Prevalence, Scope and Quality of Extemporaneous Medications in Selected Healthcare Facilities and Implications for Pharmacy Practice

Grace Lovia Allotey-Babington[1]; Irene Akwo Kretchy [2]; Esther Atiapa Asiedu[1]; Maxine Kelly Amuakwa[1]; Obedia Akwele Seaneke [4]; Daniel Ankrah [4]; Abredu Kwadwo Somuah [4] ; Agatha Dei Owusu-Nyamekye [4] ; Sarah Owusu-Ansah [5] ; Patrick Kwame Effah [5]; Johnson Debrah[5] ; Edna Acheampomaa Nai [6] ; Emmanuel Owusu [6] ; William Lamptey [7] ; Isaac Julius Asiedu Gyekye [3]; Henry Nettey [1]

[1] Department of Pharmaceutics and Microbiology, School of Pharmacy University of Ghana, P.O. Box LG 43 Legon, Ghana
[2] Department of Pharmacy Practice and clinical Pharmacy, School of Pharmacy University of Ghana, P.O. Box LG 43 Legon, Ghana
[3] Department of Pharmacology and Toxicology, School of Pharmacy University of Ghana, P.O. Box LG 43 Legon, Ghana
[4] Korle Bu Teaching Hospital P.O. Box 77, Korle Bu Ghana
[5] 37 Military Hospital Neghelli Barracks Accra Ghana
[6] Greater Accra Regional Hospital P.O. Box GP 473 Accra, Ghana
[7] Princess Marie Children's Hospital P.O. Box GP 122 Accra, Ghana

Abstract

Background: Extemporaneous compounding is the preparation of medicines for individual patients when no commercially available authorized form exists. Unlike registered medications, these products are not subjected to various tests for quality by Regulatory Authorities. Data on compounded medications in Ghana is currently inadequate or unavailable. There is the need to collate data that can be used to influence policy and to regulate preparation of extemporaneous products. *Aim*: To establish the prevalence, scope and quality of extemporaneously compounded medicines at selected hospitals in Accra, Ghana. *Methodology*: Prescriptions presented at the pharmacies in selected hospitals were reviewed to determine the requests that needed to be extemporaneously prepared as well as the prevalence and the scope of formulations. Three of the most frequently compounded medications were procured and subjected to microbial contamination tests using the pour plate method followed by differential tests if microbes were present. Content analysis of the active ingredients was determined using High Performance Liquid Chromatography (HPLC). *Results*: 641 requests comprising 49 different extemporaneous products were collated from the hospitals studied. Hydroxyurea, furosemide and spironolactone suspensions were the three most frequently prescribed. Patients aged from 0-2 years had majority of the prescriptions. *Conclusion*: A population of patients still exist who depend on compounding for their drug needs. 49 different formulations were prepared at one of the hospitals visited. Samples of products analyzed were of good quality.

Keywords: Extemporaneous products, Compounding, Pediatric, Pharmacy Practice.

Introduction

Extemporaneous compounding is a technique employed by pharmacists to produce medicines from active pharmaceutical ingredients (APIs) or from some authorized medications when no commercially available, authorized, age-appropriate or suitable dosage form is in existence [1]. It had been a fundamental function and the basis claim to professional status of the pharmacists [2]. Extemporaneous preparations are tailored to meet the needs of individual patients, including those with specialized medical needs, patients with swallowing difficulties, infants and the elderly [3]. The manufacture and usage of drug products is controlled in most countries by regulatory bodies which register the medicinal products and issue licenses [2]. Due to the fact that conditions necessitating the need for extemporaneous products are individualized and highly unpredictable, it has been almost impracticable to license each of these products.

Corresponding Author: Henry Nettey
University of Ghana,
P.O. Box LG 43 Legon, Ghana
hnettey@ug.edu.gh

Thus, extemporaneously manufactured pharmaceutical products in many countries are exempt from this licensing process and are broadly defined as unlicensed or unauthorized [2,4]. Although, extemporaneous products prepared and dispensed by pharmacists do not undergo safety, quality or efficacy evaluations, the pharmacist, is mandated by the oath of profession to ensure that only good quality medicines are supplied to patients.

As with every unlicensed product, the quality, safety and efficacy of extemporaneous products cannot be assured. Poor manufacturing practices on the part of drug compounders can result in products lacking the right strength, quality and purity [5]. Pediatrics are one large section of the population that rely mostly on these extemporaneous preparations for the majority of their health needs, thus, if compounding is banned or prohibited, the effects could be devastating due to the unmet health needs [6,7]. This group of the population is also known to have weakened or less-developed immune systems, thus, any compromises in the quality of the medications offered could be detrimental to their health and clinical outcomes [8,9].

DOI: https://doi.org/10.24926/iip.v15i1.5971

In some developed countries, data on compounded products and practices have been collated [10-12]. This information has led to the establishment and implementation of policies aimed at improving the quality and safety of compounded products. In the United Kingdom (UK), for example, a Handbook of Extemporaneous Preparation was produced in 2010 [13].

In the US for example the FDA enacted an ACT to regulate compounding of medications [14,15]. Similarly, regulatory guidelines exist in other jurisdictions such as Europe (even though not harmonized across the European countries) [12,16]. Data on compounded medications in Ghana are currently inadequate or unavailable. As a result, the skill and act of compounding is deemed by many as a thing of the past. Additionally, most pharmacies are not designed with adequate workspace to provide this service. Nonetheless, a section of patients with special needs do not have their medication needs met because of the unavailability of some commercially marketed drug products. This category of patients rely solely on compounded medications for their health needs [17].

With the incidence of conditions like congenital heart diseases becoming more prevalent in children [18-20], off-label use of medications is likely to be on the increase, and hence extemporaneous compounding. The aim of this study therefore was to determine the prevalence, scope and quality of extemporaneously compounded medicines in selected health facilities in Accra, Ghana.

The data generated from this study on compounding activities can be used to influence policies on the regulation of extemporaneous preparations in order to ensure drug safety and efficacy.

