Neonatal pearls : safety and efficacy of medication use in fetus and neonate

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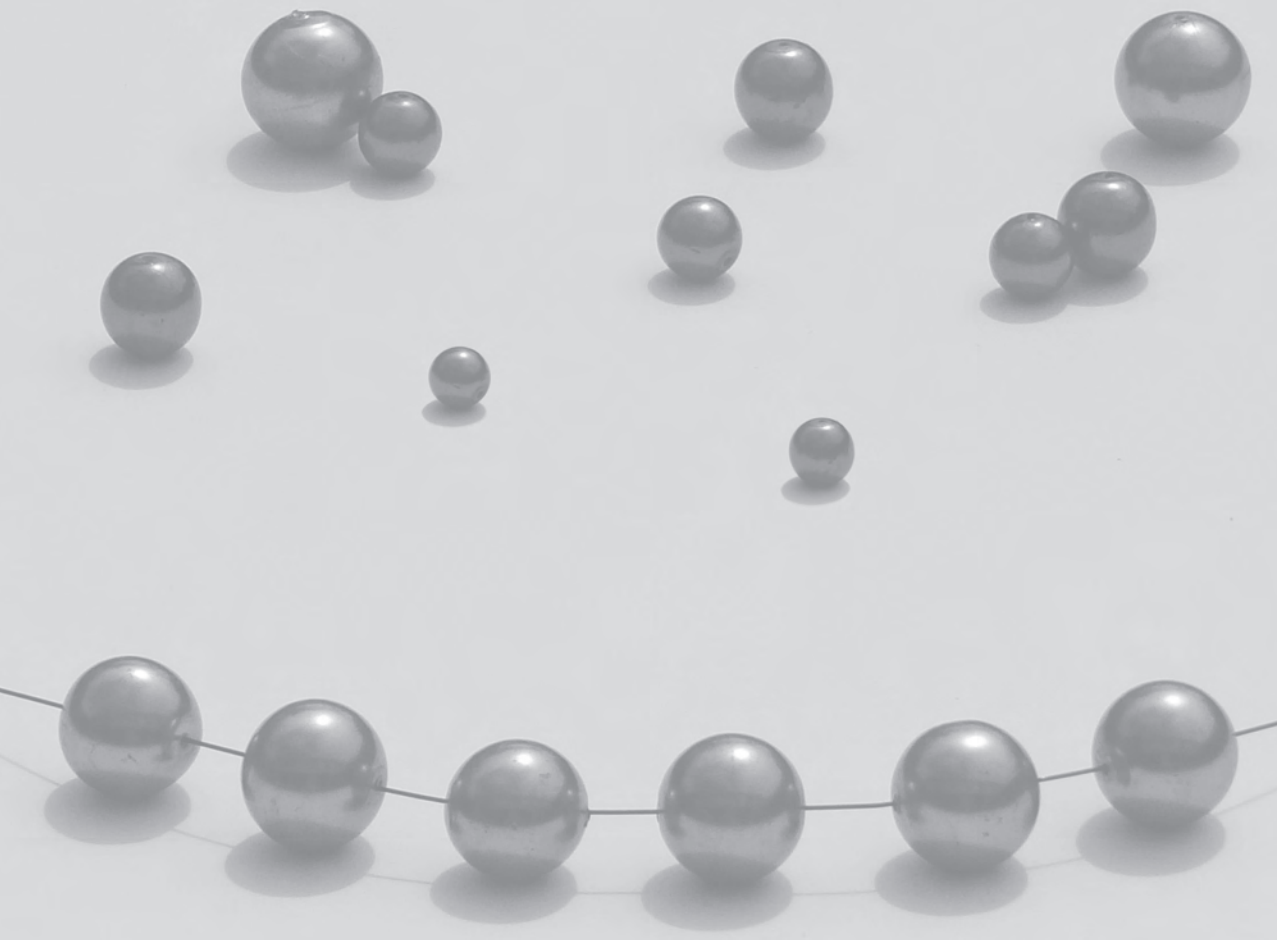
Chapter 1

