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Prospective Surveillance of Extemporaneous Dispensing of Medicines for Children

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Abstract

A prospective, systematic surveillance, of a period of 3 months, was carried out in the Ospedali Riuniti in Bergamo. Six paediatric units in one hospital participated. Extemporaneous preparations of medicines were given to 80 children, six of whom were premature newborns. The children received 97 prescriptions for medicines requiring extemporaneous formulations, corresponding to a total of 2821 doses. The drugs used most often were: chlorhexidine, captopril and acetylsalicylic acid. Prescriptions were usually for children with chronic conditions, in particular malignancy and congenital heart disease. The preparations consisted of: 57% crushed tablets, 28% mouth washes, 8% syrups and 7% solutions.

Key words: Extemporaneous dispensing – Children – Prospective surveillance – Hospital

Introduction

In Italy, as throughout Europe, only about 20% of the drugs available on the market are approved for paediatric use[1]. Many pharmaceutical companies have been reluctant to seek licenses for paediatric use of their products[2]. Nevertheless, doctors are not restricted to prescribing licensed medicines or to prescribing them only for licensed indications. Many of the medicines given to children in the hospital and the community settings, either do not have a product licence for use in children and hence are used *off-label* (outside the terms of the product licence) or are simply not licensed for use in their current formulation[3]. This is a major problem in Italy, where almost 60% of prescriptions in hospitals are off-label[4].

Young children cannot take tablets. Many liquid formulations are prepared in concentrations not suitable for administration to infants. Pharmacists faced with the problem of modifying an oral dose form intended for adult use into a suitable form for paediatric administration overcome this obstacle by making preparations extemporaneously[5,6]. This new form is achieved by either crushing the licensed tablet formulation, or opening the capsule and dissolving or suspending the content together with various excipients, or redistributing it into powder papers (sachets). Pharmacists may also make suitable preparations from chemical ingredients rather than manipulating licensed formulations. The preparation of extemporaneous formulations for paediatric patients is usually carried out in the hospital pharmacy, where suitable structures and technicians are available.

This study is a systematic prospective surveillance of paediatric extemporaneous production in a single hospital. The aims were to evaluate which medicines and conditions require extemporaneous formulations and whether there is any evidence to use the medicines in such a manner.

Materials and Methods

All medicines requiring extemporaneous formulation in six paediatric wards of the Ospedali Riuniti in Bergamo were noted over a period of three consecutive months (July – September 2000). The general patient characteristics, the extemporaneous preparations they received, the therapeutic indications for which the products were given and the context in which they were used were all noted. The drugs used to prepare extemporaneous preparations were classified according to the ATC System (Anatomical Therapeutical and Chemical), the therapeutic indications and diagnosis for hospital admission according to the ICD9. Data management and analysis was performed using the programme Microsoft Access.

Results

During the 3 months 1493 children were admitted. Eighty paediatric patients required at least one drug requiring extemporaneous formulation. The age of the patients ranged from one day to 14 years (median age 1.7 years). These children received 97 prescriptions requiring extemporaneous formulation in the hospital pharmacy. This involved a total of 2821 doses. The diagnoses of the children requiring extemporaneous formulations are shown in Table 1. The majority of these children had chronic conditions. Methods for extemporaneous dispensing consisted of powders (1661; 57% of the total) and oral liquids such as rinse (783; 28%), syrup (230; 8%) and solutions (197; 7%).

Sixteen different medicines required extemporaneous formulation. Three of the medicines however accounted for over half of the prescriptions (chlorhexidine, captopril and acetylsalicylic acid). The most frequent indication for the use of an extemporaneous formulation was prophylaxis for mucositis (Table 2).

Discussion

The preparation of extemporaneous products for paediatric use is an activity that is present in many hospital pharmacies. This activity differs from one hospital to another and from one country to another[7], and no up to date common standards or guidelines are available.

Extemporaneous dispensing is necessary to guarantee children therapeutic assistance[8]. From this study some significant examples stand out.