Materials and Method

Materials

Sodium hydrogen phosphate, Polysorbate 80, Sodium hydroxide, Tetrabutylammonium hydrogen sulphate, Di-basic potassium phosphate, 85% phosphoric acid, Glacial acetic acid, Methanol and Acetonitrile of High-Performance Liquid Chromatography (HPLC) grade were all purchased from Ginjoe Enterprise in Accra, Ghana. Nutrient agar and MacConkey agar were purchased from Greenland Medical Supplies LTD. Hydroxyurea, Furosemide, Spironolactone powders were purchased from Shanghai Yuanye Bio-Technology Co. Ltd

Methods

Study Design

A cross-sectional study design was employed for the first part of the study to determine the prevalence and scope of extemporaneously prescribed medications at the selected hospitals followed by a quality assessment of the three most prescribed products.

Study sites

Hospital A was selected as one of the research sites because it is one of the largest hospitals in Accra, Ghana. It has a wide range of specialized centres and served as a good site to gather prescriptions for diverse disease condition. It has more than 5 pharmacy outlets, serving prescriptions from the various departments within the hospital as well as from various health facilities nationwide.

Hospital B provides quality healthcare to one of the security services personnel and their families, civilian employees, ex-service personnel as well as the general public.

Hospital C is an ultra-modern Regional Hospital in the Greater Accra Region. It serves as a secondary referral center for all health facilities in the Greater Accra region and beyond.

Hospital D is a specialist children's hospitals in the west African sub region. It caters for the needs of maternal and child health care delivery. Children are among the population who usually benefit from extemporaneous products. This is one of the reasons why this hospital was chosen as one of the research sites.

Data collection

At the various sites, all prescriptions presented at the pharmacies were reviewed over a period of 4 weeks (1 month) per site. Information on only prescriptions requiring extemporaneous compounding were documented, collated, and analyzed. Patients were identified by codes instead of names, and relevant data such as the age, sex, drugs prescribed, and department of prescriber were recorded. This provided information on the types of extemporaneous medications prescribed, the frequency of prescribing and the population of patients in need of these medicines.

Data collected were then analyzed to determine the three most frequently compounded drugs to be used for the second part of the study. For the purposes of the study, prescriptions were acquired for the purchase of the most frequently prescribed extemporaneous medicines (hydroxyurea, spironolactone, and furosemide pediatric formulations). The products obtained were subjected to microbial contamination testing and content analysis at the Pharmaceutics and Microbiology laboratories in the School of Pharmacy, UG. Controls were phosphate buffer for the microbial contamination test and raw drug powder for the content analysis.

Quality analyses of products

Samples of the hydroxyurea, spironolactone and furosemide formulations (the most frequently compounded products) were obtained from the pharmacy upon the presentation of written requests by the researchers and sent to the laboratory for analysis. Three independent samples were obtained on different occasions for each product type selected.

DOI: https://doi.org/10.24926/iip.v15i1.5971

Content analysis of products

The actual drug content of all three compounds was determined using reverse phase HPLC methods described in the USP. The samples were prepared by dilution and filtration of the extemporaneous products due to the fact that all 3 formulations were suspensions. For spironolactone suspension, the HPLC method had the following chromatographic conditions: mobile phase comprised of 435 mL of water with 2.7 mL phosphoric acid and 50 mL methanol, combined with 515 mL of acetonitrile. An injection volume of 10 µL, a flow rate of 1.0 mL/min and a UV detector wavelength of 238 nm was used [21]. A Vertex Plus C18, 150 x 4 mm column was used for all analysis.

For furosemide suspension, the HPLC method had the following chromatographic conditions: mobile phase comprised of water, acetonitrile and glacial acetic acid in the ratio 165: 35: 2. An injection volume of 10 µL, a flow rate of 2.0 mL/min and a UV detector wavelength of 254 nm was used [22]. A Vertex Plus C18, 150 x 4 mm column was used for all analysis.

Hydroxyurea suspension was analyzed using a mobile phase comprising of buffer and methanol (8.5:1.5). The buffer was prepared by dissolving 1.7 g of tetrabutlyammonium hydrogen sulphate and 1.74 g of dibasic potassium phosphate (anhydrous) in 1L of water. The pH was adjusted to 5 with 85% phosphoric acid. An injection volume of 10 µL, a flow rate of 0.5 mL/min and a UV detector at wavelength of 214 nm were used [23]. The raw drug powder was the control for the content analysis.

Microbial contamination test

10 mL of each sample was diluted to 100 mL with phosphate buffer solution pH 7.2 and adjusted to a pH of 6 to 8. Where, the non-fatty product was insoluble in water, 1g/L of polysorbate 80 was added.

Using the pour plate method, six petri dishes of Nutrient Agar were prepared for each sample (n=3 for the sample and n=3 for the control) and incubated at 32°C to 35°C for 3 to 5 days.
In the petri dishes (plates) where growth was observed, the colony forming units per mL were determined [24]. A differential test was then performed for the identification of *Escherichia coli* using MacConkey Agar.

MacConkey agar was prepared and sterilized according to the manufacturer's instructions. The molten agar was stabilized at 45°C for 15 minutes on a water bath. 20 mL of the agar was septically transferred into corresponding plates, and then covered and left to set. The test was then performed by picking colonies of growth from the already incubated plates of nutrient agar using a flaming rod and streaking on the surface of the plates of the differential media. Each plate was then incubated at 37°C for 2 to 3 days and then observed. The control was phosphate buffer for the microbial contamination test.

Ethics

Ethical clearance for this study was obtained from the Ethics Committee of the College of Health Sciences, University of Ghana with protocol identification number: CHS-Et/M.5 – 4.8/2018-2019. Access to the various hospitals was obtained from directors of each study facility before data collection was done.

Reporting

Data were analyzed, described and presented using Excel, Descriptive Statistics and Graphical methods.

Results

Data was collated from 4 hospitals over a period of 4 weeks in each hospital. A total of 641 preparations were obtained from all four hospitals. 536 from hospital A, hospital B 83, hospital C and hospital D presented 15 and 7 respectively. Thus, in all the hospitals visited, extemporaneous prescribing was common.
The scope of medications and frequency of prescribing is represented in **Table 1**.

