Frequency of paediatric patients administered extemporaneous preparations at a Swedish university hospital: a registry-based study comparing two study-years, 10 years apart

Åsa C Andersson,1,2 Staffan Eksborg,2 Ulrika Förberg,3 Per Nydert,1,4 Synnöve Lindemalm1,4

ABSTRACT
Background Lack of child-friendly dosage forms and strengths often leads to manipulation of medicines at hospital units or by caregivers in the home setting. One alternative to manipulating dosage forms is the use of extemporaneous preparations. In Sweden, these are produced according to good manufacturing practice by a few extemporaneous pharmacies.

Objectives To compare frequencies of patients administered extemporaneous preparations in two separate years, 10 years apart.

Methods This registry-based study describes and compares the frequency of extemporaneous oral preparations administered to paediatric patients in 2009 and 2019 at a Swedish university hospital.

The study included 117 023 oral administrations (to 4905 patients) and 128 638 oral administrations (to 4718 patients) from 2009 and 2019, respectively.

Results The frequency of inpatients administered one or more extemporaneous preparations increased from 22% in 2009 to 40% in 2019 (p<0.0001). The increase was observed in all age groups. The use of some active pharmaceutical ingredients increased (eg, captopril, clonidine, hydrocortisone, melatonin and propranolol), and some active pharmaceutical ingredients decreased between the study years (eg, midazolam and sildenafil).

Conclusions The introduction of new authorised products has decreased the need for manipulation or extemporaneous preparations in some therapeutic groups. There remains, however, a pronounced lack of commercially available child-friendly dosage forms and suitable strengths enabling safe administration of medicines to children, indicated by the large percentage of patients receiving at least one extemporaneous preparation.

EXTEMPORE PREPARATIONS

Extemporaneous preparations made by pharmacies are important and safer alternatives to manipulation of solid dosage forms made by registered nurses or caregivers.1-3 Extemporaneous preparations can be made either from raw material adding excipients (compounding close to the process of manufacturing) or made from authorised medicines (compounding closer to the process of reconstitution or manipulation). Starting from an authorised medicine the compounding can be either authorised or not authorised according to data in the summary of product characteristics.4 Extemporaneous preparations are not only common in the paediatric setting but also frequently used in dermatology5 and for orphan diseases.6,7

In Sweden, oral and rectal extemporaneous preparations are prepared according to good manufacturing practice (GMP) by a few extemporaneous pharmacies; for example, APL (Aptek Produktion & Laboratorier) and Unimedic AB.8,9 In the present study, products prepared by these pharmacies are defined as extemporaneous preparations.

The ability to order capsules or oral liquids with age-appropriate strengths is an important advantage of extemporaneous preparations. These preparations are safer than manipulation when there is no child-friendly strength commercially available. Important disadvantages compared with authorised drugs are a prolonged time to delivery, a short shelf life and concerns regarding the chemical and microbiological stability,10-12 as well as lack of pharmacokinetic data.13

Extemporaneous preparations are often included in the terms off-label or unlicensed use of medicines to children.8,9 Therefore, reliable data are important to understand the extent to which extemporaneous preparations are used in the paediatric setting.

INTRODUCTION

Children of all ages should have access to safe and appropriate medicines. The lack of child-friendly dosage forms and strengths suitable for children of different ages, body weights and with different capabilities of taking medicines is a major problem. The use of extemporaneous preparations and manipulation of dosage forms are common alternatives when commercially child-friendly dosage forms and strengths are not available.1

The frequencies of patients administered manipulated medicines in a Swedish university paediatric hospital 2009 and 2019 has been described earlier.1

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The use of extemporaneous preparations in paediatric settings is frequent.
WHAT THIS STUDY ADDS
⇒ The frequency of inpatients administered at least one oral extemporaneous preparation increased significantly between 2009 and 2019.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Despite different paediatric regulations, there is still a lack of dosage forms and strengths suitable for paediatric use.
There are few studies on frequency of extemporaneous preparations in the paediatric setting despite numerous studies regarding off-label use. A Swedish study using data from 2008 found that extemporaneous preparations on average represented 10% of all inpatient prescriptions (22% for neonates and 4.5% for adolescents). The categorisation as extemporaneous preparations were based on the name of the product, the strength of the preparation compared with commercially available strengths and on clinical experience of the drugs used locally at the hospital. The preparations were also classified as solid or liquid dosage forms. Manipulated medicines—for example, parts of a tablet with a higher strength—were not categorised as extemporaneous preparations.

