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Information for paediatric use of medicines in a product information compendium

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Abstract

Objectives: *Many of the medicines that are prescribed to children are not licensed for use in children. We wanted to know the proportion of medicines that are licensed for use in children. We therefore assessed the paediatric licensing status of medicines in the* Repertorium 98/99, *the standard drug information compendium in the Netherlands.*

Methods: *The medicines mentioned in the* Repertorium 98/99 *were assessed for their licensing status and categorised into five mutually exclusive groups: 'registered for use in all children', 'registered for use in some child age/weight groups', 'no paediatric use mentioned', 'not registered for use in children' and 'no paediatric registration necessary'.*

Results: *1380 registration texts were identified of which 223 are not used for the treatment of childhood diseases. Of the remaining 1157, only 339 (29%) were registered for use in children of all ages.*

Conclusion: *Many drugs were not registered for use in children, often because of a lack of pharmacokinetic/pharmacodynamic data. We strongly recommend a mandatory 'paediatric use' subsection in all product information texts.*

Key words: Drug labelling – Unlicensed – Off-label – Children – Reference source – Medicines

Introduction

In co-operation with four other European groups, we have previously demonstrated a high prevalence of unlicensed and off-label drug use in children[1]. Many medicines used are not, or are insufficiently, registered for use in children or are not used according to the product license ("off-label use")[2]. Lack of financial support for paediatric drug research by pharmaceutical companies as well as governments, and lack of development of proper dosage forms for infants and neonates result in a high prevalence of unlicensed and off-label drug use.

Nearly 80% of the new molecular entities approved during 1984–1989 in the USA had no labelling for use in children[3]. Only 19% of the new molecular entities contained paediatric use information in the labelling at the time of drug approval during 1991–1995[4]. Impicciatore and Choonara showed that of the 45 new substances licensed in Europe since January 1995, 29 (64%) were of potential use in children but only 10 were licensed for paediatric use[5]. We have conducted a study to assess the percentage of medicines that had a proper licensing text for use in children in the *Repertorium 98/99*[6], the standard drug information compendium in the Netherlands.

Methods

The *Repertorium 98/99* was selected as it is the only drug information compendium in the Netherlands that gives a survey of the official scientific information texts of pharmaceutical proprietary medications approved by the Dutch Medicines Evaluation Board (MEB), the national labelling authority, or the European Medicines Evaluation Agency (EMEA), the European labelling authority that provides marketing authorisation for most new pharmaceutical products since 1995. The *Repertorium 98/99* is published by Nefarma and Neprofarm, which are the Dutch Society of Research-orientated Pharmaceutical Industry and the Dutch Society of the Pharmaceutical industry of Self-care medication and Health products, respectively. Together they represent most pharmaceutical companies in the Netherlands, and therefore the *Repertorium 98/99* contains the scientific information text of almost all of the proprietary medications licensed in the Netherlands.

The subsections 'indications', 'dosage and route of administration', 'contra-indications', and 'warnings and precautions' of all information texts of the proprietary medications mentioned in the *Repertorium 98/99* were analysed regarding use in children. None of the products had a special subsection for 'paediatric use'.

Five mutually exclusive categories were defined regarding use in children, i.e. 'registered for use in all children', 'registered for use in some child age/weight groups', 'no paediatric use mentioned', 'not registered for use in children' and 'no paediatric registration necessary', respectively.

Firstly, the indications for use of the drug were analysed regarding the probability of use in children. If highly unlikely, the product was categorised 'no paediatric registration necessary'. An example of this category is FemoStop® (estradiol/dydrogesterone) for postmenopausal women. Secondly, all subsections were analysed on disclaimers against use in children. If the product information contained a disclaimer against use in children or stated that too few paediatric data were available, it was called 'not registered for use in children'. If no paediatric use information was mentioned in any of the