At the time of the study, only Hospital A was offering compounding services. Of the requests made, 536 preparations representing 99.6% of the total requests were prepared at the facility, with 2 preparations not being made, representing 0.4% of the requests. An average of 27 preparations were made per day, with some prescriptions bearing requests for more than one preparation. About 2% of the prescriptions were from health facilities outside hospital A, about 50.4% of the prescriptions had inscriptions of the prescriber's department, while about 47.6% of the requests had the designation of the prescriber not specified. The sex of patients prescribed with extemporaneous formulations is represented in **Figure 1**.

Of the preparations requested from Hospital A, 274 preparations, representing 50.9% were for male patients while 233 preparations, representing 43.3% were for female patients. 29 preparations, representing 5.4% had no indication of sex specified on the prescription. At Hospital B, 67% of the prescriptions received were for female patients and 33% for males. Hospitals C and D had the male population dominating their prescriptions with 57% and 60% respectively and 43% and 40% respectively for the females.

Percentages (frequencies) for age were calculated as a total of prescriptions from each facility (**Figure 2**). It was observed that about 62.6 % of the total prescriptions from Hospital A were for children between the ages of 1 month to 6 years. Almost 20% of prescriptions analyzed from hospital A did not have the ages of patients specified. Age data from hospital B were distributed as follows: ≤ 1Month (40%), 1 month > 2 years (13.30%), 2 years ≥ 6 years (26.60%) and > 6 years (20%). For Hospital D, the

DOI: https://doi.org/10.24926/iip.v15i1.5971

distribution was as, 1month > 2 years (85.71%), and > 6 years (14.29%). No prescriptions for children between the ages of 2 and 6 were recorded. For the Hospital C, the distribution is as ≤ 1month (67.47%), 1 month > 2 years (16.87%), 2 years ≥ 6 years (15.66%) and no prescription received for > 6 years.

To ascertain the quality of extemporaneous products from the hospitals, content analysis and microbial contamination tests were conducted. Results of these are presented in **Table 2**. The drug content (%) of the three batches of spironolactone suspensions acquired on separate days were 106%, 102% and 104% respectively. The United States Pharmacopeia (USP) specifies that the content should not be less than 90% and not more than 110% of the labeled amount. Thus, the samples of spironolactone met the requirements.

Furosemide suspension contained: 106%, 109% and 118% respectively of the labeled amount. Drug content of batch 3 was slightly higher than the specified amount in the USP.
Hydroxyurea suspensions procured contained: 110%, 96.8% and 100% of the labeled amount. Hydroxyurea oral suspension is not in the USP, thus, no specification was indicated. The amounts determined were however, not less than 90% and not more than 110%.

The USP indicates that for oral liquid dosage forms, the allowable number of microbial colonies should not be more than 10^2 (100). The microbial load of the first two batches of products acquired had between 20-40 colonies (table 3). With the exception of hydroxyurea suspension in batch 3, which had 11 colonies, all other products acquired after the work (batches 3 and 4) had single digit number of colonies. No *E. coli* was found in any of the batches acquired after a GMP promotion exercise (**Figure 3**). Thus, the extemporaneous products sampled from the hospital A during the period of study, met the USP requirements for quality. The other facilities were not offering compounding services at the time of the study.

Discussion

Relevant data on compounding activities is needed to inform policies and to rationalize and standardize the practice of compounding in order to ensure product quality and patient safety. In a number of countries in the developed world, data has been collated on extemporaneously compounded products and practices Unfortunately, data on compounded products in Ghana is inadequate, thus, this study sought to determine the prevalence on prescriptions for extemporaneous products from four (4) hospitals in Accra, to determine the scope and quality of compounded products.

By the end of the 4-week study-period in each of the 4 hospitals (coded Hospitals A, B, C and D) a total of 641 requests for 49 different extemporaneous products were recorded. The demographic profile of the prescription obtained from the various hospitals has been duly represented in table 1, figure 1 and figure 2.

In this study, 19.7% and 6.8% of requests received at the pharmacies at hospital A did not bear the age and sex of patients respectively. However, other prescriptions had adequate information to aid in a good data collection. Recording the age of the patient on the prescription helps the pharmacist identify errors and make interventions where necessary to avoid adverse effects or therapeutic failure [25].

The three other study sites which did not record any prescription written without patients' age or sex specified, utilized electronic methods of recording patient's medical information including prescribed drugs. It has been shown that using the computerized system makes it easy to retrieve patient information by medical personnel, in cases where any prescription component, such as patient's personal data has been omitted [26]. This to an extent, contributes to the reduction in prescribing errors as compared to the traditional ways of prescribing using the handwritten mode [27]. Unlike the in the adult population, a little error in the dosage of medications given to children has a greater risk of harm. In addition, paediatric prescribing also requires age and weight-related dose adjustments and other dosing calculations, which are less commonly encountered in adult prescribing [28].

With regard to the scope, this study found majority of the extemporaneously prescribed medications written for the management of chronic conditions, with the frequently prescribed products being hydroxyurea, furosemide and spironolactone. This is in line with a previous study [29]. This emphasizes their off-label use in paediatric populations in Ghana. Many studies have reported a rise in cases of congenital heart defects among children [18-20,30], and this probably accounted for the increased demand for furosemide and spironolactone suspensions among the pediatric population. At a University hospital in Brazil, furosemide and spironolactone suspensions were among the frequently compounded preparations [31], while in a study conducted in Nigeria by Orubu et al, these suspensions were recorded among the 10 frequently compounded medications [32].

Despite the demand, no age appropriate form of these drugs are currently available in Ghana for use in children, and liquid preparations for these three medications are not on the Ghana Essential Medicines List 2017 of the Ministry of Health [33]. With the increased demand for these formulations, the Ministry of Health may potentially consider their inclusion in the Ghana Essential Medicines List as with the WHO Essential Medicines List which has spironolactone and furosemide suspensions include [34].

