Determination of the Frequency and Direct Cost of the Adverse Drug Events in Argentina

Estela Izquierdo, Claudio Rodríguez, Eneas Pampliega and Ester Filinger*

Clinical Pharmacy Unit, Department of Pharmaceutical Technology, University of Buenos Aires, Junin 956 (1113), Buenos Aires, Argentina

Abstract: To determine the frequency and the direct costs of adverse drug reactions, in an ambulatory population of the City of Buenos Aires, Argentina and its area of influence.

A retrospective study was done during a period of three months on approximately 300.000 residents of the Buenos Aires area, gathering data according to the selected variables by means of the electronic capture of prescriptions dispensed in pharmacies of the area. This method enables the detection and registration of potential conflicts that may arise between a prescribed drug and factors such as: patient's demographic, clinical and drug profile.

The analysis unit was defined as the happening of a moderate or severe adverse event reported by the system. The selected variables were the incidence of these effects and the direct cost was calculated as the value of the drugs that induced the adverse event.

The events were classified according to the following interactions: a) drug- drug, b) drug-pediatrics, c) drug- gender, d) drug- pregnancy and abuse of controlled substances.

The observed frequency shows great variability and the shortage of available data for ambulatory populations. We found 6.74% of reported events over the total of processed items, which generated an additional cost equivalent to 4.58% of the total pharmaceutical expenses.

This study has only evaluated the cost occured by the use of a drug that will lead to an adverse reaction. Moderate and severe reactions were included regardless of the important indirect costs, hospitalization costs, tests, physician fees, etc.

Keywords: Adverse drug reactions, drug interactions, direct cost, frequency of adverse events.

INTRODUCTION

Adverse Drug Reactions (ADRs) are an important issue with regards to the clinical use of drugs. ADRs increase the cost of treatment in a direct as well as indirect manner [1-3]. The direct increase in cost could be due to the utilization of other drugs used to treat the adverse drug reaction (e.g., use of corticoids or antihistaminic-based drug for treatment of rash occurred by use of azithromycin). The indirect increase in the cost could be related to the micro and macroeconomic impact (e.g., Increase in absentee days of the employee) of the reaction. ADRs are complex and multifacetic phenomena that require involvement of patients, medical practitioners, health administration and pharmaceutical manufacturers [1, 4-6]. The information technology (high quality knowledge databases and systems) allows us to prevent and decrease the occurrence and the severity level of ADRs by allowing the monitoring and evaluating of the data during the prescription and dispensing process.

The World Health Organization (WHO) defines the ADR as "noxious and unintended drug effect, which occurs at doses, employed in man for prophylaxis, diagnosis or therapy".

The Food and Drug Administration (FDA) describes ADR as "an undesirable effect, reasonably associated with the use of the drug, that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence".

The scientists and healthcare professionals may question these definitions with regards to their comprehensiveness regarding capturing all forms of ADRs, however, they do emphasize ADR as an "unwanted" event in the course of drug therapy [7-10].

The aim of our study is to determine the frequency and direct costs of adverse reactions, in an ambulatory population of the City of Buenos Aires, Argentina and its area of influence.

MATERIAL AND METHODS

A retrospective study was done during a period of three months between August and October, gathering the data according to the selected variables by means of the electronic capture of 508,893 medicines prescribed over the total number of prescriptions sold in community pharmacies of the area, corresponding to 186,916 patients. These patients belong to several major Health Maintenance Organization (HMO), with a total number of 315,222 members in the area. These prescriptions are approximately 90 % of the total consumed by those members for that period.

*Address correspondence to this author at the Clinical Pharmacy Unit, Department of Pharmaceutical Technology, University of Buenos Aires, Junin 956 (1113), Buenos Aires, Argentina; Tel: +54 11 4918 9853; Fax: +54 11 4918 9853; E-mail: efilin@ffyb.uba.ar

1574-8863/09 $55.00+.00

Data was processed through a software, which consists of a management program focused upon the improvement of the use of drugs in the health system, and the drug information was provided by First Data Bank, world's leading supplier of healthcare knowledge bases.

The analysis unit was defined as the happening of an adverse event, reported by the system during the time of the study. Moderate and severe adverse events were gathered, not considering the minors. The selected variable was the impact effect that an adverse event has on the following: cost, profile of the adverse event and profile of the consuming population. The cost was evaluated in two sub dimensions: total and conglomerate of adverse events. The event's profile was classified according to the type of the confirmed interactions: drug-drug, drug-pediatrics, drug-gender and drug-pregnancy. Finally, the profile of the affected population by gender and age, measured in three categories (pediatrics or under 15 years old, adults between 15 and 64 years old and aged over 64 years old).

The selected variables allow the following calculations: 1) the incidence of those events, measured as the ratio of reported events over the total number of patients who consumed the medicines during the considered period of time, 2) the incidence of events, measured as the ratio of adverse events for pregnancy over the total number of pregnant women and 3) the direct cost of acquisition of the events over the total spending, measured as retail price. This cost was calculated on the ingredients that caused the adverse event when interacted with the therapeutics or with the clinical condition, that means that the costs of the medicines prescribed in second term were determined, and not the costs of the original prescription.

At the same time, events were categorized according to the following interactions: a) drug-drug, b) drug-pediatrics, c) drug-gender, d) controlled substance abuse and e) drug-pregnancy.

Data was gathered for each month of the trimester, using as values of the variables the simple average.

