Drug exposure from conception till adulthood
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BACKGROUND

The period from conception till adulthood is characterised by specific developmental processes that are of influence on the way how drugs are handled. Both prenatal and postnatal drug exposure may result in a broad range of expected and unexpected effects, and there are many pathways through which exposure may occur in this period. In view of these specific pharmacotherapeutic aspects during development, the aim of this thesis was to describe drug exposure from conception till adulthood and to identify problem areas related to drug exposure in this period.

PART I - METHODOLOGICAL ASPECTS

Previous studies have demonstrated that dispensing data from Dutch pharmacies offer an accurate survey of the use of prescription drugs, and in many chapters of this thesis pharmacy dispensing data is therefore used as an approximation for drug use.

An important problem in the assessment of drug use by future fathers and future mothers using pharmacy data is, however, that neither pregnancy, nor child-parent relations are routinely documented in pharmacies. In Chapter 1, therefore, we thought out a method for retrospectively identifying parents in pharmacy data, just prior to and during pregnancy, and established the validity of this method. We applied it to the records of all 4 pharmacies in 1 town, and determined the yield by comparison of the number of identified parents with the total number of parents in the town (based on figures from Statistics Netherlands), and determined the correctness based on several validation criterions evaluated by pharmacy employees and general practitioners. The results of this validation showed that retrospective identification of parents in pharmacy data is feasible in a valid way, but that the main limitation is that not all parents can be found, possibly resulting in selection bias.

Another methodological problem related to the use of pharmacy dispensing data is that the population that is covered by pharmacies is often difficult to determine. In Chapter 2 we evaluated two methods using drug utilisation information to estimate the population size: a drug-use-based extrapolation of a known part of the population, and a capture-recapture estimation without any prior knowledge of the population. Using pharmacy dispensing data of three towns with known populations in the Netherlands, we estimated age-and-sex specific population sizes by extrapolating the
Summary

Specific drugs are always recommended as a basis for the specific problem identified; from several general rective measures, we often think in terms of drug use for the prevention of specific diseases. In addition, we applied two-source and three-source capture-recapture models with all combinations of the following drug groups as different sources: anti-asthmatics, analgesics, antibiotics and anti-histamines. Our findings suggested that if a part of the population is known, and if there is reason to assume that drug utilisation patterns do not vary within the region, it is best to use drug-use-based extrapolation. In all other situations capture-recapture may be considered, with as main limitation that we found all models to underestimate the population considerably.

PART II - GENERAL DRUG UTILISATION STUDIES FROM CONCEPTION TILL ADULTHOOD

In the second part of the thesis several aspects of drug use of future fathers, drug use of pregnant women, drug use during birth, drug use of lactating women and drug use of children were investigated.

Despite the increasing attention for the role of paternal exposures around the period of conception, there is no factual information about drug utilization of fathers. In Chapter 3, therefore, we described the drugs dispensed to fathers around conception, using pharmacy dispensing data of community pharmacies in Denmark and the Netherlands. We found that one third of all fathers had taken up prescriptions for at least one drug in the half year before conception, both in Denmark and in the Netherlands. In the majority of fathers only one type of drug was dispensed, but in both countries at least 57% of all fathers had redeemed three or more types of drugs. The main drugs purchased by fathers in Denmark and the Netherlands were antibiotics (14.3% and 6.3% of all fathers, respectively), analgesics (6.1% and 7.6%), antihistamines (2.0% and 2.0%) and anti-ulcer drugs (1.6% and 2.5%). We concluded that a large proportion of fathers used drugs in the preconception period, and that this emphasises the importance of safety information on therapeutic drugs with respect to potential paternal teratogenicity.

In Chapter 4 drug use during pregnancy was examined. The interpretation of the available studies of drug use in pregnancy is often hampered because it is not clear to what extent women have changed their drug choice. Based on pharmacy data we described drug use in pregnancy, and compared drug use of pregnant women and comparable non-pregnant women, both with reference to the Australian risk classification system. Overall, 35% of all prescriptions for non-pregnant women were classified as safe for use in pregnancy (Australian classification A), 14% were classified as drugs with an unknown risk (B1,B2), 49% were potentially harmful drugs (B3,C,D,X), and
for 3% the drug was not included in the classification. For pregnant women these figures were 86, 3, 10 and 2% respectively. In non-pregnant women drug groups with the highest percentages of prescriptions for unsafe drugs were psycholeptics (99% of the prescriptions not classified as safe), psychoanaleptics (100%), anti-inflammatory and antirheumatic products (100%), systemic antihistamines (94%), drugs for acid related disorders (81%), antiepileptics (100%), beta blocking agents (100%), systemic antimycotics (100%), antiprotozoals (97%), diuretics (100%) and immunosuppressive agents (100%). In pregnant women this pattern was comparable, except for systemic antihistamines (22%) and drugs for acid related disorders (3%). We concluded that many drugs used by non-pregnant women should be avoided in pregnancy, and that pregnant women indeed do so. Our findings suggested, however, that for a number of drug groups the available safe alternatives are limited.