Local pharmaceutical manufacturers could also consider the large-scale production of these medications to meet the ready

DOI: https://doi.org/10.24926/iip.v15i1.5971

market. More infants and children are being diagnosed with diseases that used to be common among the adult population. Without appropriate dosage forms of these medications, it is evident that extemporaneous compounding will be inevitable, despite the risks involved [35]. This emphasizes the need to ensure that medicines produced, though not licensed, are prepared with a great deal of care and expertise to ensure their quality, safety and efficacy.

Caffeine citrate was among the top prescribed medications at hospital B and hospital C. Most of their prescriptions were for patients in less than one-month-old age category, however no prescription for this age group was recorded for patients at the hospital D. This could be attributed to the fact that hospital D has no neonatal intensive care unit (NICU). Interestingly, Requests for caffeine citrate were not recorded from hospital A in this study. Further enquiries, which are not documented in this study revealed that, there were requests for the formulation, however, the pharmacy at the Children's Department of the hospital had the product in stock supplied by the manufacturing unit as bulk compounded formulations. Thus, they did not qualify as extemporaneous products.

Caffeine citrate is used routinely to reduce the frequency of apnea, intermittent hypoxemia, and also the incidence of broncho-pulmonary and patent ductus arteriosus in pre-term infants [36]. Caffeine citrate has recently been licensed in some countries for parenteral and oral administration, but the arbitrary preparation of caffeine citrate is still widely used because of its lower cost to the public health service [37]. With apnea, the most frequent cause in infants is idiopathic, though it is usually associated with tonsil/adenoidal hypertrophy which often coexists with obesity [38]. Amongst the drugs used for the treatment of apnea was caffeine citrate, the study also captured the use of aminophylline syrup as an alternative. It is however known that they cause adverse drug reactions such as tachycardia [39] especially if cardiovascular drugs like dobutamine and dopamine are administered concurrently.

Hospital B was the only hospital that had the majority of its patients requiring compounded products being females (figure 2). The other three hospitals had males as the majority. Similar outcomes were observed in previously conducted studies [40-42]. This has been attributed, partly to the fact that male infants are more vulnerable to both communicable and non-communicable diseases than the females, as the biological fragility of the male fetus is less understood and not widely known [43]. Additionally, biological studies reveal that XY chromosomes, which are present in males, are more susceptible to X-linked recessive disorders than are XX chromosomes, which are present in females; thus, male children are less likely to be healthy than their female counterparts [44].

Over the years, the pediatric population has been known to be the highest beneficiaries of extemporaneous preparations due to the lack of age-appropriate medications for their diverse health needs. In a study by Pereira et al., the neonatal intensive care unit (NICU) had the highest number of requests, followed by pediatrics [31]. A review article by Giam & McLachlan revealed that pediatric preparations were the frequently compounded drugs in 20 papers studied [2]. Similarly, in this study, children just after birth to 2 years of age were the highest beneficiaries of these medicines across the four study sites.

According to De Lima Costa et al., nearly all newborns are exposed to off-label medicines and about two-thirds to unlicensed drugs during their stay at the NICU [37]. The absence of specific paediatric formulations, is compensated for by the huge demand of extemporaneously prepared products [45]. It is therefore recommended that all facilities with NICU should have compounding areas in their pharmacies as this would save care-givers the time and cost of moving from one pharmacy to the other, in search of specialized medications.

From the studies performed the products analyzed were of acceptable quality. The drug content analysis revealed that all the preparations procured contained the drug specified on the label. Percent drug content of spironolactone suspension was within the range specified by the USP while the third batch of the furosemide suspension was a slightly above the specification. However, for hydroxyurea, although all three batches were between 90 and 110 percent of the labeled amount, there no specifications in the USP. Compounding pharmacies are not equipped to test for the quality of existing dosage forms on the shelves prior to using them as their starting materials for production. Usage of marketed sub-standard dosage forms has the tendency to affect the quality of extemporaneous products formulated. This emphasizes the importance of post market surveillance of medicines in pharmacies by Food and Drugs Authorities.

Compounded products are prone to microbial contamination either from the personnel preparing the products, the raw materials and equipment used or from the environment. There have been reported cases of morbidity with the use of compounded products [46]. For example, in 2002, about four patients developed meningitis after receiving epidural injections of methylprednisolone acetate, which lacked a preservative. This was prepared by a compounding pharmacy that was contaminated with *Exophiala dermatitidis* [35]. An analysis of 10 progesterone suppositories from 10 pharmacies chosen at random found that nine of these pharmacies did not meet the specifications set for approved products. Suppositories supplied by another pharmacy were contaminated with *Comamonas acidocerans* [35]. In Ghana, no such outbreaks are known to have been reported. However, extemporaneous compounding is speculated to be on the

DOI: https://doi.org/10.24926/iip.v15i1.5971

increase because of the increase in adult diseases among infants and children [18,47].

The results of the microbial assay revealed microbial contamination. Upon further test to identify the organisms present, *Escherichia coli* was identified in one of three repeats of the same sample. As this was not suggestive enough a second batch of products were procured from the facility on different day for analysis. Similarly, the differential test performed on the MacConkey agar was positive in one of three repeats of the same sample analyzed for *E. coli. Escherichia coli* is a gram negative, rod-shaped, non-spore forming bacteria responsible for different clinical manifestations of diarrhea [48,49]. The differential test using MacConkey agar is both growth-promoting and indicative for *E. coli* [24]. These pathogenic bacteria must not be present in medications.

Although the study at the point could not confirm the source of the pathogenic bacteria, the facility was notified, the unit was shut down for a period during which time decontamination was conducted and all Good Manufacturing practices promoted.
The study continued after this intervention. Batches obtained blindly from the unit for analysis, passed the USP test for microbial contamination. That is, no *E. coli* was identified in any of the samples and also the microbial load was all below 20 colony-forming units, which is far below the 100 colonies limit stated in the USP. It is important to mention that the unit of the hospital has subsequently, adopted the interventions and currently, conducts frequent laboratory tests to ensure the production of quality and safe medications. With the advances in technology, measures to improve quality and reduce errors such as: the integration of artificial intelligence technologies [50-52], 3-D printing technologies; and the employment of compounding robots [53] could be adopted.