Aim
The aim of this study was to describe and compare the frequency of patients administered at least one extemporaneous preparation, as well as frequencies of different active pharmaceutical ingredients administered as extemporaneous preparations, in 2009 and 2019.

Ethics approval
The study was approved by the Ethical Review Agency in Uppsala (Dnr: 2019-02811).

METHODS
Setting
This study is based on data from the electronic health record (EHR) at one of the largest Swedish paediatric university hospitals, Astrid Lindgren Children’s Hospital, during two separate years, 2009 and 2019. The paediatric hospital offers care to approximately 25% of all Swedish children and generally admits patients from birth up to <18 years old. Different specialties including oncology, surgery, neonatology, orthopaedic, intensive and acute care are available at the hospital, and were available during both study years. The hospital has 250 beds and around 2000 employees.

Data collection
This is a retrospective registry study, based on data from the hospital-based electronic data registry from the EHR, TakeCare (KarDa). The drug chart in this EHR was introduced at the paediatric hospital in late 2008. The first year with complete data, 2009, was chosen as the first study year. Data was also collected for 2019 as a comparison. All patients aged from 1 month to <18 years, with a registration of a medicine administered orally or rectally at the hospital, were included.

Patients in the paediatric and neonatal intensive care units were not included, as they changed EHR during the study period.

In both study years, a few patients (n=111 (0.7%) in 2009; n=93 (0.4%) in 2019) had no documentation of sex, and were excluded. In 2019, data regarding age was lacking for some patients (n=290 (1.2%)), but since they had given data on body weight, they were assigned an age based on the growth chart. All patients had an encrypted ID, making it possible to link all administrations for a given patient.

Age groups above 1 month, proposed by the European Medicines Agency (EMA) were used. To better reflect differences in the developmental changes in different ages the age groups infants and toddlers (1 month to 2 years) and children (2 to 11 years) were further divided into two groups, respectively.

All data was thoroughly scrutinised by the first author for coding mistakes and omissions. Some ATC codes (Anatomical Therapeutic Chemical Classification System) were changed to represent the main indication in paediatrics; for example, sildenafil was classified as C02 (antihypertensives for pulmonary hypertension), clonidine as N02 (analgesics), naloxone given orally as A06 (drugs for constipation) and concentrated electrolytes given orally as A12 (mineral supplements).

RESULTS
The frequency of patients administered at least one extemporaneous preparation varied depending on study year, setting and route of administration, table 1.

The number of extemporaneous administrations increased from 22405 (of 117023 administrations) in 2009 to 26124 (of 128638 administrations) in 2019 (p<0.0001). The number of inpatients administered one or more oral extemporaneous preparations increased from 1072 (of 4905 patients) in 2009 to 1882 (of 4718 patients) in 2019 (p<0.0001). There were no major differences based on patient sex (p=0.477 and p=0.828, for 2009 and 2019, respectively). The increase was observed in all age groups, figure 1.

Oral extemporaneous preparations contained 52 different active pharmaceutical ingredients (APIs) 2009 and 46 different APIs 2019. Most administrations of extemporaneous oral preparations to inpatients (91% of 22405 extemporaneous administrations and 89% of 26124 extemporaneous administrations, in 2019 and 2019 respectively) are from merely 12 APIs, table 2, online supplemental material.

