

A Retrospective Study of Oral Medications Compounded for Pediatric Patients at Kenyatta National Hospital

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A retrospective study of oral medications compounded for pediatric patients at the Kenyatta National Hospital main pharmacy, manufacturing unit, was carried out for the study period January, 2012 to December, 2013. The aim of the study was to characterize compounding involving oral solid dosage form modifications. A total of 392 oral liquid formulations, comprising one (1) of nineteen (19) active pharmaceutical ingredients, were compounded from oral solid dosage forms over the study period. Sildenafil, furosemide and spironolactone suspensions were the most frequently compounded formulations (41.6%, 21.4% and 10.5% respectively). Sildenafil, furosemide and spironolactone suspensions accounted for 74.5% of the total volume of compounded formulations, with suspensions of all other active pharmaceutical ingredients accounting for only 25.5%. All formulations were prepared using syrup simplex B.P. as diluent, packed in white plastic bottles and assigned beyond-use dates of 2 weeks. Apart from sildenafil suspensions which were recommended for storage at 4 - 8 °C, all other formulations were stored at room temperature.

Keywords: Compounding, retrospective, pediatric, dosage form modifications, Kenyatta National Hospital

INTRODUCTION

Compounding, often referred to as extemporaneous preparation, involves the preparation, mixing, assembling, altering, packaging and labeling of a drug in accordance to a prescription. Compounding may be as simple as reconstituting a dry powder in accordance with the manufacturer's instructions to more challenging modifications of commercially available dosage forms.

Pediatrics, defined as preterm/term newborns, infants, toddlers and children below 11 years [1], are a special patient population for whom compounding is frequently necessary due to their inability to swallow oral solid dosage forms (tablets, capsules). A recent study of the local pharmaceutical market [2] has shown that there is a relative shortage of oral liquid dosage forms in comparison to oral solid dosage forms. This observed shortage of oral liquid dosage forms could be due to the fact that many pharmaceutical industries routinely invest in the

manufacture of oral solid dosage forms neglecting oral liquid dosage forms which are expensive to manufacture and unprofitable. Secondly the use of off-label drugs, with respect to indication, among pediatrics is common practice due to the long-standing absence of clinical trials among children [3]. Many of these drugs initially intended for adult population, e.g., carvedilol, enalapril and sildenafil, may only be available in adult dosage forms (tablets/capsules) and strengths depending on the particular country/region.

In an effort to provide age-appropriate liquid formulations for pediatrics, adult solid dosage forms have often been modified by slicing of tablets, crushing of tablets/opening of capsules before mixing with food or with diluents to prepare a liquid dosage form [4, 5]. The diluents used for compounding oral liquid dosage forms include water, sugar syrup, methyl cellulose, as well as commercial diluents such as Ora-Blend[®], Ora-Plus[®] and Ora Sweet[®].

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While compounding enables administration of drugs tailored for the adult population to pediatrics, it is a practice ridden with challenges. Errors in drug dosing may occur either from pharmaceutical calculations or inhomogeneity of the compounded formulation. Chemical instability of the drug within the compounded formulation leads to decreased efficacy and in some cases increased toxicity of the formulation. Microbiological contamination of the compounded formulations is another concern. It is therefore the onus of the compounder to ensure the quality and safety of the extemporaneously prepared product by paying attention to the prescription, pharmaceutical calculations, suitability and purity of excipients/diluents used as well as formulation homogeneity.

Compounding involving oral solid dosage form modifications (slicing, crushing tablets/opening capsules and mixing resultant powder/granules with diluents) to address the lack of pediatric oral liquid formulations of essential drugs has been reported in Kenya [6, 7]. However, no study elucidating the nature and extent of this compounding in any health facility in the country was found by the authors in the literature.

The current study addresses part of the aforementioned knowledge gap, allowing an insight into compounding of oral formulations for pediatric patients at Kenyatta National Hospital; a regional referral and teaching hospital. The aim of the study was to identify the compounded oral formulations (drug, strength and dosage form), excipients used, frequency of compounding, volumes compounded, packaging, storage conditions and the assigned beyond-use dates.

METHODOLOGY

Study site

The research was carried out at the Kenyatta National Hospital (KNH) manufacturing unit located in the main pharmacy (Pharmacy No. 40).

Study design

This was a retrospective study conducted by collecting data on oral medications compounded for pediatric patients from the compounding logs for the period from January, 2012 to December, 2013. The data collection tool was designed to capture the following information on the compounded oral formulations; date of preparation, drug name and strength, dosage form, excipients used, frequency of compounding, volume prepared, packaging, storage conditions and assigned beyond-use dates. The extent of compounding for each particular drug was assessed using two measuring indices namely frequency of compounding and volume compounded. The compounded drugs were also classified according to the biological systems on which they act.

