Paediatric and Perinatal Drug Therapy, 2004; 6 (2)

National study of extemporaneous preparations in English paediatric hospital pharmacies

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Background: **Licensed formulations are not always suitable for young children. Pharmacy departments at paediatric hospitals produce in-house extemporaneous preparations for children. The Department of Health in England has recently announced a major investment in hospital production units to improve the manufacturing facilities. However, there is no published systematic study to investigate the extemporaneous production activities in paediatric hospitals in England in order to support future planning.**

Objectives: **To identify the methods, frequencies and types of medications prepared extemporaneously in the pharmacies of paediatric hospitals in England and the percentage of above preparations that were available from specials manufacturers.**

Methods: **A national survey of in-house extemporaneous preparations by the seven paediatric hospitals in England was conducted over a period of 12 months. The drug, type of product and frequency of each preparation were recorded, and analysed.**

Results: **All seven hospitals (100%) replied to our survey. On average, 1.5 items per day per hospital were manufactured. The top 20 drugs represented more than 58% of the workload, indicating the repetitive nature of the work. 76% of the final preparations were in liquid dosage forms. Only 27% of medicines extemporaneously prepared were unlicensed chemical entities. However, 50% of the extemporaneous products made could be provided by specials manufacturers.**

Conclusions: **The extent of extemporaneous dispensing in paediatric pharmacies was lower than anticipated. The top 20 commonly used drugs (58% of the workload) could be produced by licensed units or specials manufacturers to reduce the risk of production errors. As the diversity of strengths of the same medicines that are produced in different centres creates opportunities for medication errors, the idea of establishing a national extemporaneous formulary to standardise the strengths and presentations should be explored.**

Paed Perinatal Drug Ther 2004; 6: 75–80

Keywords: Extemporaneous preparations – paediatric hospitals

Introduction

It has been widely acknowledged that licensed formulations are not always suitable for young children. Most licensed oral medicines are intended for adults and are presented as solid single dosage forms or as liquids of an unsuitable concentration for children. Pharmaceutical companies have traditionally been reluctant to invest in developing specific treatments or adapting existing medicines to meet the needs of the paediatric population, mainly because the market is small and therefore of a lower priority[1]. For children who cannot take adult dosage forms[2-4], a number of medicines have to be prepared extemporaneously in-house or by specials manufacturers or alternatively need to be imported. There is a growing awareness of the use of unlicensed medicines in children amongst medical professions[5,6] and lately within the government in England. The 'Standards for Hospital Services' National Service Framework for Children[7] recognises that unlicensed medicines and "off-label" licensed medicines are used routinely in children. It also points to the need to fractionate or dilute the adult dosage forms adding to the potential for error. One of the set standards is to ensure that formulations of medicines are appropriate to the age and ability of the child.

To meet the challenge of providing appropriate formulations for a range of age groups and the requirement for a diverse range of medicines, pharmacy departments at various specialised paediatric hospitals produce in-house extemporaneous preparations. A European study has shown that this is a practice wide-spread within different European hospitals[8] and there are ongoing debates concerning the risk of extemporaneous dispensing. The common thread emerging from these debates is that a reduction in extemporaneous dispensing within hospital pharmacies is required to improve safety. In the UK, manufacturers who hold manufacturer's (specials) licenses issued by the Medicine and Healthcare Products Regulatory Agency (MHRA) are allowed to supply unlicensed medicinal products formulated in accordance with the requirement of a doctor[9]. The licence allows the holder to supply extemporaneously prepared products to other institutions. Therefore a hospital that supplies extemporaneous products within the hospital is not covered or regulated; whereas when it supplies to other hospitals it is. Buying specials products from specials manufacturers (including suitably licensed NHS units) would reduce the risk of production errors because specials manufacturers adhere to quality assurance systems such as batch tracking, record keeping, GMP (Good Manufacturing Practice), adverse reaction reporting, and inspections by the MHRA at regular intervals.