General introduction



General introduction

Pharmacological research in pediatrics

More than 100 years ago the founding father of pediatrics in the United States of America, Dr. Abraham Jacobi, stated "Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but has its own independent range and horizon".[1] With this statement the need for age-appropriate pharmacological research for children was already emphasized more than a century ago. Several physical aspects with a great influence on distribution and metabolism of drugs change in growing children, such as body composition, motility and pH of the gastro-intestinal tract, perfusion of skeletal muscles, composition of plasma proteins, concentration of CYP-enzymes, glomerular filtration rate etcetera. As this large amount of factors change disproportional, dosing formulas to determine age-specific doses are almost totally unusable, especially for children younger than 8 years.[2] Despite this important argument to develop age-appropriate pharmacological research in children, this kind of research is still limited, particularly in the field of Neonatology. The relatively small pediatric and neonatal population and the need for testing drugs extensively for different age categories make research in children very expensive and therefore less attractive for the pharmaceutical industry. In addition, national law rules, ethical questions and the need for parental consent are other major problems for developing ethical justified clinical trials in children. A direct consequence of the lack of pharmacological research in children is a high amount of unlicensed (not registered in the Netherlands or modified formulations of registered drugs) and off-label (not registered for the used dosage, age, indication and/or route of administration) drug prescriptions.[3,4] These unlicensed and off-label prescriptions are most common in very ill children, especially those admitted on the neonatal intensive care unit (NICU). At least one off-label or unlicensed drug is prescribed to 80-93% of the NICU population.[3] The main reason for being off-label is the lack of age specific dosage regimes. Concerning the prescription of unlicensed and/or off-label drugs, we must consider if we want to deprive children of potential therapeutic benefits of unlicensed drugs instead of exposing them to possible unknown adverse effects.[3] This is a difficult consideration as several clinical conditions could not be treated without unlicensed and off-label prescriptions. Otherwise is usage of unlicensed and off-label drugs associated with an increased risk for adverse effects, urging for careful usage.[4,5]

Until when pharmacological trials in pediatrics become more extensive, pediatricians will have to deal with the limited availability of licensed and on-label drugs and work with alternative sources of evidence concerning safety and efficacy of medicine usage in children.

Retrospective research design

The most appropriate alternative design to evaluate safety and efficacy of medication use in children is a retrospective study. The lack of acquiring reliable evidence from retrospective studies is a common heard argument against this design, as it has a low ranking in the pyramid of evidence. However, an example of a pioneering discovery detected with a case-control study, was the finding of the relationship between smoking and lung cancer, confirming the usefulness of retrospective study design.[6]

When prospective evidence is not available, retrospective studies can be very valuable for evaluation of medical policies. Unlicensed and/or off-label drugs can be analyzed using a cohort of children over a fixed (passed) time period, which received a particular drug. Analysis of baseline characteristics of the population and details about achieving treatment goal, dosage, duration of administration and possible adverse effects, can demonstrate the advantages and disadvantages of the drug, so usage can be fine-tuned.

In addition to unlicensed drugs, the usage of licensed drugs also needs to be evaluated and fine-tuned on a regular basis. When a specific treatment protocol is started after a time-consuming process, it is often considered to be effective and safe enough to be used extensively. However, diversity of diseases, comorbidity and treatment possibilities may change during time. Frequent re-assessments of current management guidelines are thus of paramount importance including evaluation of their efficacy and safety. Nevertheless, evaluations of current management protocols are not frequently performed, since it is probably more "rewarding" or "exiting" to invent completely new treatment strategies. Based on these evaluations, the incidence and associated comorbidity among current policies can be surveyed and compared with other centers and populations (benchmarking). Unexpected outcomes may provide new insights and can be used as guidance for protocol adjustments or provide a basis for new randomized controlled trials. In many cases, these randomized controlled trials are only ethically justified when the advantages of possible new interventions are supported by strong evidence from retrospective cohort studies.

Another great benefit of retrospective studies is that they offer the opportunity to investigate relatively rare diseases, a common problem in the field of Neonatology. In these situations sample sizes are often small and prospective investigation of a large enough number of cases for reliable statistical analysis is sometimes very difficult if not impossible.