The results in table 2 are presented based on the descending number of total oral administrations to inpatients in 2009. The ranking order between the study years differs for several APIs, but clonidine and naloxone were the two APIs most frequently administered as oral extemporaneous preparations, in both years.

In the emergency department there were almost no oral extemporaneous administrations 2009, and in 2019 the majority were clonidine (96%). Not many rectal extemporaneous preparations are manufactured, and hence, only a small proportion of rectal administrations are extemporaneous preparations. For inpatients, midazolam (35%) and pentobarbital (36%) were most frequently prescribed 2009, and in 2019, 82% of the rectal extemporaneous administrations were paracetamol. The few rectal administrations in the emergency department in 2009 were all midazolam.

Most extemporaneous administrations were from liquid solutions, with an increase from 86% in 2009 to 93% in 2019 (p<0.0001), respectively. Solid preparations were mainly capsules, mostly prescribed to the youngest age groups (1 month to <1 year and 1 to <2 years) in 2009, and to the youngest and...
oldest age groups (1 month to <1 year and 12 to <18 years) in 2019, figure 2. The most frequently administered API as an extemporaneous capsule was sildenafil (41% of all capsules) in 2019 and hydrocortisone (32% of all capsules) in 2009.

DISCUSSION

The lack of medicines appropriate for paediatric use forces caregivers and healthcare staff to find alternatives. The hierarchy of medicines and dosage forms suitable for paediatric patients might differ between different countries owing to national settings. In Sweden, the following hierarchy is used by tradition in the paediatric setting:

1. Age-appropriate, ready-to-administer dosage forms approved and available.
2. Child-friendly dosage forms that require authorised reconstitution before administration.

3. License to use a medicine approved in another country (i.e., unlicensed in Sweden).
4. Extemporaneous preparations compounded according to GMP.
5. Unauthorised manipulation being done by registered nurses or caregivers.

This hierarchy share a lot of similarities to guidelines from WHO/FIP (International Pharmaceutical Federation) on points to consider when specific preparations are not available as authorised products.19 Information regarding unlicensed medicines and extemporaneous preparations is not easily accessible for physicians, and it is also problematic to prescribe these products in the EHR if no prefilled drug order sets are available.

Extemporaneous preparations

The frequency of patients administered extemporaneous preparations increased significantly between the study years 2009 and 2019. The increase in extemporaneous administrations from 19% to 20% of all administrations, however, seems to be of limited clinical importance despite being statistically significant. The frequencies of extemporaneous administrations in the present study are higher compared with findings previously reported.15 The probable explanation for this is the different settings. Our study has data from one large university hospital, the other study had data from hospitals in all Sweden. A widespread need for pharmacy compounded products in the paediatric setting was also seen in Dutch hospitals.20

Some of the differences in APIs in extemporaneous preparations between the study years have a clear link to available authorised products. Sildenafil (cardiovascular system in this study)
Captopril was highly prescribed as extemporaneous capsules in 2009, but not in 2019, owing to the introduction of an authorised powder for oral suspension (Revatio) with the label pulmonary hypertension. The decrease of all oral administrations of sildenafil, as well as midazolam and phenobarbital, during the study years reflects a shift in practice rather than in available products.

Oral administrations of hydrocortisone increased more than the extemporaneous preparations between the study years. This increase is partly due to the use of Alkindi, hydrocortisone granules in child-friendly strengths in capsules intended to be opened, introduced to the Swedish market between the study years. There remains, however, a lack of extemporaneously compounded hydrocortisone, since Alkindi granules are not authorised for administration via enteral feeding tubes.

