PRESCRIPTION ANALYSIS FOR EXTEMPORANEOUS PREPARATIONS IN HOSPITAL PHARMACIES OF SOUTHERN NIGERIA

Today community and hospital pharmacies worldwide (including Nigeria) experience an increased demand for extemporaneous preparations. Due to “per body weight” dosing system, difficulty in swallowing, frailty in organs of metabolism and unavailability of required dosage forms, the reconstitution/tailoring of medications to individual patients needs has become necessary. In Nigeria most (>95%) of the extemporaneously prepared medications are oral dosage forms. It is a common practice for these medications to be prepared from a commercially available oral solid dosage form by crushing tablets or mixing contents with a dispersion medium (base/vehicle). The aim of the work was to analyse frequently compounded prescriptions in south-south geopolitical region of Nigeria, bases/vehicles used in compounding and stability study concerns of compounded preparations. For this purpose a survey of prescriptions in hospital pharmacies in the south-south geopolitical region of Nigeria was conducted. The prescriptions that required extemporaneous preparation were selected and sorted into active pharmaceutical ingredients (APIs), doses, regime and duration of treatment. Most prescribed preparations that required compounding include antibiotics (24.9%) and drugs indicated for cardiovascular diseases (60.0%). While the treatment duration prescribed for extemporaneous preparations ranged from two days to a month, the most recurring duration was one week. Syrups of ascorbic acid and Vitamin B Complex were occasionally used as bases for compounding, but stability study of extemporaneous preparations made from these medicated syrups is yet to be conducted in Nigeria. APIs as part of commercial drugs were mostly (92.9%) used in compounding. Stability study of extemporaneous preparations in Nigeria is an urgent problem that needs to be resolved.

Key words: Extemporaneous preparations; active pharmaceutical ingredient; base/vehicle; survey; syrups; stability

STATEMENT OF THE PROBLEM

Today extemporaneous preparations find greater use in community and hospital pharmacies worldwide, including Nigeria. This is chiefly due to reconstitution/tailoring of medications to individual patients needs either by reason of “per body weight” dosing system, difficulty in swallowing, frailty in organs of metabolism or unavailability of required dosage forms. In Nigeria most (>95%) of the extemporaneously prepared medications are oral dosage forms.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

In Nigeria, USA, Australia, Malaysia and some European countries, it is a common practice for these medications to be prepared from a commercially available oral solid dosage form by crushing tablets or mixing contents with a dispersion medium (base/vehicle) [2, 9, 12-16]. According to the British Pharmaceutical Codex, medicated and flavouring syrups provide a convenient form of stock solution of certain drugs for use in extemporaneous preparations [3].

IDENTIFICATION OF ASPECTS OF THE PROBLEM UNSOLVED PREVIOUSLY

While other nations have progressed with finding solutions to this not so recent development, stakeholders in Nigeria are yet to give the much needed attention. For stability studies to be undertaken for compounded preparations, one must sort out the local needs of the region in terms of frequently prescribed medications, cost and availability of components of extemporaneous preparations etc.
OBJECTIVE STATEMENT OF THE ARTICLE

The aim of the work was to analyse frequently compounded prescriptions in south-south geopolitical region of Nigeria, stability study concerns of compounded preparations and bases/vehicles used in compounding.

PRESENTATION OF THE MAIN MATERIAL OF THE RESEARCH

The study was conducted using prescriptions obtained from the University of Port-Harcourt Teaching Hospital, Rivers State (UPTH) and another major hospital in the southern part of Nigeria, which preferred to remain anonymous (XGH). A combination of closed and open-ended format questionnaires, distributed to pharmacists in the UPTH, was used to obtain information on APIs and vehicles/bases used in compounding.

A total of 1157 relevant prescriptions from the period of January 2014 – September 2015 were assessed for the study. Hospital XGH allowed access to information on compounded prescriptions under the conditions of anonymity but did not give permission to conduct a questionnaire survey. A total of 42 out of 43 questionnaires distributed to compounding pharmacists were returned, representing a 97.7% response rate of the sample size. Mean scores were determined for each item and the summarized data presented below.

