Pattern of adverse drug reactions reported by the community pharmacists in Nepal

ABSTRACT
The pharmacovigilance program in Nepal is less than a decade old, and is hospital centered. This study highlights the findings of a community based pharmacovigilance program involving the community pharmacists.

Objectives: To collect the demographic details of the patients experiencing adverse drug reactions (ADR) reported by the community pharmacists; to identify the common drugs causing the ADRs, the common types of ADRs; and to carry out the causality, severity and preventability assessments of the reported ADRs.

Methods: The baseline Knowledge-Attitude-Practices (KAP) of 116 community pharmacists from Pokhara valley towards drug safety was evaluated using a validated (Cronbach alpha=0.61) KAP questionnaire having 20 questions [(knowledge 11, attitude 5 and practice 4) maximum possible score 40]. Thirty community pharmacists with high scores were selected for three training sessions, each session lasting for one to two hours, covering the basic knowledge required for the community pharmacists for ADR reporting. Pharmacist from the regional pharmacovigilance center visited the trained community pharmacists every alternate day and collected the filled ADR reporting forms.

Results: Altogether 71 ADRs, from 71 patients (37 males) were reported. Antibiotics/antibacterials caused 42% (n=37) of the total ADRs followed by non steroidal anti-inflammatory drugs [25% (n=22)]. Ibuprofen/paracetamol combination accounted for ten ADRs. The most common type of ADR was itching [17.2 % (n=20), followed by generalized edema [8.6 % (n=10)]. In order to manage the ADRs, the patients needed medical treatment in 69% (n=49) of the cases. Over two third (69%) of the ADRs had a ‘possible’ association with the suspected drugs and a high percentage (70.4%) of the ADRs were ‘definitely preventable’.

Conclusion: The common class of drugs known to cause ADRs was antibacterial/antibiotics.

Ibuprofen/paracetamol combination use of the drug was responsible for more number of ADRs and the most common ADRs were related to dermatological system. Strengthening this program might improve safe use of medicines in the community.

Keywords: Adverse Drug Reaction Reporting Systems. Community Pharmacy Services. Pharmacists. Nepal.

PATRÓN DE LAS REACCIONES ADVERSAS COMUNICADAS POR FARMACÉUTICOS COMUNITARIOS EN NEPAL

RESUMEN
El programa de farmacovigilancia de Nepal tiene menos de una década de antigüedad, y está centrado en los hospitales. Este estudio muestra los resultados de un programa de farmacovigilancia comunitario, que involucra a farmacéuticos comunitarios.

Objetivos: Recoger detalles demográficos del número de pacientes que sufren reacciones adversas a medicamentos (RAM) comunicadas por farmacéuticos comunitarios; identificar los medicamentos que causan las RAM y los tipos comunes de RAM; y realizar las evaluaciones de causalidad, gravedad y preventabilidad de las RAM reportadas.

Métodos: Se evaluó, mediante un cuestionario validado (Cronbach alfa=0.61) 20 preguntas [(conocimiento 11, actitud 5 and práctica 4) máxima puntuación posible score 40], el valor inicial de Conocimiento-Actitudes-Práctica (KAP) de 116 farmacéuticos comunitarios del valle de Pokhara. Se seleccionó a los 30 farmacéuticos comunitarios con puntuaciones más altas para realizar 3 sesiones formativas, cada sesión duraba de una a dos horas, que cubrían los conocimientos básicos que requerían los farmacéuticos para comunicar RAM. Los farmacéuticos del centro regional de farmacovigilancia visitaron a los farmacéuticos comunitarios formados en días alternos y recogieron las comunicaciones rellenas.