Propranolol, captopril, calcium, hydrocortisone, and phosphate are also APIs where total administrations have increased between the study years. This increase might be owing to a change in practice. Four out of the most used 12 APIs are cardiovascular drugs. Captopril, propranolol and spironolactone, in addition to silde-nafil, are APIs, where most of the prescriptions are made from extemporaneous preparations. In a European survey from 2003, both captopril and spironolactone were frequently made as extemporaneous preparations, even though authorised preparations were available in countries outside the responding country.\(^1\) In Sweden, captopril is available in child-friendly dosage forms merely as unlicensed or extemporaneous preparations. Propranolol is licensed in Sweden as an oral solution (Hemangiol) with the indication hemangioma. The oral syringe included in the package is graded in mg, and since the EHR will produce prescriptions in mL, this is not optimal. To administer spironolactone to young children in Sweden, manipulations of adult dosage forms need to be carried out,\(^2\) or it has to be prescribed as an extemporaneous preparation, despite being listed in the WHO Model List of Essential Medicines for Children.\(^21\)

Melatonin was hardly prescribed in 2009. During the period from 2019 there has been an increase in the use of melatonin and other sleeping remedies among children in Sweden.\(^22\) In 2019, the available child-friendly products were either extemporaneous preparations or unlicensed medicines. Since 2021, authorised products (tablets and oral solutions) have appeared on the market, and consequently, the extemporaneous preparations of melatonin can no longer be prescribed.

Naloxone (alimentary tract in this study) was exclusively prescribed as an extemporaneous preparation in both 2009 and 2019. Naloxone is administered orally to diminish opioid-related constipation. In 2019, there were some brands of tablets authorised on the Swedish market, but these tablets are fixed combinations with different opioids in strengths not suitable for the paediatric population. Clonidine is another substance frequently administered as an analgesic. Clonidine is mostly prescribed from extemporaneous preparations and as parts of tablets, an unlicensed product in Sweden. Thus, there is still a lack of child-friendly dosage forms and strengths of these substances, frequently used in the paediatric setting.

As presented in \textbf{Table 2}, single patients with frequent administrations and long hospital stay can influence the results.

\begin{table}[h!]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
ATC & API & All oral administrations, n & Dosage form extemporaneous & \% extemporaneous* \\
\hline
N02 & Clonidine & 9848 & 12287 & Liquid & 84 & 90 \\
A06 & Naloxone & 4852 & 5102 & Liquid & 100 & 100 \\
N05 & Midazolam & 2247 & 760 & Liquid & 95 & 90 \\
N03 & Phenobarbital & 1909 & 935 & Liquid & 84 & 64 \\
C03 & Spironolactone & 1719 & 1073 & Liquid/Solid & 51 & 57 \\
C02 & Sildenafil & 1645 & 483 & Solid & 80 & 0 \\
C07 & Propranolol & 712 & 1381 & Liquid & 87 & 77 \\
C09 & Captopril & 492 & 910 & Liquid/Solid & 80 & 98 \\
A12 & Calcium/Calcium lactate & 239 & 862 & Liquid/Solid & 100 & 100 \\
H02 & Hydrocortisone & 165 & 1019 & Solid & 8 & 56 \\
A12 & Minerals (eg, phosphate) & 158 & 986 & Liquid/Solid & 100 & 100 \\
N05 & Melatonin & 13 & 994 & Liquid/Solid & 0 & 86 \\
\hline
\end{tabular}
\caption{Most frequently administered oral extemporaneous preparations to inpatients (short summary table, please see online supplemental material for further information)}
\end{table}

The shift from manipulation at the inpatient unit to the use of extemporaneous preparations is regarded as a shift from a sometimes hazardous and time-consuming way of working to a safer, more convenient way of administration of medicines to paediatric patients. However, extemporaneous medicines should be available in the correct strength so to eliminate the need for manipulation. Overall, few extemporaneous administrations had to be manipulated. In 2009, 5.7% of all oral extemporaneous administrations for inpatients were solids manipulated to generate the prescribed dose owing to inappropriate strength.
(mostly sildenafil and bosentan capsules). In 2019, only 0.34% were manipulated. The active Paediatric Drug Therapy Group at Astrid Lindgren Children’s Hospital started writing order sets for prescribing medicines in the electronic medical record in 2008, including extemporaneous preparations. The prefilled order sets were successfully introduced and simplified for the prescribers and registered nurses to find these products. The system with prefilled drug order sets has been developed between the study years to also include paediatric drug dose information. Pharmacists were also employed at most paediatric units in 2019, but only to a minor extent in 2009. One of the assignments for these pharmacists is ordering extemporaneous preparations with appropriate strengths.