Frequently compounded medications in the southern part of Nigeria. These include active pharmaceutical ingredients (APIs) used in gastroenterological (cimetidine, ranitidine, omeprazole), cardiovascular (amlodipine, captopril, digoxin, enalapril) and antimicrobial (ciprofloxacin) diseases; diuretics (furosemide, spironolactone, hydrochlorothiazide); antineoplastics (hydroxyurea); vitamins (pyridoxine); antituberculosis (rifampicin, isoniazid); opioid analgesics (tramadol); urinary anti-infectives (nitrofurantoin) and anti-HIV (nevirapine).

From the results, ciprofloxacin and spironolactone are the most frequently compounded prescriptions for XGH and UPTH respectively. These drugs are indicative of infectious diseases and ailments associated with the cardiovascular system. Other frequently compounded drugs include digoxin, hydro-
**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fixed dose (tab/caps)</th>
<th>Required (prescribed) dose</th>
<th>Regime</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>500 mg/250 mg</td>
<td>80 mg, 47.2 mg</td>
<td>Tds x 1/52</td>
<td>2-12/12,</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>10 mg/5 mg/2.5 mg</td>
<td>3.6 mg</td>
<td>Od x 2/52</td>
<td>8-10 years</td>
</tr>
<tr>
<td>Captopril</td>
<td>50 mg/25 mg/12.5 mg</td>
<td>1 mg, 0.4 mg</td>
<td>Tds x 5/7, Bd x 1/52</td>
<td>2-7/12, Neonate</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100/50/25/10 mg</td>
<td>1.4 mg</td>
<td>Qds x 2/52</td>
<td>9/7, 1-5/12</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>800 mg/400 mg/200 mg</td>
<td>29.5 mg, 67 mg</td>
<td>Bd x 1/52, Tds x 1/52</td>
<td>2-8/12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg</td>
<td>150 mg, 90 mg, 52 mg, 45 mg, 105 mg</td>
<td>Bd x 5/7, Bd x 1/52, Bd x 2/52, Bd x 10/7, Bd x 2/7</td>
<td>2-18/12, 3 years</td>
</tr>
<tr>
<td>Digoxin</td>
<td>250 mcg</td>
<td>260/130/130/65 mg, 80/40/40/20 mg, 240 µg</td>
<td>Stat/8hrs/16hrs/bd, Bd x 1/52</td>
<td>2-7, 3-6/12, 8 years</td>
</tr>
<tr>
<td>Frusemide</td>
<td>40 mg/20 mg</td>
<td>4 mg, 8 mg</td>
<td>Bd x 1/52</td>
<td>Neonate, 2-5/12</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>50 mg/25 mg/12.5 mg</td>
<td>8 mg, 16.2 mg, 20.2 mg</td>
<td>Bd x 1/52, Od x 1/52</td>
<td>12-19/12, 9 years</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>500 mg</td>
<td>240 mg, 250 mg</td>
<td>Od x 2/52</td>
<td>12-17/12, adult</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300 mg/100 mg</td>
<td>80 mg</td>
<td>Od x 1/52</td>
<td>4-6 years</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg</td>
<td>15 mg, 36 mg</td>
<td>Bd x 2/52</td>
<td>1-3/12</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>200 mg/100 mg/50 mg/25 mg</td>
<td>12.5 mg</td>
<td>Od x 2/52</td>
<td>9/7</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>300 mg</td>
<td>26 mg</td>
<td>Bd x 1/52</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>300 mg/150 mg</td>
<td>120 mg</td>
<td>Od x 1/52</td>
<td>4-6 years</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100 mg/50 mg/25 mg</td>
<td>10.2 mg, 11.8 mg, 20.2 mg, 5.2 mg</td>
<td>Od x 1/52, Bd x 1/52, Bd x 2/52</td>
<td>3/12, 8/12, 19/12, 2/52</td>
</tr>
</tbody>
</table>

chlorothiazide, furosemide, acetazolamide and captopril.

At XGH (Tab. 2), the most recurring duration (regime) for which the compounded drugs were prescribed was one week while the maximum duration was two weeks. In UPTH (Tab. 3), the most recurring duration was also one week while the maximum duration was for one month.

It was observed that most of the extemporaneous preparations in UPTH are made using APIs from commercial drugs. Although imported bases/vehicles (ORA-Plus, ORA-Sweet etc.) are used, pharmacists admit to have used (one time or the other in their years of practice) locally available medicated syrups (LAMS) as dispersion medium for prescribed active components. Compounding in Nigeria is done majorly in hospital pharmacies. This writer and majority of pharmacists are not aware of any stability tests on extemporaneous formulations conducted in/for the country.