Table 1. Diagnosis of patients receiving extemporaneous formulations

Diagnosis	Children	Prescriptions	Doses
Malignancy	33	34	726
Congenital heart disease	17	20	458
Transplant	11	21	578
Supraventricular tachycardia	5	5	40
Congenital malformation	4	5	237
Prematurity	2	4	427
Neonatal withdrawal syndrome	1	1	210
Epilepsy	1	1	78
Miscellaneous	6	6	67
TOTAL	**80**	**97**	**2821**

Captopril is currently available in Italy as tablets of 25 or 50 mg each (in Europe as tablets of 12.5 mg, 25 mg, 50 mg or 100 mg). The amount required for a newborn infant ranges from 10–50 micrograms/kg per dose and, for a child of 12 years, is 100 micrograms/kg [9]. No liquid dosage form for administering these doses based on body weight is available. A liquid formulation must therefore be prepared[10]. Captopril stability data in liquid is not available, although in Italy as in Europe, this formulation has been used in infants for several years[11]. Stability data are lacking for numerous drugs frequently used in paediatric patients[10]. Extemporaneous powders (sachets) can be prepared using crushed tablets. This requires preparation of individual doses by the pharmacist and may result in delivery of incomplete doses or errors in dosage preparations, increasing the potential of adverse reactions[12].

In general, if stored under suitable conditions away from moisture, powders should have greater stability than oral liquids but are more time consuming to prepare. They are fixed dosage forms so many different strengths may be required to satisfy the varying dosage requirement of children of different ages. Oral liquids are comparatively quick to prepare and can allow flexibility in dosage from a single strength preparation by accurately measuring the volume required using a syringe or pipette designed for oral administration. However, oral liquids may be difficult to formulate to ensure stability, physical, chemical and microbial stability. The formulations may contain excipients (especially preservatives) that produce adverse reactions in some babies or children[6,13].

Chlorhexidine oral rinse, the most requested extemporaneous preparation in the study, is

Table 2. Formulation and indication for drugs requiring extemporaneous dispensing

Drug	**Formulation**	**Indication**	***Prescriptions***		***Dispensing***	
			n	**%**	**n**	**%**
Chlorexidine	Oral rinse	Prophylaxis for mucositis	32	34	630	22
Captopril	Sachets	Cardiovascular disease	6		74	
	Sachets	Congestive heart failure	4		159	
	Sachets	Hypertension	2	17	25	18
	Solution	Congestive heart failure	4		188	
	Solution	Cardiovascular disease	1		9	
Acetylsalicylic acid	Sachets	Antithrombotic prophylaxis	8	9	162	6
Ursodiol	Sachets	Biliary stones	6	6	252	9
Benzidamine	Oral rinse	Stomatitis	6	6	153	5
Chloral hydrate	Sachets	Sedation	5	5	20	1
Omeprazole	Sachets	Haemorrhagic acute peptic ulcer	5	5	165	6
Spironolactone	Sachets	Congestive heart failure	2		42	
	Sachets	Neonatal chronic respiratory disease	2	5	212	10
	Sachets	Ascites	1		22	
Amiodarone	Sachets	Supraventricular tachycardia	4	4	34	1
Propranolol	Sachets	Haemorrhagic oesophageal varices	2	2	142	5
Hydrochlorothiazide	Sachets	Neonatal chronic respiratory disease	2	2	215	8
Acetazolamide	Sachets	Intracranial hypertension	1	1	21	1
Clobazam	Sachets	Epilepsy	1	1	78	3
Morphine	Syrup	Neonatal withdrawal syndrome	1	1	210	7
Propafenone	Sachets	Supraventricular tachycardia	1	1	6	–
Warfarin	Sachets	Antithrombotic prophylaxis	1	1	2	–
Total			97	100	2821	100

available on the Italian market in six pharmaceutical products, three of which are contra-indicated in children under the age of 6 years. These preparations were requested for children on chemotherapy for oral mucositis and microbial burden prophylactic prevention. The clinical efficacy and safety of chlorhexidine oral rinse have not been established in children under 18 years of age[14,15].

A different example is that of chloral hydrate. Chloral hydrate is considered by some to be the drug of choice for sedation of children before diagnostic, dental, or medical procedures [16]. In Italy, as in the rest of Europe, no commercial products containing chloral hydrate are available: the dispensing of liquid dosage forms are thus justified.

This study is the first Italian step for implementing effective paediatric therapeutic interventions. Further studies evaluating the extemporaneous dispensing of medicines for children are required.

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