Establishing the relevance of extemporaneous compounding in the health care delivery system will guide in the provision of appropriate workspaces within hospital pharmacies where such preparations need to be produced. This study has demonstrated that prescribing of extemporaneous products is very prevalent in the selected hospitals. Thus steps (availability of pharmacists and the needed infrastructure) must be taken to ensure that patients are able to obtain their medications. Alternatively, outsourcing compounding facilities can be set up across the country so that patients can acquire their medicines with ease, because currently, it is reported that some patients travel from all over the country to Accra and Kumasi (the 2 biggest cities in Ghana) just to obtain compounded drugs [17,29]. It is believed that licensed pharmacists are well trained and should be encouraged to utilize their compounding skills to prepare extemporaneous products on demand.

Guidelines regulating the practice of pharmaceutical compounding must also be put in place to ensure that no outbreak of infections due to extemporaneous products is recorded. The drug regulatory authority needs to come up with policies to conduct frequent site inspections and conduct product testing to ensure adherence to good manufacturing processes.

Conclusion

There still exists a population of patients who depend on compounding for their drug needs at the selected hospitals in Accra. The scope of extemporaneously compounded drugs revealed 49 different medications from various drug classifications. Three of the most frequently prescribed medications analyzed were of good quality. Establishing the prevalence of extemporaneous compounding in the health care delivery system will support the need for appropriate workspace and equipment within hospital pharmacies for compounding services. The results support the need for regulation of extemporaneous compounding to ensure that risks associated with compounding are minimal, as it is evident that compounding is a practice that will continue to exist. Finally, this study highlights the need for more research into developing age-appropriate medicines for pediatrics.

Data Availability

The data that support the findings of this study are available from the corresponding author [Henry Nettey], upon reasonable request.

Conflict of Interest

All authors have no conflict of interest to declare.

Funding

There are no funding sources to declare.

Notes on Contributors

GLAB, HN and IAK were involved in conceptualization of the research. EAA, MKA, OAS, DA, SAK, ADO, SO, PKE, JD, EAN, EO, and EL were involved in data collection and analysis. GLAB, HN, EAA, MKA and MFK conducted the research. Interpretation and drafting of manuscript were conducted GLAB, EAA, MKA, IAK, IJAG and HN. All authors reviewed, edited and approved the final manuscript.

Acknowledgement

The authors acknowledge Mrs. Elizabeth Bruce and staff of the Pharmacy Department of the KBTH, Staff of the Pharmacy Department of the 37 Military Hospital, Staff of the Pharmacy Department of the Greater Accra Regional Hospital, Dr. Nana Yaa Nyarko and Staff of the Pharmacy Department of the Princess Marie Louise Children's Hospital.

List of Abbreviations

ADR – Adverse Drug Reactions
API - Active Pharmaceutical Ingredient
CHDs - Cardiovascular Heart Diseases
CHS - College of Health Sciences

FDA - Food and Drugs Authority
GMP - Good Manufacturing Practices
HPLC – High Performance Liquid Chromatography
KATH - Komfo Anokye Teaching Hospital
KBTH - Korle Bu Teaching Hospital
NICU – Neonatal Intensive Care Unit
NMT- Not More Than
UK- United Kingdom
UG – University of Ghana
USA- United States of America
USP- United States Pharmacopoeia
UV- Ultraviolet
WHO- World Health Organization

Dislaimer: The statements, opinions, and data contained in all publications are those of the authors.

References

1. Belayneh A, Tessema Z. A systematic review of the stability of extemporaneous pediatric oral formulations. Sci World J. 2021; 2021: 8523091. 2021.

2. Giam JA, mclachlan AJ. Extemporaneous product use in paediatric patients: a systematic review. International journal of pharmacy practice. 2008;16(1):3-10.

3. Glass BD, Haywood A. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. J Pharm Sci. 2006;9(3):398-426.

4. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs in R&d. 2013;13:1-8.

5. Riley R. The regulation of pharmaceutical compounding and the determination of need: balancing access and autonomy with patient safety. 2004;

6. Heitman T, Day A, Bassani AS. Pediatric compounding pharmacy: taking on the responsibility of providing quality customized prescriptions. Children. 2019;6(5):66.

7. Esquerrà NS, Carrizosa EL, Casas MB, Martínez AF, Agustí MB, Sague LV, Pla AP. Analysis of paediatric pharmaceutical compounding in a hospital pharmacy department. European journal of hospital pharmacy: science and practice. 2012;19(2):216-216.

8. Simon AK, Hollander GA, mcmichael A. Evolution of the immune system in humans from infancy to old age. Proceedings of the Royal Society B: Biological sciences. 2015;282(1821):20143085.

9. Raza MA, Yao BF, Shi HY, Xu HY, Hao GX, Van Den Anker J, Zhao W. Optimal dose of meropenem for the treatment of neonatal sepsis: dosing guideline variations and clinical practice deviations. British journal of clinical pharmacology. 2022;88(7):3483-3489.

10. Helin-Tanninen M. Extemporaneous preparation of paediatric oral formulations: studies conducted in nifedipine powders, capsules and sunpensions in a hospital pharmacy. 2010;

11. Yusuff KB. Extent of extemporaneous compounding and pattern of prescribing and use of extemporaneous medicines in a developing setting. Journal of pharmaceutical health services research. 2019;10(2):255-260.

12. Kiseļova O, Mauriņa B, Šidlovska V, Zvejnieks J. The extent of extemporaneous preparation and regulatory framework of extemporaneous compounding in Latvia. Medicina. 2019;55(9):531.

13. Jackson M, Lowey A, Committee NPQA. Handbook of extemporaneous preparation: a guide to pharmaceutical compounding. 2010.

14. Reynolds KA, Hellquist K, Ibrahim SA, Kang BY, Poon E, Alam M. State medical board regulation of compounding in physician offices. Archives of dermatological research. 2022;314(4):363-367.

15. Vivian JC. New rules for compounding drug products. US Pharm. 2014;39(2):40-42.

16. Minghetti P, Pantano D, Gennari CGM, Casiraghi A. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy. 2014;117(3):328-333.