Limitations

Any incomplete records lacking any of the required fields of data were excluded from the study. This exclusion may have slightly underestimated the total number/volume of compounded formulations reported.

Ethical approval

Ethical approval for the study was obtained from the Kenyatta National Hospital – University of Nairobi Ethics Research Committee (Reference number KNH-UP257/05/2014).

Data analysis

Data analysis was carried out using Microsoft Excel 2013.

RESULTS AND DISCUSSION

It was observed that the compounding carried out at the KNH manufacturing unit involved dosage form alterations/modifications (e.g., preparation of oral liquids from tablets), while simple compounding (e.g. reconstituting of oral antibiotic powders) was carried out either in the ward or outpatient pharmacies. A total of 392 oral liquid formulations were compounded for pediatric patients over the two year study period.

The oral liquids, all reformulated as suspensions, comprised of formulations containing one (1) of nineteen (19) active pharmaceutical ingredients (APIs) namely acetazolamide, captopril, carvedilol, clonazepam, dapsone, digoxin, enalapril, folic acid, furosemide, haloperidol, isoniazid, nitrofurantoin, omeprazole, propranolol, pyridoxine, pyrimethamine, sildenafil, spironolactone and thyroxine. The sources of the APIs for all the compounded liquid formulations were commercially available tablets.

A previous survey of pharmaceutical products registered in Kenya revealed that for majority of the aforementioned APIs (84%), only oral solid dosage forms (tablets/capsules) were available during the study period [8]. Oral liquid formulations of folic acid, pyridoxine and pyrimethamine were available; however these liquid formulations were combination products e.g., sulfadoxine-pyrimethamine syrup.

comprising of the different APIs, over the study period. Sildenafil suspension was the most frequently compounded product prepared 41.6% of the times. Sildenafil is used for management of pulmonary hypertension in children [9]. During the study period, oral sildenafil products registered in the Kenyan market included tablets of 25, 50 and 100 mg strengths and a jelly containing 100 mg sildenafil/5 g, none of which are suitable for pediatric dosing [8]. Furosemide, spironolactone and enalapril suspensions accounted for 21.4%, 10.5% and 8.2% of the total percentage frequency respectively. Furosemide and spironolactone are diuretics while enalapril is an angiotensin converting enzyme (ACE) inhibitor, all of which are used in the management of heart disease in children [10]. The rest of the APIs were each prepared less than 5% of the times. Clonazepam, dapsone, haloperidol, isoniazid and nitrofurantoin were prepared only once during the study period, each contributing only 0.2% to the final percentage.

Figure 1 presents the percentage frequency of compounding of the various formulations,