**Dosage forms**

Most administrations in all age groups were oral liquids, but in contrast to normal practice, this study shows that especially in 2009, the youngest age group (1 month to <1 year) receive the highest percentage of capsules. This finding confirms results from a French study. Extemporaneous capsules are in many cases opened and the content dissolved in some liquid or food to facilitate drug administration, especially to younger children. There is a lack of data regarding pharmacokinetics for most extemporaneous preparations, including differences between administering capsules intact and opening the capsules and dissolving the content. In addition, oral liquids often contain preservatives not suitable for infants, another reason for choosing capsules to the youngest age group, even though the use of capsules in the youngest age group has decreased between the study years.

Sweden is among the countries where most extemporaneous preparations are compounded as oral liquids, while divided powders are mostly used in other countries (eg, Finland and Italy).

**EU Paediatric Legislation**

On 1 January 2007, the EU Paediatric Legislation was implemented. The main aims of the legislation were to obtain more data regarding the use of medicines in children, to improve the information available to prescribers and families and to encourage drug companies to develop more child-friendly dosage forms and strengths of medicines. In the present study, the first study year of 2009 is too close to the implementation of the regulation to make an impact. Our results from 2019, 12 years after the implementation, show that there is still a lack of child-friendly medicines. The 10-year report showed a positive and promising development of new drugs and new pharmaceutical forms, but the incentive for drug companies to perform studies in children on older off-patent drugs seemed to be low. Even though the number of paediatric medicinal products has increased, authorisation of medicines is not always the same as marketing of the medicine, thus affecting the availability in different countries. Even though there are authorised, suitable medicines, extemporaneous preparations are compounded owing to problems with importing medicines from another country, and high costs for several newly developed child-friendly medicines. This problem was described 30 years ago, but is still present today.

In 2003, a survey was performed in Europe which highlighted the need for harmonisation of extemporaneously prepared paediatric formulations and stability data. Since then, a pan-European initiative has been launched under the European Pharmacopoeia, called the European Paediatric Formulary, with the aim to collect suitable drug monographs and make them available online for APIs where paediatric formulations are missing.

**Strengths and weaknesses**

To our knowledge, there is no other study including administrations of extemporaneous preparations to paediatric patients from two full years 10 years apart, at a large university hospital. The study was performed at one Swedish paediatric hospital with an active Paediatric Drug Therapy Group, and there was an increase in the number of ward pharmacists between the study years. The importance of ward pharmacists is pointed out in the present study, but this change in setting can be regarded as a weakness in the study design. The classification of extemporaneous preparations was made based on the name of the product and the strength of the preparation compared with commercially available products. A strength of this study is that this classification was made by one author (ÅCA), a paediatric pharmacist within the Paediatric Drug Therapy Group, with extensive clinical experience of paediatric medicines.

A limitation of the study is that children younger than 1 month old were excluded; it would be interesting to include these children in future studies. Another limitation is that the study design did not reveal lengths of stays or frequency of readmissions, making comparisons between the study years difficult. There is also a risk that the recording of data in the EHR is more robust in a system that has been in place over 10 years, compared with 1 year.

**CONCLUSION**

The frequency of patients with extemporaneous oral preparations has increased in all age groups between 2009 and 2019, but in some therapeutic groups, the introduction of new drugs has decreased the need for manipulation or extemporaneous preparations. There is, however, still a pronounced lack of commercially available child-friendly dosage forms and suitable strengths enabling safe administration of medicines to sick children. Efforts should be made to ensure that paediatric formulations authorised in any country are available in all European countries.

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