Despite this common consensus of shifting extemporaneous work to specials licensed facilities, dispensaries throughout England still carry out extemporaneous dispensing daily. There has not been a published systematic study to investigate the extent and type of extemporaneous production in the pharmacies of paediatric hospitals in England; therefore we conducted this study to investigate the above aspects. This study is timely in view of the forthcoming publication of the next part of the National Service Framework for Children[10] and the Department of Health announcement of a major investment in hospital manufacturing units[11]. The data from this study will assist paediatric hospitals in England to work together and develop a common strategy in extemporaneous production.

Objectives

(1) To identify the frequencies and types of non sterile medications prepared extemporaneously in the pharmacies of paediatric hospitals in England.

(2) To identify the method of manufacturing of extemporaneous preparations in the pharmacies of paediatric hospitals in England.

(3) To identify which of the above preparations were available from specials manufacturers.

Methods

There are seven specialist paediatric hospitals in England (Alder Hey Hospital in Liverpool, Birmingham, Royal Alexandra Hospital in Brighton, Derby, Great Ormond Street Hospital in London, Manchester and Sheffield). All of them were contacted through the Neonatal and Paediatric Pharmacists Group web network to request data of extemporaneous non-sterile preparations which were systematically recorded in their dispensary batch books between 1st January 2002 and 31st December 2002. Additionally, the chief pharmacist of each hospital was contacted by phone or email to provide the information requested. Parenteral preparations such as TPN and/or intravenous preparations were not covered by this study. A preset format was requested which included drug name, type of product, total quantity made and frequency of each preparation. However, the batch size of each preparation was not recorded. The items were categorised according to:

Table 1 Top 20 drugs prepared extemporaneously

Rank	Drug	*n*	Frequency (%)	Cumulative (%)
1	Potassium chloride	435	11.7	11.7
2	Midazolam	168	4.5	16.2
3	Vancomycin	158	4.2	20.4
4	Clonidine hydrochloride	132	3.6	24.0
5	Isoleucine	111	3.0	27.0
6	Valine	106	2.8	29.9
7	Potassium dihydrogen phospate	101	2.8	32.6
8	Mercaptopurine	101	2.7	35.3
9	Co-Careldopa	101	2.7	38.0
10	Dichloroacetate sodium	93	2.5	40.6
11	Cholesterol	89	2.4	43.0
12	Sodium chloride	84	2.2	45.2
13	Aspirin	75	2.0	47.2
14	Didanosine	62	1.7	48.9
15	Acetylcysteine	61	1.6	50.5
16	Diazoxide	60	1.6	52.1
17	Clobazam	59	1.6	53.7
18	Sucralfate	57	1.5	55.2
19	Cysteamine	57	1.5	56.8
20	Warfarin	53	1.4	58.2

i. British National Formulary (BNF) chapter to indicate their therapeutic category[12].

ii. Types of modification of the original dosage forms were classified according to the production methods:

(a) The liquid preparations were classified as suspensions and solutions, prepared either from dilution of the original liquid dosage form, from solid dosage forms or from raw material.

(b) The solid preparations were classified as segmented tablets, unit-doses or multi-doses. A sub classification was made based on the sources of the powder (pharmaceutical or non-pharmaceutical grade raw material, crushed tablets or content of opened capsules).

iii. Availability as a special product from special manufacturers.

iv. Nature of licensed status of the original product before manipulation.

Results

All seven paediatric hospitals provided us with the requested information. A total of 3728 preparations were recorded, ranging from 10 to 1492 preparations per year. The average number of extemporaneous preparations manufactured was 1.5 items per day per hospital.

Table 1 shows that the top 20 drugs represented more than 58% of the workload, indicating the repetitive nature of the work. Conversely, there were 25 drugs which represented 24% of the total which were only prepared less than twice a year. Drugs to treat metabolic diseases constituted 20% of the top 20 which was followed by electrolytes (15%) and CNS drugs (15%). Over 10% total extemporaneous preparations involved potassium chloride.