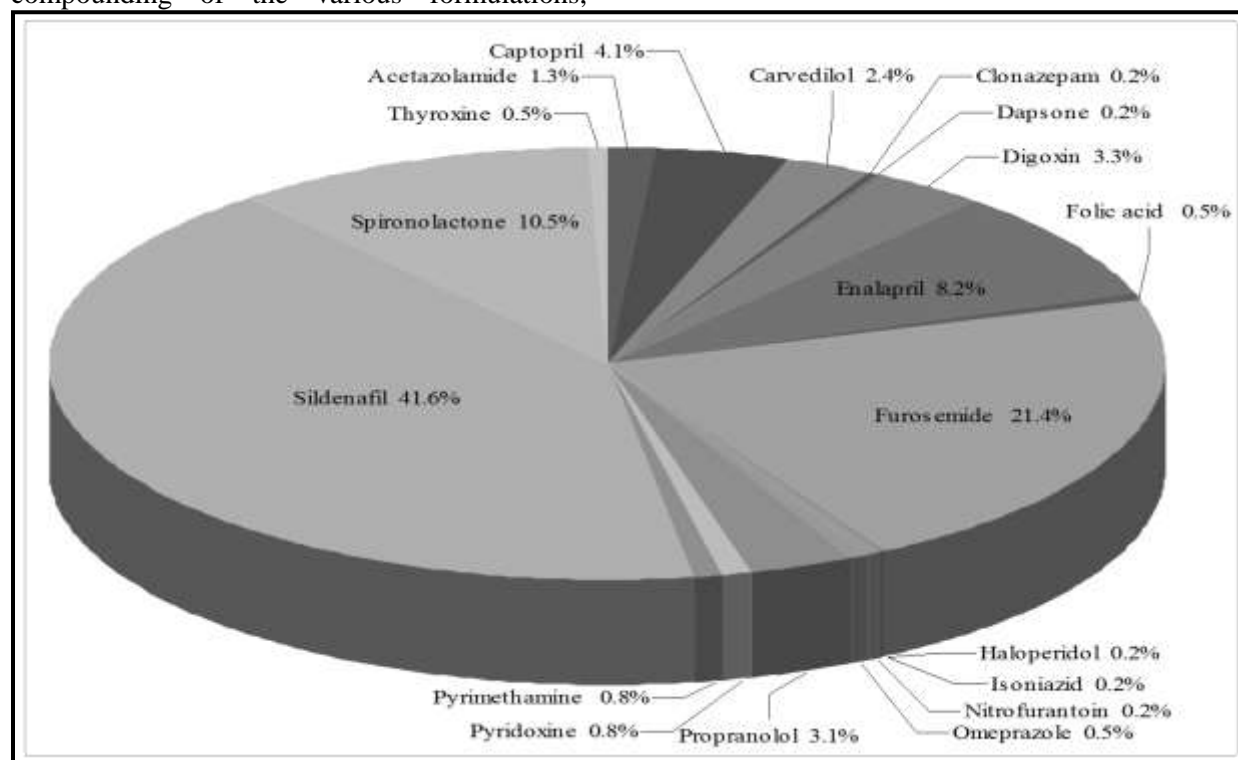


Figure 1: Frequency of compounding of the various formulations, comprising the different active pharmaceutical ingredients, expressed as percentages.

The total volume of liquid formulations compounded during the study period was 38.4 L. Figure 2 shows the percentage contributed by the various formulations, comprising of the different APIs, to the total volume. Sildenafil (43.6%), furosemide (19.5%) and spironolactone (11.4%) suspensions contributed the largest volumes to the total volume of compounded formulations. Indeed, the volume of suspensions of these three APIs was approximately 28.6 L, with formulations of all other APIs accounting for only 9.8 L. Notably, the volume of compounded suspensions of some APIs (clonazepam, dapson, folic acid and isoniazid) was less than 100 mL each.

A comparison of the frequency of compounding of the various formulations with volumes

compounded was performed using Spearman's rank correlation coefficient and revealed a strong correlation (0.959) between the two measures.

For most of the APIs (acetazolamide, captopril, carvedilol, digoxin, enalapril, furosemide, omeprazole, propranolol, sildenafil and spironolactone), multiple strengths of the oral formulations were compounded. This was necessitated by the age-weight dosing of drugs in the pediatric population. Single strength formulations were compounded for the rest of APIs, which in some cases (clonazepam, dapson, haloperidol, isoniazid, and nitrofurantoin) was as a result of only one suspension of the API being prepared over the study period.

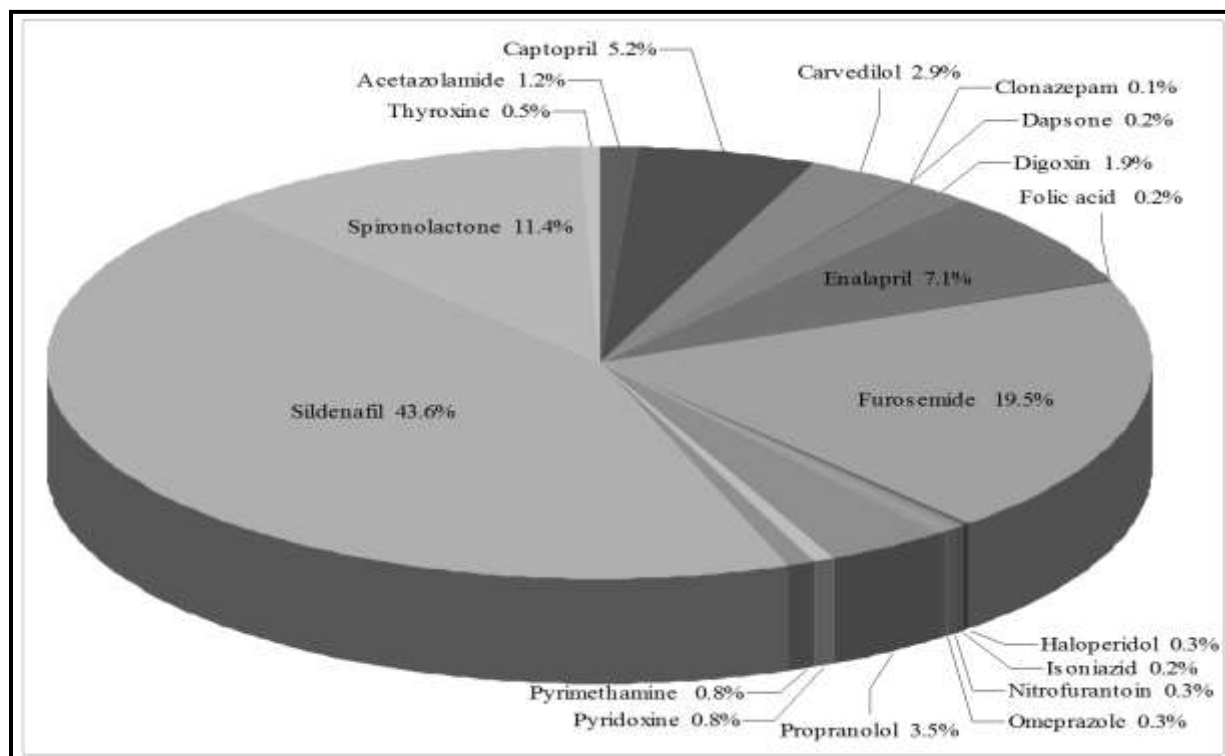


Figure 2: Volumes of the various compounded formulations, comprising the different active pharmaceutical ingredients, expressed as percentages of the total volume.