17. Ankrah DN, Turkson JT, Boateng EB, Amegavie FT, Bruce E. Insufficient access to oral paediatric medicines in Ghana: A descriptive study. BMC health services research. 2016;16:1-5.

18. Amuna P, Zotor FB. Epidemiological and nutrition transition in developing countries: impact on human health and development: The epidemiological and nutrition transition in developing countries: evolving trends and their impact in public health and human development. Proceedings of the nutrition society. 2008;67(1):82-90.

19. Daar AS, Singer PA, Leah Persad D, et al. Grand challenges in chronic non-communicable diseases. Nature. 2007;450(7169):494-496.

20. Biritwum R, Gyapong J, Mensah G. The epidemiology of obesity in Ghana. Ghana medical journal. 2005;39(3):82.

21. USP-NF. Spironolactone. Official Monographs. United States pharmacopeia; 2000;29.

22. USP-NF. Furosemide. Official monographs. United States pharmacopeia; 2007.

23. Allotey-Babington GL, Seaneke OA, Williams AA, Asiedu EA, Amuakwa MK, Nettey H. Hydroxyurea granules for the management of sickle cell disease in children. Scientific African. 2022;16:e01271.

24. Gholizadeh-Hashjin A, Hallaj-Nezhadi S. Quality control of non-sterile drug product according to United States' pharmacopeia instruction. Iranian journal of medical microbiology. 2019;13(5):321-345.

25. Carson-Stevens A, Edwards A, Panesar S, Parry G, Rees P, Sheikh A, Donaldson L. Reducing the burden of iatrogenic harm in children. The Lancet. 2015;385(9978):1593-1594.

26. Atasoy H, Greenwood BN, mccullough JS. The digitization of patient care: a review of the effects of electronic health records on health care quality and utilization. Annual review of public health. 2019;40:487-500.

27. Yang J-h, Liao Y-f, Lin W-b, Wu W. Prescribing errors in electronic prescriptions For outpatients intercepted by pharmacists and the impact of prescribing workload On error rate in a Chinese tertiary-care women and children's hospital. BMC health services research. 2019;19:1-11.

28. Organization WHO. Promoting safety of medicines for children. World Health Organization; 2007.

29. Mbabila DB. Assessing the stability of paediatric oral formulations prepared at Komfo Anokye teaching hospital (KATH). 2016.

30. Chelo D, Nguefack F, Menanga AP, Um SN, Gody JC, Tatah SA, Ndombo POK. Spectrum of heart diseases in children: an echocardiographic study of 1,666 subjects in a pediatric hospital, Yaounde, Cameroon. Cardiovascular diagnosis and therapy. 2016;6(1):10.

31. Pereira acds, Miranda ES, Castilho srd, Futuro DO, Teixeira LA, Paula grd. Magistral drugs in hospitalized newborns and children. Revista paulista de pediatria. 2016;34:403-407.

32. Orubu ESF, Okwelogu C, Opanuga O, Nunn T, Tuleu C. Access to age-appropriate essential medicines: a retrospective survey of compounding of medicines for children in hospitals in Nigeria and implications for policy development. Health policy and planning. 2017;32(2):225-235.

33. Ministry of health (GNDP) Ghana. Essential Medicines List (2017).

34. Organization WHO. World Health Organization model list of essential medicines: 21st list 2019. 2019.

35. Guharoy R, Noviasky J, Haydar Z, Fakih MG, Hartman C. Compounding pharmacy conundrum:"we cannot live without them but we cannot live with them" according to the present paradigm. Chest. 2013;143(4):896-900.

36. Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. World journal of clinical pediatrics. 2015;4(4):81.

37. Costa htmdl, Costa TX, Martins RR, Oliveira AG. Use of off-label and unlicensed medicines in neonatal intensive care. Plos one. 2018;13(9):e0204427.

38. Kondamudi NP, Khetarpal S. Apnea in children. 2017;

39. Balain M, Johnson K. Neonatal abstinence syndrome: the role of breastfeeding. Infant. 2014;10(1):9-13.

40. Ameyaw E, Rhule G. Spectrum of diseases seen on neonatal ward at komfo Anokye teaching hospital, kumasi, Ghana. Pediatr infect Dis. 2017;2(52)

41. Hassanzadeh Bashtian M, Armat MR, Khakshour A. Assessment of the recorded causes of neonatal hospitalization and the related factors in neonatal wards and NICUs in Bojnord. Iranian Journal of Neonatology. 2014;5(2):21-24.

42. English M, Ngama M, Musumba C, et al. Causes and outcome of young infant admissions to a Kenyan district hospital. Archives of disease in childhood. 2003;88(5):438-443.

43. Kraemer S. The fragile male. Bmj. 2000;321(7276):1609-1612.

44. Waldron I. Sex differences in illness incidence, prognosis and mortality: issues and evidence. Social science & medicine. 1983;17(16):1107-1123.

45. Ali AA, Charoo NA, Abdallah DB. Pediatric drug development: formulation considerations. Drug development and industrial pharmacy. 2014;40(10):1283-1299.

46. L.M C. Filling the gap : An overview of the role and risks of pharmacy compounding historically , what has been the role of compounding who oversees and regulates compounding pharmacies ? . 2012:1-9.

47. Kouame BD, n'guetta-Brou IA, Kouame GSY, et al. Epidemiology of congenital abnormalities in West Africa:

results of a descriptive study in teaching hospitals. In Abidjan: Cote d'Ivoire. African journal of paediatric surgery. 2015;12(1):51-55.

48. Clausen CR, Christie DL. Chronic diarrhea in infants caused by adherent Enteropathogenic Escherichia coli. The Journal of Pediatrics. 1982;100(3):358-361.

49. Robins-Browne RM, Hartland EL. Escherichia coli as a cause of diarrhea. Journal of gastroenterology and hepatology. 2002;17(4):467-475.

50. Huanbutta K, Burapapadh K, Sriamornsak P, Sangnim T. Practical application of 3D printing for pharmaceuticals in hospitals and pharmacies. Pharmaceutics. 2023;15(7):1877.