Resultados: Se comunicaron 71 RAM de 71 pacientes (37 hombres). Los antibióticos/antibacterianos causaron el 42% (n=37) del total de RAM, seguidos de los antiinflamatorios no esteroides [25% (n=22)]. La combinación ibuprofeno/paracetamol totalizó 10 RAM. El tipo de RAM más frecuente fue el picor [17.2 % (n=20)], seguido del edema generalizado [8.6 % (n=10)]. Para resolver las RAM, el 69% del total de los pacientes (n=49) requirió tratamiento médico. Mas de 2 tercios de las RAM (69%) tenía una ‘posible’ asociación con el medicamento.
Nepal is also very low (1:23,000). The hilly terrain, portion of the country has a poor transportation and lands to high altitude mountains. A significant The geography of the country varies from plain qualification. In addition, the doctor-patient ratio in the rural areas are manned by community health assistants who do not possess a medical healthcare practitioners for their healthcare needs. The health posts and the primary health centers in areas and hence the rural patients rely upon local country often do not practice in the rural and remote areas and thereby the national centers at present. These centers are located at teaching hospitals namely Tribhuvan University Teaching Hospital (TUTH) Kathmandu; Nepal Medical College, Kathmandu; KIST Medical College, Lalitpur; and Manipal Teaching Hospital (MTH) Pokhara, Nepal. These centers collect the ADR reports and send to the national center at DDA through the ‘vigiflow online’ (the WHO database) program.

The existing system of ADR monitoring in the country is beneficial only in reporting the ADRs that occur in hospital setups. This system remains unanswered for reporting ADRs that occur with over the counter (OTC) medications and in the ambulatory patient settings. This had led to the development of community based ADR reporting and monitoring system which could play an active role in collecting reports of ADRs occurring at the community level. The regional pharmacovigilance center of Western Nepal has been involved in reporting the ADRs occurring in the MTH. The members from the department of hospital and clinical pharmacy, and pharmacology are involved in the center. In the beginning the center did not focus towards the ADRs occurring in the community. Recently, in the year 2008, the members of the center have decided to setup a community based Pharmacovigilance system in which the community pharmacists report the ADRs. The outcome of such an initiative taken by the center is presented in the present article. Thus, the study was conducted with the following objectives:

1. To collect the demographic details of the patients experiencing adverse drug reactions in the community
2. To identify the common drugs causing the adverse drug reactions
3. To identify the common types of adverse drug reactions
4. To carry out the causality, severity and preventability assessments of the reported adverse drug reactions

METHODS
Study design: A cross sectional study evaluating the pattern of ADRs was carried out by analyzing the filled ADR reporting forms received from the community pharmacists (Figure 1).

Selection of community pharmacists: The baseline KAP of 116 community pharmacists from Pokhara valley towards drug safety was evaluated using a validated (Cronbach alpha of 0.61) KAP
Development of ADR reporting form: An ADR reporting form was developed by the regional pharmacovigilance center and was used in the research. The reporting form had information on reporter, patient details and information on the reaction and medications. A pilot study was initially carried out with six community pharmacists and their inputs were taken while designing the ADR reporting form.9

Training the community pharmacists: The training for pilot group (six community pharmacists) included three sessions spreaded over two months, covering the basic information and expertise needed to identify and report ADRs by filling the ADR reporting forms. After completion of the training for pilot group, the test group also received three sessions of training similar to the pilot group but spreaded over six months duration.

Method of collecting ADR reports: The pharmacists from the regional pharmacovigilance center visited the trained community pharmacists every alternate day and collected the filled ADR reporting forms. Any additional help needed for the community pharmacists were provided by the pharmacovigilance center pharmacists.

Data analysis: All the ADRs reported to the regional pharmacovigilance centre by the community pharmacists were collected. The demographic details were analyzed. The causality, severity and preventability assessments were carried as per the Naranjo10, Hartwig11 and Modified Schumock and Thornton scales12, respectively.

RESULTS

During the study period, 71 cases of ADRs from 71 patients were reported and the details are summarized below.

Demographic details of the patients experiencing ADRs: Among the total 71 patients, 52.1% (n=37) were males and the remaining 47.8 % (n=34) were females. Twenty two (30.9 %) of the patients were within 20 years of age, 50.7 % (n=36) were between 21 to 40 years of age, 14 % (n=10) were between 41-60 years of age and 4.2% (n=3) were more than 60 yrs of age.

Onset of the ADRs: In ten cases (14%), the patient was exposed to the suspected drug for less than a day; in 20 (28.1%) patients, 1-2 days; in 10 (14 %) patients, 3-4 days; in 10 (14 %) patients, 5-6 days; in 5 (7%) patients, 7-8 days; in 5 (7%) patients, more than 8 days in one (1.4 %) patients. The duration of use of the suspected drug was not available in 20 (28.1%) patients.