Table 1 summarizes the biological systems on which the various drugs act. Formulations containing drugs acting on the cardiovascular system, including ACE inhibitors (captopril, enalapril), beta blockers (carvedilol, propranolol), a cardiac glycoside (digoxin),

diuretics (furosemide, spironolactone) and a vasodilator (sildenafil), constituted the majority both in terms of frequency of compounding and volumes compounded. Indeed the treatment of pediatrics with congenital or acquired heart disease is a challenge due to lack of suitable

drugs/formulations and inadequate clinical information [9, 10]. The utilization of compounded adult dosage forms of drugs is quite prevalent, and more research needs to be carried out to effectively manage heart disease in this population. While off-label prescribing enables treatment of pediatrics with rare diseases, such prescribing should always be evidence-based to avoid exposing patients to harmful effects [11].

Drugs acting on the central nervous, endocrine and gastrointestinal systems accounted for less

than one percent frequency and percent volume of the total formulations compounded in each case. Drugs classified as 'others', prepared 4% of the times, included anti-infectives (dapson, isoniazid, nitrofurantoin and pyrimethamine) and nutritional supplements (folic acid) as well as drugs with multiple uses (acetazolamide and pyridoxine). Acetazolamide is a mild diuretic used to manage raised intracranial pressure, glaucoma and epilepsy, while pyridoxine is used as an adjunct in TB therapy and megaloblastic anaemia.

Table 1: Frequency of preparation and volume of the various compounded formulations expressed as percentages and classified according to target biological system

System	Drug/s	Percent frequency	Percent volume
Cardiovascular system	captopril, carvedilol, digoxin, enalapril, furosemide, sildenafil, spironolactone, propranolol	94.6%	95.1%
Central nervous system	clonazepam, haloperidol	0.4%	0.4%
Endocrine system	thyroxine	0.5%	0.5%
Gastrointestinal system	omeprazole	0.5%	0.3%
Others	acetazolamide, dapson, isoniazid, folic acid, nitrofurantoin pyridoxine, pyrimethamine	4.0%	3.7%

Syrup simplex B.P., locally prepared in the pharmacy, was the sole diluent used for compounding all of the liquid formulations. No other excipients were added to the compounded formulations. The high concentration of sugar in the syrup deters microbial growth of bacteria. However, osmophilic yeasts e.g. *Sachromyces spp.*, have been reported to thrive in high sugar solutions [12]. In addition the high sugar content may encourage development of dental caries in the pediatrics. With regard to the chemical stability of compounded drugs, sugar syrup is not a suitable diluent in all cases; for instance an incompatibility between sucrose and isoniazid [13] has been reported. The compounders' choice of sugar syrup as the sole diluent could be driven by the fact that alternative diluents are either time consuming to

prepare (methyl cellulose NF) or quite expensive (Ora-Plus[®], Ora-Blend[®], Ora-Sweet[®]).

All the compounded formulations were packaged in white plastic bottles and assigned a beyond-use date of 2 weeks. Owing to the light-sensitive nature of the APIs contained in the compounded formulations, stability studies investigating the effect of different light resistant packaging e.g. amber colored bottles and secondary cardboard boxes would be advantageous. The conservative beyond-use date of 2 weeks was in keeping with the USP guidelines for water-containing oral preparations lacking extensive stability data [14]. The storage temperature specified for most compounded formulations was room

temperature, with the exception of sildenafil suspension that was recommended for storage at 4 - 8 °C.

CONCLUSION

The study revealed that compounding, involving oral solid dosage form modifications, was carried out at the KNH main pharmacy, manufacturing unit, during the study period. Majority (94.6%) of the compounded oral liquid formulations comprised of drugs which act on the cardiovascular system. The rest of the compounded formulations (5.4%) included central nervous, endocrine and gastrointestinal drugs, as well as a miscellaneous class of drugs.

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The results obtained in this study are of interest to the pharmaceutical industry, researchers and academicians as it highlights areas where formulation development efforts can be focused to ensure availability of age-appropriate formulations for the pediatric population locally. In addition the results provide a list of drugs for inclusion in the development of a national compounding formulary, to standardize compounding practices in health facilities in the country.

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