51. Melnyk LA, Oyewumi MO. Integration of 3D printing technology in printed medicine. 2021;4:100035.

52. Srivastava V, Parveen B, Parveen R. Artificial intelligence in drug formulation and development: applications and future prospects. Current drug metabolism. 2023;24(9):622-634.

53. Yang C, Ni X, Zhang L, Peng L. Intravenous compounding robots in pharmacy intravenous admixture services: A systematic review. Medicine. 2023;102(19):e33476.

Table 1: Scope and frequency of prescribing of medications at the various hospitals

Scope of Extemporaneous prescribing at the various hospitals

	Frequency (%)			
Drugs	**Hospital A**	**Hospital B**	**Hospital C**	**Hospital D**
Acyclovir suspension	0.19			
Allopurinol suspension	0.19			
Amitriptyline suspension	0.19		1	
Baclofen suspension	0.56			
Caffeine citrate syrup		40	54	
Capecitabine suspension	0.19			
Captopril suspension	0.19			
Carbamazepine suspension	0.37			
Carbimazole suspension	0.19			
Ciprofloxacin suspension	0.19			
Clobazam suspension	0.93			
Clonazepam suspension	3.16			
Dexamethasone suspension	0.37			
Digoxin suspension	0.19			
Enalapril suspension	0.37			
Fluconazole suspension	0.19			
Folic acid suspension	1.86		25	
Folinic acid suspension	0.19			
Furosemide suspension	18.96	13	2	43
Hydroxyurea suspension	33.09		6	
Imatinib suspension	0.19			
Itraconazole suspension	0.37			
Lamutrigine	0.74			
Levamisole	0.19			
Levetiracetam	1.12			
Lorazepam suspension	0.19			
Metoclopramide suspension	0.19			
Nifedipine suspension	0.56			
Nitrazepam suspension	0.19			
Nitrofurantoin suspension	4.28			
Paracetamol suspension	0.19			
Pencillin V suspension	0.74			
Phenobarbitone suspension	0.93		1	14
Phenytoin suspension	0.19		6	

Podophylin tincture	0.19			
Prednisolone suspension	0.74	7		
Propranolol suspension	5.20			
Pyridostigmine suspension	0.37			
Pyrimethamine suspension	0.19			
Risperidone suspension	0.37			
Saline 3% (hypertonic)	0.19			
Salicylic ointment	0.19			
Sildenafil suspension	0.37			
Sodium Valporate suspension	0.37	40	1	
Spironolactone suspension	18.4		2	43
Sulphadiazine suspension	0.19			
Ursodeoxycholic acid suspension	0.19			
Vit B6 suspension	0.93			
Zinc suspension	0.19			
Total number of products	**536**	**15**	**83**	**7**
Types of medication	**49**	**4**	**9**	**4**

Table 2: Content Analysis of frequently compounded products

Labelled amount of product	Batch 1 n=3		Batch 2 n=3		Batch 3 n=3		USP specified amount
	Analyzed amount	Drug content (%)	Analyzed amount	Drug content (%)	Analyzed amount	Drug content (%)	
Furosemide 10mg/2.5mL	10.6 mg/ 2.5mL	106	10.9 mg/ 2.5mL	109	11.8 mg/ 2.5 mL	118	NMT 110 and NLT 90
Hydroxyurea 250mg/5 mL	275 mg/ 5 mL	110	242 mg/ 5mL	96.8	250 mg/ 5mL	100	-
Spironolactone 10mg/2.5mL	10.6 mg/ 2.5 mL	106	10.2 mg/ 2.5 mL	102	10.4 mg/ 2.5 mL	104	NMT 110 and NLT 90

Table 3: Microbial contamination assay of frequently compounded products

Products	Batch 1 n=3		Batch 2 n=3		Intervention	Batch 3 n=3		Batch 4 n=3	
	Microbial colonies	*E. coli*	Microbial colonies	*E. coli*		Microbial colonies	*E. coli*	Microbial colonies	*E. coli*
Furosemide	32	0	27	1 of 3	Collaborated with facility for enhanced cleaning and promotion of good manufacturing practices	9	0	9	0
Hydroxyurea	27	1 of 3	38	0		11	0	4	0
Spironolactone	22	0	21	0		7	0	5	0

DOI: https://doi.org/10.24926/iip.v15i1.5971

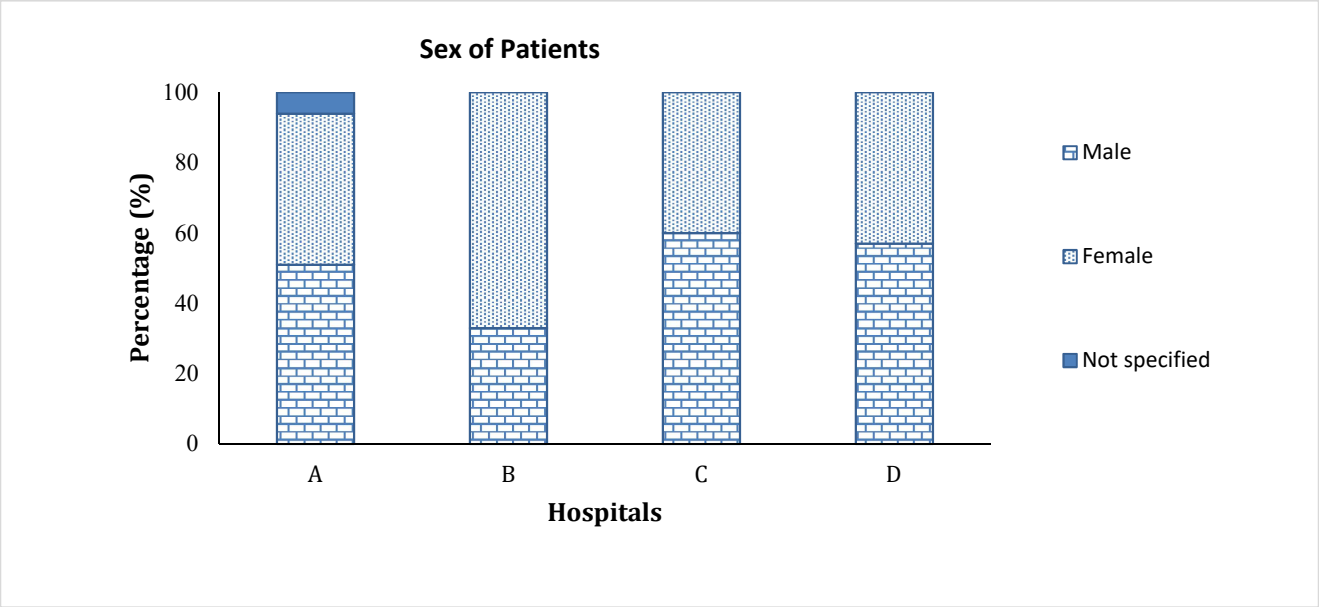


Figure 1: Graph showing sex distribution of patients.