Suspected drug category causing ADRs: More number (42%) of ADRs was caused by Antibiotics/antibacterial class of drugs. Further details on the suspected drug categories responsible for causing the ADRs are listed in Table 1.

Table 1. Suspected drug category causing ADRs (n=88)

| Drug category               | Number | Percentage |
|-----------------------------|--------|------------|
| Antibiotics/ antibacterial  | 37     | 42.0       |
| NSAIDs                      | 22     | 25.0       |
| Vitamins                    | 4      | 4.5        |
| Antiamoebics                | 4      | 4.5        |
| Antifungals                 | 3      | 3.4        |
| Antisecretory agents        | 4      | 4.5        |
| Sex hormones                | 4      | 4.5        |
| Miscellaneous               | 10     | 11.3       |

Top ten drugs causing the ADRs: Of the 71 reports, 10 were caused by the fixed dose combination (FDC) Ibuprofen/ paracetamol. The most common drugs responsible for causing the ADRs are listed in Table 2.

Table 2. Top ten drugs causing the ADRs

| Drugs                                      | No. reports |
|--------------------------------------------|-------------|
| Tab. Ibuprofen/ paracetamol combination    | 10          |
| Cap. Amoxicillin                           | 8           |
| Cap. Ampicillin/ cloxacillin combination   | 6           |
| Tab. Metronidazole                         | 5           |
| Tab. Diclofenac                            | 5           |
| Inj. Ceftriazone                           | 4           |
| Inj. Gentamicin                            | 2           |
| Tab. Folic acid                            | 2           |
| Cap. Omeprazole                            | 2           |
| Tab. Paracetamol+phenylephedrine+ chlorpheniramine maleate combination | 4 |

Types of adverse drug reactions: The types of ADRs observed are listed in Table 3. System affected by adverse drug reactions (n=116): The most affected system by the ADRs was dermatological (37.9%; n=44), followed by gastrointestinal system (18.9%; n=22), cardiovascular (11.2%; n=13), central nervous system (7.7%; n=9), immune system (5.1%; n=6), ocular (4.3%; n=5), hematological (2.5%; n=3), endocrine (1.7%; n=2) and miscellaneous (10.3%; n=12).
Table 3. Types of adverse drug reactions (n=116)

| Reaction type                      | No. of reports | Percentage |
|-----------------------------------|----------------|------------|
| Itching                           | 20             | 17.2       |
| Vomiting                          | 10             | 8.6        |
| Generalized edema                 | 10             | 8.6        |
| Macular rashes                    | 9              | 7.7        |
| Swelling                          | 8              | 6.8        |
| Abdominal pain                    | 6              | 5.1        |
| Urticaria                          | 6              | 5.1        |
| Fever, rigor and chills           | 5              | 4.3        |
| Tingling in body, giddiness       | 5              | 4.3        |
| Contact dermatitis                | 4              | 3.4        |
| Generalized itchy maculopapular rash | 3          | 2.5        |
| Blurred vision                    | 2              | 1.7        |
| Diarrhea                          | 2              | 1.7        |
| Shivering and feeling cold        | 3              | 2.5        |
| Swelling in upper and lower limbs | 2              | 1.7        |
| Positive skin test                | 1              | 0.8        |
| Sore throat/tonsillitis/fever     | 2              | 1.7        |
| Miscellaneous                     | 18             | 15.5       |

Table 4. Treatment of the reaction, action taken and outcome of the reaction

| Features                              | Parameters       | Number | Percentage |
|---------------------------------------|------------------|--------|------------|
| Treatment                             | Medical treatment | 49     | 69.0       |
|                                       | Non medical      | 5      | 7.0        |
|                                       | Unknown          | 17     | 23.9       |
| Outcome                               | Recovered/resolved | 27     | 38.0       |
|                                       | Not recovered/not resolved | 3     | 4.2        |
|                                       | Unknown          | 41     | 57.7       |
| Action taken                          | Drug withdrawn   | 33     | 46.4       |
|                                       | Dose reduced     | 2      | 2.8        |
|                                       | Dose increased   | 2      | 2.8        |
|                                       | Dose not changed | 8      | 11.2       |
|                                       | Unknown          | 26     | 36.6       |

DISCUSSION

Upon training, the community pharmacy...
practitioners started reporting the ADRs to the regional pharmacovigilance center. During six months, they reported 71 ADR reports. The analysis of these 71 ADR reports revealed the sex distribution of the patients experiencing ADRs to be almost equal. In general, female are prone to cause ADRs. It is however, difficult to generalize as the number of patients was low.

