual trials it will be useful to publish the rationale for drug development programmes [15]. When efficacy can be assumed from older age-groups we need to focus on PK studies and safety registries.

Clinicians want to do research that delivers clinically relevant information quickly and have often used a “best guess” approach to the design of pragmatic trials. This approach would not be allowed by regulators for new drugs and has not delivered results consistently. For example, the best guess approach to trials of PDA treatment is yet to provide definitive evidence about the management of PDA, despite several decades of research [2]. Pilot studies (small-scale studies that test key aspects of process or sample size assumptions) go some way to improving the chances of success of large trials. However, pilot studies are no replacement for a carefully reasoned programme of research that addresses key uncertainties in small studies in order to position large studies for success. Some areas that could influence the design of large trials about PDA are indicated in Table 3.

9. Conclusion

The effective use of medicines in neonates requires a comprehensive step-by-step approach to NDD. In the EU the way to develop this

approach for new drugs is well defined. Similar work would enhance attempts to optimise the use of existing medicines.

10. Conflict of interest statement

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Table 3
State of the art for drug development relating to patent ductus arteriosus (PDA).

| Aspects of drug development | Ideal state | Current state | Implication |
|-----------------------------|--|---|--|
| Indication | Needs to be related to outcome and agreed by enough people | Unclear what is the best indication to use – how big a duct is important. Consensus guidelines have not been fully validated or qualified | Significant risk to the generalisability of a pragmatic trial. Some work is needed to validate inclusion criteria and any large trial needs to capture data relating to qualification of the chosen indication |
| Inclusion criteria | Validated for use in multi-centred trials | No pilot work has described the extent of inter-observer variation within and between centres | Significant risk to the validity of a pragmatic trial. Any trial of efficacy or effectiveness needs prior work to establish the validity of selected method to ascertain PDA |
| Outcomes | Needs to be relevant and reliable | The proportion of long-term disability that can be attributed to treatable PDA is not clear | Need research about natural history Difficult to define meaningful sample size calculation |
| Efficacy | Needs to have a realistic prospect of making an important difference. | How to handle death, which may or may not be related to PDA or its treatment. | |
| Safety | What to measure, validated and qualified measurements | No agreed scales or processes to assess safety outcomes | Any trial of efficacy or effectiveness needs prior work to establish the validity of selected methods to ascertain safety |
| Study feasibility | Validated estimates of patient flow for all stages of the trial (screening, recruitment, consent, treatment, progress before). | Uncertainties include: how many families would consent; how many babies would require rescue treatment. | Need observational studies of patient flow. Need pilot studies of recruitment |
| Medicines | Age-appropriate formulation on the market. Placebo easy to make. | Age-appropriate formulation on the market. Placebo easy to make. | |
| Importance | A large concern to many neonatologists. | Good PK–PD data available [16] | |

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