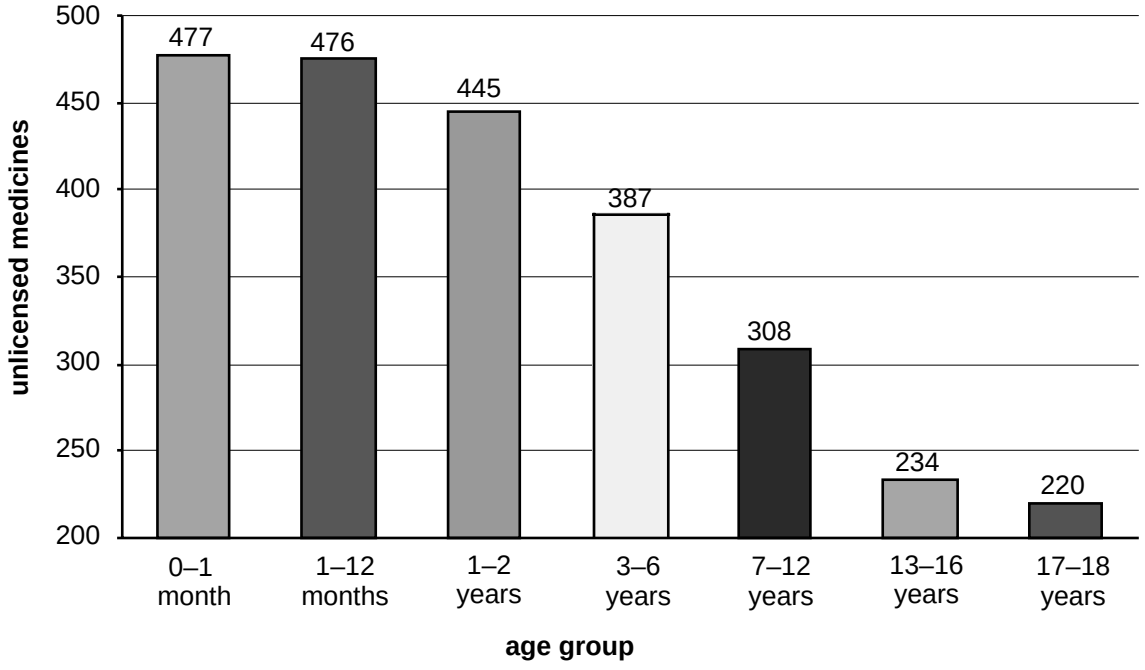

Figure 1. Number of medicines not licensed for use in each age category.

Table 1. Drug registration status of use in children in the Dutch product information compendium

Category	Number	% of drugs with potential use in children
Registered for use in all children	339	29.3
Registered for use in some child age/weight groups	257	22.2
No paediatric use mentioned	341	29.5
Not registered for use in children	220	19.0
Total of drugs with potential use in children	1157	100
No paediatric registration necessary	223	
Total number of drugs in the *Repertorium 98/99*	1380	

subsections of the information text, the product was categorised 'no paediatric use mentioned'. If there was a restriction on age or weight, the product was called 'registered for use in some child age/weight groups' and the restriction was mentioned in the research form used for the study. If a drug was licensed for all paediatric age/weight groups the product was called 'registered for use in all children'.

Not all restrictions on age were numerical, sometimes terms like neonates, toddlers, infants and children were used instead. We used the following definitions; 'newborn' (0 – 1 month), 'infant' (1 month up to 12 months), 'toddler' (1 year up to 2 years), 'small child' (3 years up to 6 years), 'child' (7 years up to 12 years) and 'adolescent' (13 years up to 18 years).

Results

The *Repertorium 98/99* contains 1606 registration texts. Some of them, however, were variants in dosage or dosage form of the same products. To obtain a conservative estimate of the percentage of unlicensed and off-label drug use, only the most child-friendly registration text of a drug with the same Anatomical Therapeutic Chemical (ATC) classification[7] was maintained, the others were removed from the analysis. A total of 1380 registration texts were analysed. Of all medicines with a potential use in children (n=1157), only 339 (29%) were 'registered for use in all children'. Of the remaining 71%, 257 (22%) were 'registered for use in some child age/weight groups', 341 (29.5%) gave no information at all on paediatric use whereas in 220 (19%) registration texts contained too little information or a disclaimer against use in children (Table 1).

The medicines that were registered for use in some child age/weight groups were subdivided into age categories as described in the methods section. Figure 1 shows the number of medicines not licensed for the children in the separate age categories.

Discussion

Approximately 71% of the medicines in the *Repertorium 98/99* with a potential use in children are not fully registered as such. The lack of scientific research on the pharmacokinetics and pharmacodynamics of many of these medicines in children may lead to trial and error based use which endangers safety and efficacy. Many of the modern generation medicines, like ACE-inhibitors, have not been studied in children although they are relevant for therapy.

With these data no strong conclusion can be made on the exact number of medicines that need further investigation. Moreover, the Repertorium contains the names of products registered by members of Nefarma and Neprofarm. It is unlikely, however, that our results cannot be extrapolated to all products registered in the Netherlands. The categories 'registered for use in some child age/weight groups' and 'not registered for use in children' include medicines of two different classes. There are medicines that are preferably not used in particular child age/weight groups, e.g. because of organ immaturity, which have been studied well, but were considered as unsafe in the age/weight categories for which the registration text contains a disclaimer. On the other hand, there are medicines that lack pharmacokinetic and pharmacodynamic data and need further investigation. Sometimes the registration text is very explicit, but often the formulation of the disclaimer is very vague, and no conclusion on this subject can be drawn. Therefore we made no distinction between information texts that contained too little information about the use in children and information texts that contained a disclaimer against use in children.

The high prevalence of medicines that had 'no paediatric use mentioned' in the information text (30%) pleads for the introduction of a 'paediatric use' subsection in the information text. In the USA, the Food and Drug Administration (FDA) introduced this 'paediatric use' subsection in 1979. In Europe, the European Medicines Evaluation Agency and national drug registration agencies still allow pharmaceutical companies to register their products without any information regarding use in children included in the information text, as can be concluded from our results. Such a subsection is important as paediatric use information is often difficult to find. Changes to the format and content of the product information texts, as proposed by the FDA's new proposed rule[8], would enable health care practitioners to prescribe medicines more safely and effectively. The amount, detail and complexity of the labelling information have increased over the last decades. Technological advances in the products themselves and recognition of the importance of including new or additional labelling information, use of labelling in product liability and medical malpractice lawsuits, and increasing litigation costs are important causes. This has made it harder for health care practitioners to find specific information, and to discern the most critical information in product labelling. Suggestions in this Proposed Rule include a "Highlights of Prescribing Information" subsection and an index for the comprehensive prescribing information. We strongly support the suggestions, and hope the EMEA will seriously consider reviewing European regulations.

Children deserve an equal approach in drug registration and equal quality of information. We regard the current situation regarding the availability of paediatric use information as insufficient.

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