Table 2 is a breakdown of the list of products according to BNF categories. Over a quarter of the chemical entities were not licensed and 50% of the preparations were available from special

Table 2 Categories of extemporaneous products based on British National Formulary (BNF) classifications

BNF Category	Products manufactured		Frequency of manufacture		Unlicensed chemical entities used*	Specials available
	n	%	*n*	%	*n*	
Nutrition and blood	37	31.6	1692	45.4	22	13
Central nervous system	15	12.8	288	7.7	2	12
Cardiovascular system	13	11.1	540	14.5	0	10
Infections	8	6.8	316	8.5	0	2
Malignant disease and immunosuppression	8	6.8	184	4.9	1	2
Skin	8	6.8	128	3.4	3	5
Endocrine	6	5.1	137	3.7	0	6
Anaesthesia	5	4.3	256	6.9	0	2
Ear, nose and oropharynx	4	3.4	42	1.1	0	2
Musculoskeletal and joint diseases	4	3.4	41	1.1	1	2
Respiratory system	3	2.6	73	2.0	0	1
Gastrointestinal system	2	1.7	14	0.4	1	1
Others	4	3.4	17	0.5	1	3
Total	117	100.0	3728	100.0	31	61

*Unlicensed refers to the chemical entity itself, not the formulation or indication/dosage.

manufacturers. The majority of unlicensed chemical entities came from the BNF "Nutrition and Blood" category (31.6% in terms of the number of drugs and 45.4% of the workload). Drugs under the BNF "Gastrointestinal" category were required sporadically whilst drugs under the BNF "Anaesthesia" category were made nearly once a week.

The majority of the products were liquid preparations (76%). Table 3 shows the type of liquid extemporaneous preparations manufactured. Two thirds were solutions and one third were suspensions. The solid extemporaneous preparations are shown in Table 4. Approximately one third consisted of segmenting tablets and two thirds of the preparation of powders, packaged mainly in sachets with only a few packaged in multi-dose containers for extemporaneous reconstitution**.** There were no capsules prepared extemporaneously.

Discussion

This is the first systematic study to investigate extemporaneous activities in the pharmacy departments of the specialist paediatric centres in England. All seven paediatric hospital pharmacies provided us with information, which demonstrates the willingness of paediatric pharmacists to assist research. In contrast to most people's beliefs, the present study revealed that the extent of extemporaneous dispensing in paediatric pharmacies is low, the average number of preparations recorded was 621 per year and the range was between 10 and 1492. The low figure observed in some hospitals indicates the different policies where extemporaneous preparations are carried out only in emergencies. Hospitals with such policies would carry stock of specials and patients may have to wait when the products are out of stock. Additionally, there will be wastage due to short expiry date of the specials.

Table 3 Methods of manufacturing liquid extemporaneous products

	Solution (%)	Suspension (%)	Total (%)
Dilution	45.0	0.1	45.1
From raw material	20.2	8.8	29.0
From crushed tablets	4.0	21.4	25.4
From capsules	0.0	0.5	0.5
Total	69.2	30.8	100.0

Table 4 Methods of manufacturing solid extemporaneous products

	Sachets (%)	Multidose bottles* (%)	Segmenting of tablets (%)	Total (%)
From raw material	50.9	4.7	0.0	55.6
From crushed tablets	2.7	1.3	0.0	4.0
From segmented tablets	0.0	0.0	36.0	36.0
From capsules	4.4	0.0	0.0	4.4
Total	58.0	6.0	36.0	100.0

*Powder for extemporaneous reconstitution.

Table 1 is a simplistic presentation of drugs which have been extemporaneously prepared by various children's hospitals. This does not reflect the true extent of the use of unlicensed medicines in children where extemporaneous manipulations are carried out on the ward or by parents at home. The procedures of cutting/grinding tablets and "dispersing/suspending" in agents such as food/ beverages prior to administration are the ones associated with the highest risk of errors in extemporaneous dispensing. It is difficult to determine how frequently this occurs, the bioavailability of such manipulations are unpredictable and there is no compatibility and stability back up.