**Stability concerns.** Hitherto, there hasn’t been a stability study of extemporaneous preparations made from these medicated syrups in Nigeria. Syrups of ascorbic acid and Vitamin B Complex have been occasionally (frequently in some cases) used [1] although stability tests haven’t been conducted or made available.

Some internationally published stability tests have been conducted using APIs from specific commercial drugs [4, 7, 15, 16]. However, one cannot guarantee that all compounding pharmacists (worldwide) make use of those APIs from specific pharmaceutical firms with which stability test was conducted. Rather, there is a greater possibility that APIs of commercial drugs used by most compounding pharmacists may be different from those used in successfully carried out and published stability data.

Secondly, different pharmaceutical firms use different excipients in producing one and the same class of drugs [6]. Absence of a standard recipe and APIs (of commercial fixed-dose drugs) of specific pharmaceutical firms paves the way for use of different APIs and dispersion media of which different excipients may constitute. This produces different risks in stability [8, 19] and consequently, increase uncertainty in allocated beyond-use-dates (BUDs).

The APIs generally used for compounding in hospital pharmacies in Nigeria are commercially available fixed-dose drugs (tablets, capsules, injections etc.). Pure substances (as APIs) for compounding are rarely purchased. All drugs, extemporaneously prepared in the hospitals were packaged in well closed amber bottles to prevent photolabile degradation [9]. Patients were advised to store at recommended temperatures and away from children’s reach. Suspensions were labelled “shake well before use”.

**Prospective substitutes.** Not all hospital pharmacies in the country use imported vehicles (IMPVs) such as ORA-Sweet, ORA-Sweet SP, ORA-Plus, Cherry syrup etc. in compounding. During shortage of supply, patients won’t be turned away [5]; hospital pharmacies may have to improvise by using alternative vehicles for dispersing prescribed APIs. This leaves the option of locally readily available syrups (LAMSs) such as medicated syrups of ascorbic and Vitamin B complex. It is imperative that such tests be carried out for these syrups since they have occasionally been used. The results of these tests will provide assured BUDs. The problem of

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**Table 3**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fixed dose (tab/cap)</th>
<th>Required (prescribed) dose</th>
<th>Regime</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>500 mg/250 mg</td>
<td>12.5 mg, 20 mg, 25 mg, 100 mg,</td>
<td>Bd x 1/5, Bd x 2/5, Bd x 1/2</td>
<td>2-15/12, 3 years</td>
</tr>
<tr>
<td>Captopril</td>
<td>50 mg/25 mg/12.5 mg</td>
<td>3.125 mg</td>
<td>Bd x 5/7, Bd x 1/5, Bd x 1/2</td>
<td>2-9/12, 1 year</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg</td>
<td>70 mg, 100 mg, 150 mg, 160 mg, 170 mg</td>
<td>Od x 3/7</td>
<td>7-12/12, 2 years, 4 years</td>
</tr>
<tr>
<td>Enalapril</td>
<td>20 mg/10 mg/5 mg</td>
<td>3.125 mg</td>
<td>Bd x 1/5, Bd x 1/2</td>
<td>2/12, 3 years</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>100 mg/50 mg/25 mg</td>
<td>20 mg, 30 mg, 40 mg</td>
<td>Bd x 1/5, Td x 1/5, Od x 1/5, Nocte x 1/5</td>
<td>1-9/12, 2 years, 11 years</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40 mg/20 mg</td>
<td>10 mg</td>
<td>Od x 1/5</td>
<td>4-10 years</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100 mg/50 mg/25 mg</td>
<td>3.125 mg</td>
<td>Bd x 1/5, Bd x 2/5, Bd x 1/2</td>
<td>2-3/12</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100 mg/50 mg</td>
<td>25 mg</td>
<td>Bd x 5/7</td>
<td>4-7 years</td>
</tr>
</tbody>
</table>

Key: 3/7 – three days, 3/52 – three weeks, 3-4/12 – three to four months, Od – once daily, Bd – twelve hourly, Tds – eight hourly, Qds – six hourly, Nocte – at night.
palatability of compounded formulation is significantly alleviated with the sweet taste of LAMSs which masks unpleasant taste of APIs.

Cost Benefits of Prospective Alternatives. The average cost of the LAMSs (60-100 ml) is within the range of $0.7-$0.8 (United States Dollars), while cost for 100ml equivalent of ORA-Plus, ORA-Sweet, ORA-Sweet SF and BLEND (excluding shipment) in the United States goes for $4.10.