Although randomized controlled trials continue to provide the best evidence to guide clinical treatment and retrospective cohort studies may suffer from a various methodological limitations, especially errors due to confounding and bias, the latter play an important role in the evaluation of clinical treatment protocols and continue to be essential in medical research.

Neonatal pearls

In this thesis we present six clinical studies, six 'Neonatal pearls' reflecting our current neonatal practice (using licensed as well as unlicensed medicines). Although topics may seem very diverse at first sight, the common denominator is the evaluation of management guidelines with focus on effectiveness and risk of a particular drug. The problems chosen to investigate are all based on important practical questions with clinical relevance. All described clinical conditions are severe but rare, which results in restricted availability of literature. Our aim is to provide additional evidence with recommendations, directly usable in clinical practice. Due to the lack of literature and the small sample sizes, both caused by the rarity of the studied conditions, a retrospective cohort study was the only appropriate design to evaluate efficacy, safety and/or long term outcome of the current protocols. These six 'Neonatal Pearls' can serve as potential foundations for adjustment of clinical protocols and guidance on future prospective studies and randomized controlled trials.

Outline of the thesis

The general aim of this thesis was to emphasize the importance of retrospective research in Neonatology and the necessity of regular and careful evaluation of already existing treatment policies. We describe six retrospective studies investigating effectiveness, safety and/or long term consequences of various drugs used in neonates.

Chapter 1 provides background information on the choice of the various conditions reported in chapters 2 to 7 and the choice of retrospective cohort studies.

Chapter 2 investigates fetal, neonatal and developmental outcome of children exposed to maternal lithium use during intrauterine life to gain more knowledge about the safety of lithium use during pregnancy. Lithium is the main treatment for women with a bipolar disorder; discontinuation of lithium during pregnancy increases the risk of relapse postpartum. Follow-up was collected prospectively with assessment of growth, neurological examination, cognitive and behavioral assessments.

In **Chapter 3,** we evaluated the efficacy and safety of antenatal treatment of fetal and neonatal allo-immune thrombocytopenia (FNAIT) with weekly maternal IVIG and postnatal matched platelet transfusions (if necessary). Important outcomes were the occurrence of intracranial hemorrhage (ICH), petechiae, hematomas and severe neonatal thrombocytopenia. The postnatal course of neonatal platelet counts was

followed and graphically analyzed.
Chapter 4 investigates the efficacy of repeated courses of ibuprofen for closure of a patent ductus arteriosus (PDA). Ibuprofen is the first treatment of choice for PDA in preterm infants; in most centers failure of a second course is followed by surgical closure. Recent studies suggest that surgical intervention is associated with adverse outcome. The closure rate and safety of a second and third course of ibuprofen in preterm infants was retrospectively evaluated, in order to postpone surgical closure. Risk factors for failure of PDA closure and its clinical consequences were also studied.

Chapter 5 evaluates the combination therapy with rifampin and vancomycin in persistent Coagulase Negative Staphylococcal (CNS) sepsis in neonates. Infection parameters, such as C-reactive protein (CRP) levels before and after start of rifampin therapy, and peak and trough serum levels of vancomycin before the start of rifampin therapy were analyzed for efficacy of this treatment regimen.

In **Chapter 6** we analyzed the outcome of infants of mothers with idiopathic thrombocytopenic purpura (ITP) during pregnancy by scoring the occurrence of intracranial hemorrhage (ICH) and graphical analysis of the postnatal course of neonatal platelet counts. Effectiveness and safety of various postnatal treatment strategies, such as platelet transfusions, IVIG and/or prednisone were evaluated.

Chapter 7 describes a retrospective follow-up study to determine the long term effects of insulin treatment for hyperglycemia on growth and neurodevelopmental outcome of preterm infants. Outcome at two years of age of preterm infants with hyperglycemia and controls, matched for gestational age and birth weight, were compared to estimate the efficacy and safety of insulin therapy for hyperglycemia.

Chapter 8 – In the general discussion the main results of this thesis will be discussed from a broader perspective, focusing on future perspectives. The discussion will end with a short main conclusion, reflecting on the points emphasized in the general introduction.

Chapter 9 – Summary of this thesis.

References

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