When we examined the raw data provided by the paediatric hospitals, we were astonished to find the diversity of strengths of the same medicines that are required in different centres. Due to the sheer volume of the data, it would not be feasible to report all of them in this article; however, we provide the following two examples to illustrate the situation: diazoxide suspension had been prepared as 10, 35 and 50 mg/ml and clonidine solution as 2.5, 5, 10, 15 and 60 micrograms/ml. One child received his regular supplies of diazoxide suspension, an extemporaneously prepared suspension of 10 mg/ml, from the local pharmacy. He was given a 50 mg/ml solution following a visit to a paediatric hospital. His parents did not realise it was a different strength and gave the same volume of the suspension which caused a five fold overdose. Consequently, the child required hospitalisation. The above case highlights the increased risk of medication errors due to non-standardised strengths from different pharmacies. A recent report produced by the Royal College of Paediatrics and Child Health (RCPCH) also suggested that mistakes were being made because of the lack of consistent standards in extemporaneous dispensing procedures and the varying quality of ingredients[13].

Based on our findings and the recommendation of the above RCPCH report[13], we recommend that the Department of Health explore the possibility of establishing a national extemporaneous formulary to standardise the strength and presentation in order to minimise risk. This would be consistent with plans by the Department of Health to invest in improving hospital manufacturing units[11] and to develop a British National Formulary for Children.

The fact that the top 20 drugs represent 58% of the workload indicates the repetitive nature of the work. Many of the most frequently prepared drugs are used on a long term basis for the

treatment of a wide range of conditions, *e.g.* dichloroacetate for metabolic disorders, diazoxide for hypoglycaemia, didanosine for HIV infection and clobazam for epilepsy. All these drugs are required for several years, and some could be life long. Repeat prescriptions are therefore dispensed on a regular basis. The repetitive nature of the demand makes it an ideal scenario for hospitals to consider the use of specials manufacturers. As 52% of the drugs are available as specials, it is possible to significantly reduce the amount of extemporaneous dispensing in paediatric hospital pharmacies and the subsequent risk. Children's hospitals such as Birmingham's Children Hospital have adopted a policy to cut back on extemporaneous dispensing in the pharmacy in a bid to minimise the risk of mistakes[13].

There are a number of factors that hinder the wholesale adoption of specials products. The primary factor is the short expiry associated with most of the specials. This is due to the lack of research of chemical stability on the wide range of products and strengths required by patients. The short expiry leads to frequent ordering and wastage. The second reason is the lack of immediate availability. Whereas it is suitable to carry stock of products that are used by a pool of patients on a regular basis, it is difficult, if not impossible to predict the use of some rare products. Some products prepared were only made once or twice per year. Therefore, the patient has to wait for such products which may not be possible in some situations where the treatment must start immediately or if patients live far away from the specialist centres.

The majority of the drugs (73.5%) are licensed products but do not have an appropriate pharmaceutical formulation for children; therefore they required extemporaneous manipulation. The establishment of the Paediatric Expert Group by the European Medicines Evaluation Agency to coordinate the development and the use of medicinal products in children is a step forward[14]. The proposed EU regulations on medicinal products for paediatric use will provide an incentive to manufacturers and researchers to develop appropriate paediatric formulations[15] and hopefully in the future, more high quality paediatric formulations will be available from the pharmaceutical industry.

Most of the products produced by specials manufacturers or hospital pharmacies have very little supporting data on their quality, efficacy and safety. Only drastic changes in funding bodies' attitudes towards researching medicines for children can improve the current "non-evidence based practice".

Conclusion

The extent of extemporaneous dispensing in paediatric pharmacies is lower than generally believed. The 20 most frequently prepared drugs (58% of the workload) could be produced by licensed units or specials manufacturers to reduce the risk of production errors. As the diversity of strengths of the same medicines that are produced in different centres creates opportunities for medication errors, the idea of establishing a national extemporaneous formulary to standardise the strengths and presentations should be explored.

Acknowledgement

CT is funded by Pfizer and IW is funded by UK Department of Health Public Health Career Scientist Award. We thank all the hospitals for their data collection.

Conflict of interests

The authors have received funding from different pharmaceutical manufacturers in researching paediatric medications.

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Paper PPDT–0114, *Accepted for publication:* 15 September 2004
Published Online: 01 November 2004
doi:10.1185/146300904X12668