Drug use during childbirth was examined in Chapter 5. Using a prospective registration by community midwives of medication use during births outside the hospital, we found that medication was used in 58.4% of the deliveries outside the hospital, with an average of 1.4 drug per delivery. The drugs used mostly were oxytocine (35.6% of all deliveries) and local anesthetics (32.9%). When medication was used, it was administered before cutting the umbilical cord in 16.7% of the cases. Prophylactic or routine administration, local anesthesia, postpartum hemorrhages and retained placenta were the most frequent indications for using medication. We concluded that the use of medication during childbirth outside the hospital in the Netherlands was low and children were minimally exposed to medication.

In Chapter 6 we surveyed drug use by breastfeeding women, and compared this with non-breastfeeding women. In addition, we examined whether drug use was of influence on the decision to give breastfeeding, and the other way around. During a 6-week period a questionnaire was handed out to all women with a child not older than 6 months, who visited a Well-Baby Clinic. More than half (65.9%) of all breastfeeding women had used drugs, however they used drugs less frequently than non-breastfeeding women (79.6%). Also the pattern of drug use differed: oral contraceptives, iron preparations, drugs for peptic ulcer, and several psychotropic drugs were more frequently used by non-breastfeeding women, while vitamins were more frequently used by breastfeeding women. Our findings further indicated that drugs play an important role in breastfeeding: women frequently hesitated to use drugs during breastfeeding, stopped either breastfeeding or drug use to avoid combining the two, took a measure to minimize exposure to the child, did not use any drug because of breastfeeding, or did not breastfeed because
of drug use. We concluded that drugs are frequently though reluctantly used during breastfeeding, and that drugs play an important role in the decision to start and stop breastfeeding. This emphasises that information how to deal with drugs is indispensable in efforts to promote breastfeeding.

In the last chapter of this part, Chapter 7, drug use of children was assessed using pharmacy data. We found that drug use was the highest among infants, decreased till adolescence and increased from there. Overall, approximately 60% of all children used at least one drug in 1998. At younger age, boys used more drugs than girls and at older age girls used more drugs than boys. Systemic antibiotics were used by 21% of the children and were by far the most widely used drugs. Other frequently used drugs were analgesics (10%), corticosteroids for dermatologic use (9%), antihistamines (8%) and anti-asthmatics (7%). Approximately 10% of the children had used at least one drug at the age of 1 month and at the age of 2 years this proportion was 81%. We concluded that the majority of children was exposed to one or more drugs, and that this exposure started at very young age.

PART III - DRUG USE AFTER BIRTH IN MORE DETAIL

Several aspects of drug use after birth were examined in more detail in the third part of this dissertation.

In Chapter 8 we investigated the use of psychotropic medication in children in the Netherlands using pharmacy dispensing data, and compared this with earlier reported figures from the United States of America (U.S.A.). We found that stimulants were used to the greatest extent by 0-19-year-olds (prevalence 7.4/1000 in 1999), followed by hypnotics/anxiolytics (6.9/1000) and antidepressants (4.4/1000). Prevalence rates of stimulants increased from 1.5/1000 in 1995 to 7.4/1000 in 1999. Incidence rates, proportion of girls, and duration of stimulant treatment increased too. Changes in prevalence rates of other psychotropics were much smaller than those of stimulants. Finally, the vast majority of children treated with psychotropic agents used only one psychotropic. It was concluded that prevalence of stimulant use in the Netherlands is much lower than earlier reported from the U.S.A. (28/1000 children in 1995) and differences also existed with regard to the use of other psychotropics and combinations of psychotropics. However, the increase in Dutch stimulant use agrees with the earlier reported 2.5-fold increase in the U.S.A., and shows that the increased use of stimulants is not limited to the United States of America.
Chapter 9 focussed on anti-asthma medication, and described the choice of drugs as well as the dosage forms of anti-asthmatic drugs in children with regard to different age groups, based on pharmacy dispensing data. Inhaled beta2-agonists and inhaled corticosteroids were the most widely used anti-asthmatic drugs in all age groups (respectively 59 and 58 users per 100 anti-asthmatic using 0-16 year-olds). Cromones were rarely used. Up to four years of age the use of treatment with aerosol inhalers increased simultaneously with a decrease of oral dosage forms. The use of dry powder inhalers started at the age of approximately 4 years old and increased to about 85% of the users at the age of 11, with the strongest increase around the age of 6 and 7. We concluded that the choice of drugs and dosage forms corresponds with what might be expected based on guidelines for the treatment of asthma in children, except for the high use of desmopine in the youngest age group. Anti-asthmatic drugs for preventive treatment are used so frequently without beta2-agonists that questions about possible overtreatment need to be raised.