Market price of 16 oz IMPVs (473.176 ml) is $19.41 100 ml (3.38 oz) of IMPV = $4.10

The costs of IMPVs exceed the LAMSs 4.5 times, excluding shipment/mark-up. Considering the cost benefits and availability of LAMSs, they serve as potential alternatives to IMPVs.

For a population with 30 % below the poverty line of $1.25 power purchasing parity (PPP) [20], affordability of drugs is a significant factor in total therapeutic outcome.

At XGH, the most frequent duration (regime) for which the compounded drugs were prescribed was one week while the maximum duration was two weeks. In UPTH, the most frequent duration is also one week while the maximum duration was one month. If these LAMSs could maintain the integrity of the APIs for a month, they will serve as a readily available substitute. In a situation where the APIs are stable for two weeks or 10 days, the patients could be asked to come for a refill when the conservative BUD approaches.

Most of the prescriptions have an average duration of seven to ten days (Tab. 2). This is to help physicians assess response to treatment or reduction of disease indicators. Also, it encourages adherence/compliance to treatment, which becomes difficult when prescription is for a long duration [18]. Nigerian parents are not comfortable either taking their children for prolonged visits or leaving their children in hospitals beyond two weeks. Offentimes alternative solutions to health problems are sought after [7, 10, 17]. They include spiritual (prayers and prayer houses), local massage therapists, proven and unproven herbal (non-orthodox) formulations sold by vendors.

Based on the average duration in table 2 and 3, initial/low-cost stability tests could be conducted for up to 40 days maximum, for which BUDs could be established.

CONCLUSIONS AND PROSPECTS FOR FURTHER RESEARCH

Based on the analysis of frequently compounded prescriptions, ciprofloxacin, spironolactone, digoxin, hydrochlorothiazide, acetazolamide, furosemide and captopril constitute majority of extemporaneous medications prepared in these hospitals. The APIs used for compounding in hospital pharmacies in southern Nigeria are commercially available fixed-dose drugs (tablets, capsules and injections).

Oral dosage forms make up more than 99 % of extemporaneous prescriptions analysed in these hospitals. Imported vehicles/bases such as ORA-Sweet, ORA-Sweet SF, ORA-Plus and Cherry syrup, used as the dispersion media, are more expensive than the proposed cheaper locally available medicated syrups. In order to reduce cost of these extemporaneously prepared medications the vehicles/bases have to be replaced by cheaper locally available medicated syrups.

Where successful stability studies have been conducted using APIs of commercially available drugs (of specific pharmaceutical firms), such APIs should be preferably used in formulation of compounded preparations; as APIs of different firms may be constituted of different excipients which may not produce the same shelf-life. The same applies when and if proposed medicated syrups pass stability tests. It is pertinent that government, hospital and all stakeholders in the Nigeria pay more attention to funding for stability tests and full equipment of compounding laboratories.

REFERENCES


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АНАЛИЗ РЕЦЕПТУР ЄКСТЕМПОРАЛЬНИХ ЛЕКАРСТВЕННИХ СРЕДСТВ В ГОСПИТАЛЬНИХ АПТЕКАХ ПІВДЕННОЇ НІГЕРІЇ

На теперішній час екстемпоральні лікарські засоби користуються все більшим попитом і виготов-ляються у комунальних і госпітальних аптеках всього світу, в тому числі Нігерії. Це пояснюється головним чином потребою індивідуального приготування лікарських засобів через вагу тіла, підбір доzuвання, труднощі при ковтанні, недоліки обміну речовин або відсутність необхідних лікарських форм. У Нігерії більшість (> 95 %) екстемпоральних лікарських засобів є пероральними лікарськими формами. Звичайною практикою для цих лікарських засобів є приготування з комерційно доступних таблеток або змішування вмісту з дисперсною речовиною. У Нігерії більшість (> 95 %) екстемпоральних лікарських засобів є пероральними лікарськими формами. Звичайною практикою для цих лікарських засобів є приготування з комерційно доступних таблеток або змішування вмісту з дисперсною речовиною. У Нігерії більшість (> 95 %) екстемпоральних лікарських засобів є пероральними лікарськими формами. Звичайною практикою для цих лікарських засобів є приготування з комерційно доступних таблеток або змішування вмісту з дисперсною речовиною.