Analgesics were the second most common class of drugs implicated for causing ADRs. Analgesics have caused several ADRs including gastric problems. Many times, they are used as OTC by the general public. The community pharmacist can play an important role in minimizing these ADRs by providing simple information to the patients regarding the precautions to be taken while taking medicines like either before or after food accordingly, and having more water with the medicine. In Spain, a pharmacist mediated intervention at community pharmacies improved the practice of adequate gastroprotection for patients asking for NSAIDS.

We found antibiotics to be the most common class of drugs causing ADRs. The irrational use of antibiotics/antibacterial by community pharmacy practitioners has already been demonstrated by researchers a decade ago in Nepal. Moreover, in Nepal the community pharmacists dispense antimicrobials without a prescription. Few studies from the hospital settings in Nepal have already raised concerns regarding irrational antimicrobial use. Though, it is a common problem in both hospital and community settings, the impact may be higher in the community since antimicrobials are available even without having a prescription.

We found the ibuprofen/paracetamol to have caused more number of ADRs. Use of ibuprofen/paracetamol combinations is common in Nepal. Since it is an OTC medication; very often the patients consider these medications to be very safe. However, this medication is not approved in many countries and hence not available. There is also a claim that this combination is irrational. This finding suggests the need for more vigilance regarding the dispensing of OTC products by the retail pharmacists.

More number of ADRs reported was related to dermatological system suggesting topical ADRs. Topical ADRs are usually mild. However, they can contribute to significant economic loss 28 and impairment in quality of life of patients. Among the total 71 patients, 13 of them required medical treatment for ADRs and in 14 of the cases the suspected drugs were withdrawn. The skin and the mucosa are the commonest sites for initial presentation of many ADRs. In general, it is easy to identify a cutaneous ADR. The community pharmacy practitioners can play a vital role in minimizing the cutaneous ADRs by educating the patients regarding common early symptoms (eg, erythematous rash, edema, urticaria, mucosal erosions, itching, and burning of skin) especially during the start of the therapy.

Slightly more than two third (69%) of the ADRs required a medical treatment in managing the ADRs. Thus, there is an economic burden to the patient experiencing the ADR in addition to the suffering and impaired quality of life. A preliminary evaluation of the cutaneous ADRs reported to the regional pharmacovigilance center reported a cost burden of USD 1.58 (SD=1.41) for drug therapy. Though this finding included the ADRs occurring in the hospital, it provides a rough idea on the economic impact of the ADRs in Nepal.

In this study, 46 (nearly 64.7%) of the total ADRs to be definitely preventable. It is well established that more than half of the ADRs are preventable with appropriate care. Since the ultimate objective of a pharmacovigilance program is to minimize the occurrence of similar ADRs in the future; one should take adequate steps in preventing the ADRs.

Limitations: Our study was conducted for a short period of time (six months) and included only a few (30) community pharmacists. Similar studies covering more retail pharmacists for a longer period of time are needed to validate our finding. Moreover, there is high possibility of under reporting by the community pharmacists.

Future directions: The present study was preliminary one which evaluated the ADRs reporting pattern by community pharmacists in a developing country like Nepal. Similar training programs are needed for other community pharmacists in order to strengthen the program. In addition, measures have to be taken to sustain the program. This can be achieved by involvement of professional pharmacy associations in the country and commitment and vision from the national pharmacovigilance center. The community pharmacists should also be oriented to send the reports directly to the regional pharmacovigilance center in spite of the pharmacovigilance center staffs visiting the community pharmacists to collect the reports.

CONCLUSIONS

The study was successful in analyzing the pattern of ADRs reporting by retail pharmacists. The common class of drugs known to cause ADRs was antibiotic/antibacterial. Ibuprofen/paracetamol combination was the drug responsible for more number of ADRs and the most common ADRs were related to dermatological system. Upon strengthening the community based pharmacovigilance system there can be more rational use of medicines in community. It will also help in minimizing the occurrence of ADRs in the community.

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**CONFLICT OF INTEREST**

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