The aims of Chapter 10 were, firstly, to determine the amount of unlicensed prescriptions for children in the community, and secondly, for all drugs with a product license, to investigate paediatric labelling in detail to determine the extent of off-label drug use. Using pharmacy dispensing data we found that many licensed drugs that were used by children were poorly labelled for use in children: in 20.6% of the cases, use in children was not even mentioned in the product license, and in 19.6% children were mentioned without any indication of age. Unlicensed (16.6% of all prescriptions) and off-label (22.7%) drug use was frequent among children in the community. We concluded that many licensed drugs that children use outside the hospital are poorly labelled with respect to use in children, resulting in high percentages of off-label drug use.

Risk factors of unlicensed and off-label drug use by children outside the hospital were examined in Chapter 11. We used pharmacy dispensing data, and performed a logistic regression was done that models the odds of receiving an unlicensed or off-label prescription as a function of several possible risk factors. We found that unlicensed drug use in Dutch children is the highest among 0-1-year-olds, and off-label drug use is the highest among 12-16-year-olds. Drug groups with highest percentages of unlicensed and off-label drug use were ophthalmologics/otologicals (80.7% of all prescriptions in this group), blood and blood forming organs (mainly vitamin K for breastfed newborns) (75.7%), cardiovascular drugs (74.7%) and dermatologicals (73.3%). Prescriptions by specialists (outpatient), prescriptions for new drugs, prescriptions for drugs with a low use in the pediatric population, and
prescriptions for infants were risk factors for using a systemic drug unlicensed or off-label.

Appropriate dosage forms are essential in paediatric pharmacotherapy. In Chapter 12 therefore, we surveyed the use of different dosage forms by children in the community, and examined the reported lack of liquid dosage forms and dosage forms of the appropriate strength, both in relation to the licensing status (authorised, off-label or unlicensed) of the drugs. We found that in all age groups, approximately half of all prescriptions were for systemic drugs. The only major age-related changes were within systemic drugs with younger children more likely to be prescribed oral solutions. For authorised drugs the proportion of tablet/capsules exceeded oral solutions at the age of 7 years, whereas for off-label drugs this occurred at 3 years of age. Prescriptions with a dosage form that was classified as too strong were almost exclusively found in the group of unlicensed/off-label prescriptions, especially for children under the age of 4 years. We concluded that the lack of licensing results in a lack of liquid dosage forms and dosage forms with the appropriate strength. In addition to the unknown safety and efficacy aspects of unlicensed and off-label drugs, these findings emphasise the importance of labelling for children.

Finally, Chapter 13 looked at adverse drug reactions (ADRs). The interpretation of the available studies on ADRs in children outside the hospital is hampered because none of these studies used a control group. The aim of this study was to describe ADRs in children outside the hospital, controlled for drug use in the pediatric background population. Using a case-control design, we compared drugs on which a suspected ADR was reported to the Netherlands Pharmacovigilance Centre LAREB, and drugs used in the general paediatric population from the InterAction pharmacy database. The main findings were that ADRs were disproportionately more often reported on systemic drugs (OR 3.0; [CI95% 1.9-4.8]), new drugs (2.4; [1.6-2.7]), anti-infective drugs (1.7; [1.1-2.7]) and nervous system drugs (2.1; [1.3-3.5]), whereas unlicensed drugs (0.1; [0.0-0.4]), frequently used drugs (0.3; [0.2-0.5]), and dermatologicals (0.1; [0.0-0.4]) were less likely to be associated with a reported ADR. Overall, the proportion of off-label prescriptions did not differ between drugs suspected of an ADR and drugs used by children in a general population. We concluded that the pattern of drugs associated with a reported ADR could not be solely explained on basis of drug utilisation patterns in the general population.
FINAL REMARKS

Studies that characterise exposure are needed to identify and understand all potential problems with drug use, and to set targets for intervention strategies. This thesis has shown that throughout the entire period from conception till adulthood drug exposure is considerable. Shortcomings in both knowledge and the dissemination of knowledge make that pharmacotherapy in this period is characterised by limitations, either by a limited number drugs with sufficient safety information to choose from, or by use of drugs with limited safety information. To increase our knowledge, more efforts should be made to register and evaluate actual drug exposures and their outcomes. The results of this thesis will hopefully increase the awareness of the problems associated with drug exposure between conception and adulthood, so that adequate actions will be taken.