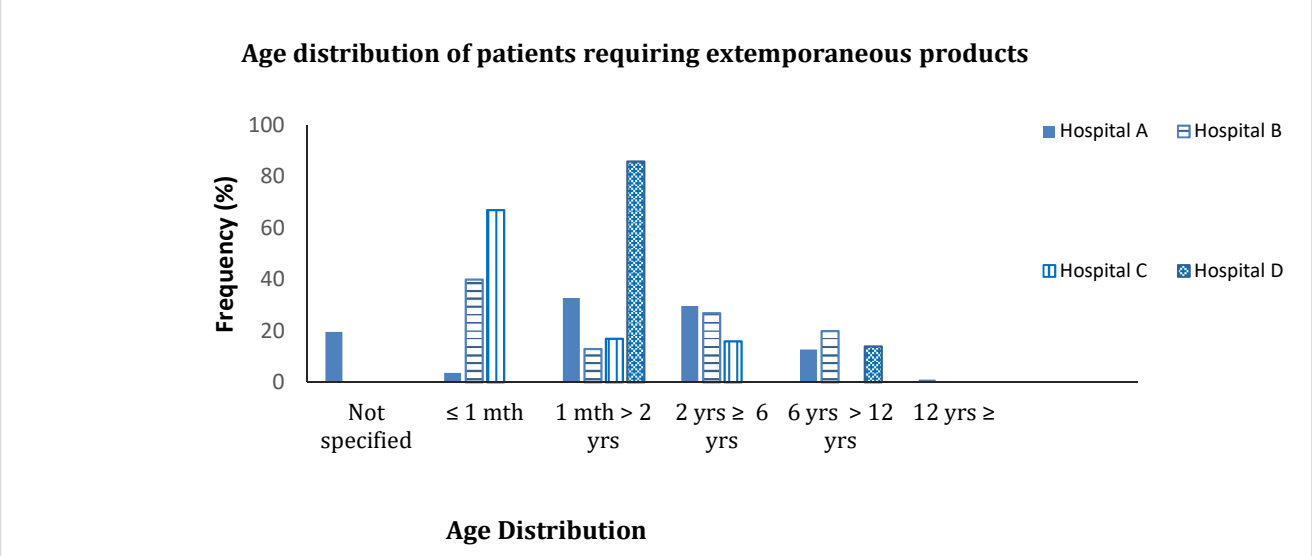
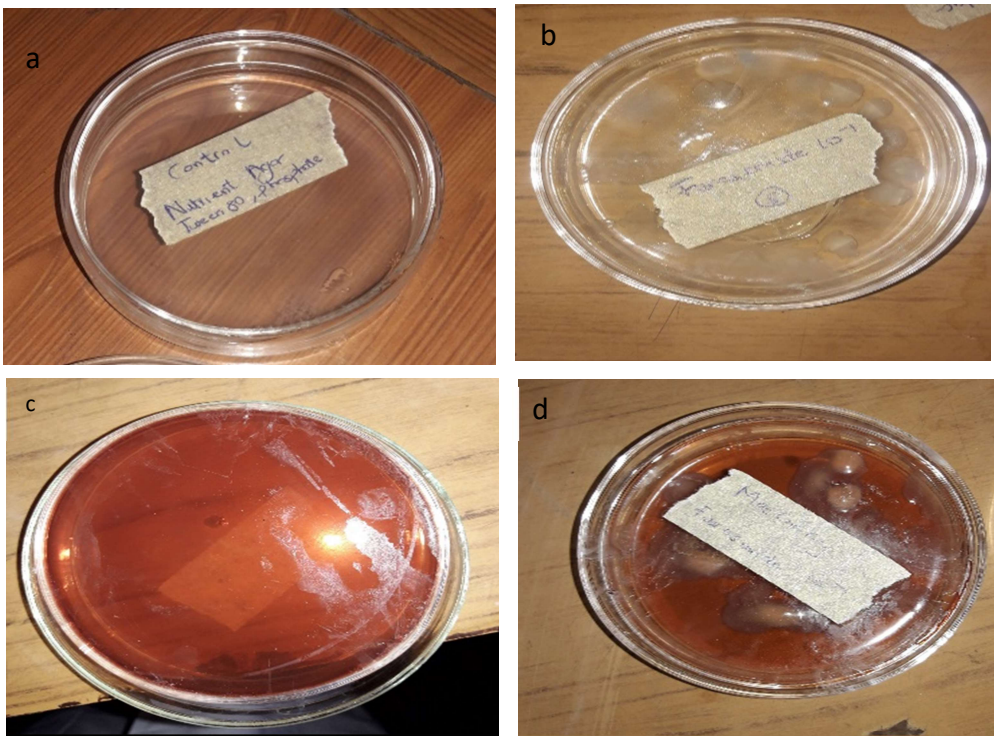


Figure 2: Graph showing age distribution of patients who were prescribed extemporaneous products.

Figure 3: Pictorial Images of microbial contamination test.



a - Control plate of nutrient agar showing no growth
b - Sample plate of nutrient agar showing microbial growth of furosemide.
c - Control plate of MacConkey agar showing no growth.
d - Plate of MacConkey agar showing growth indicating the presence of *Escherichia coli* in the sample.