Through this method it is possible to detect and record the potential conflicts (adverse events) that may arise when a drug is prescribed related to factors such as demographic profile (gender, age), clinical profile (allergies, health condition, diseases, pregnancy, etc.) and drugs' profile (interactions, duplicate therapy, over and under use, etc.).

RESULTS

The global incidence rate of adverse events was 15.2 %. The incidences for each type of categorization were 7.7 % for drug-drug, 4.8 % for controlled substance abuse, 2.5 % for drug-pediatrics, and 0.3 % for drug-gender (Fig. **1**).

In general, 28,446 interactions were recorded, 50.38 % of the total events were drug-drug, followed by controlled substance abuse (31.29 %), drug-pediatrics (16.50 %) and at last drug-gender (1.84 %) (Fig. **2**).

The direct cost of acquisition of the drugs that caused the adverse event was US$ 202,50, that is 4.92 % of the total expenditures processed (Table **1**). As can be seen in the table, the costs for each category were: US$ 106,30 (2.58 %) for drug-drug, US$ 62,43 (1.52 %) for controlled substance, US$ 24,04 (0.58 %) for drug-pediatrics, and US$ 9,73 (0.24 %) for drug-gender.

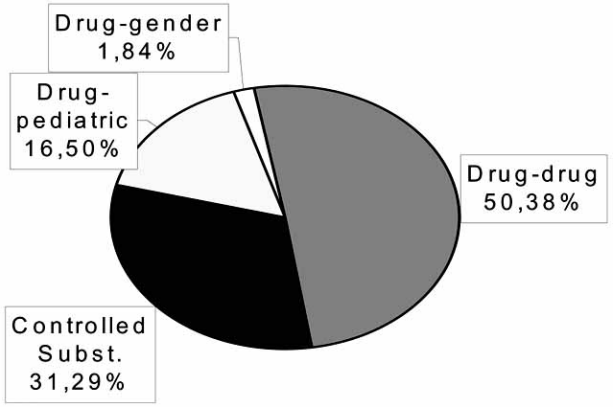

Fig. (1). Distribution of Adverse Events Per Frequency (Trimester August-October 2000).

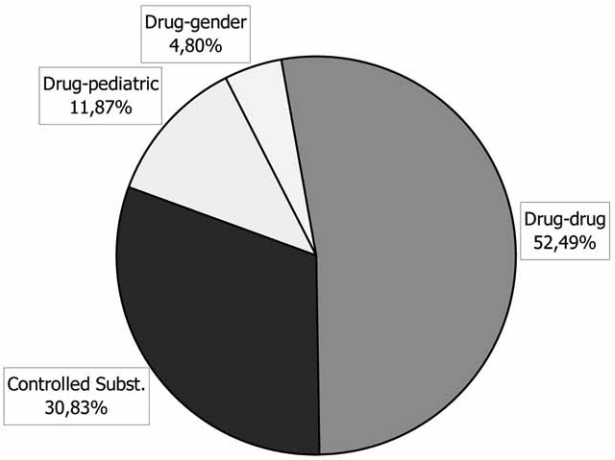

Fig. (2). Cost distribution per category (Trimester August-October 2000).

Table **2** shows that for pregnant women, the specific incidence rate of adverse events was 15.8 % for this particular group.

Specific incidence rates were also determined for gender and age profiles, obtaining 15.3 and 15.1 for women and men, respectively. For age, three categories were considered: patients under 15 years old, patients between 15 and 64 years old and patients over 64 years old. The obtained values were 21.8; 10.9 and 21.6, respectively (Table **3**).

DISCUSSION

The incidence ratio of adverse events (moderate and severe) was a 15.2 % of the studied sample. This indicates that the way the drugs were used, are far from rational,

Table 1. Drugs that Caused Adverse Events

Check	Events	Incidence Ratio (%)	US$ Events	% $ Events/Total Spending
Drug-drug	14331	7,7	106.30	2,58%
Controlled Substances	8900	4,8	62.43	1,52%
Drug-pediatric	4693	2,5	24.04	0,58%
Drug-gender	522	0,3	9.73	0,24%
Totals	28446	15,2	202.50	4,92%

Consumering population = 186.916 patients .
Total population = 315.222 patients.
Total cost as retail price = US$ 4.117.171.

which is a concerning fact by itself, according to other authors [8-10].

Table 2. Drug-Pregnancy Checks in Pregnant Women

Month	Events	Pregnant Women	PWIE Ratio (%)
August 00	175	1023	17,1
September 00	170	1033	16,5
October 00	145	1048	13,8
Average	163	1035	**15,8**

With regard to specific incidence rates, we did not find noticeable differences between men and women (15.1 and 15.3, respectively). For the age profile, a strong polarization to the extremes (21.8 for under 15 years old, 10.9 for the range 15/64 years old and 21.6 for over 64 years old), was probably due to the fact that these segments represent the patients which are most exposed to risk.

The latest findings encourage the need of greater supervision over these age groups, using special programs of pharmacotherapeutic follow up [6,11-14].

The 4.92 % of cost added by these events shows a pharmacoeconomic vision of the problem. Undoubtedly, the total costs were much greater than those shown here, given that we only considered the cost of the drugs that interacted with the original drug therapy but not, among others, the ones caused by i.e. duplication of therapy, maximum dose, minimum dose, drug-geriatric, known disease, etc. or the patient with special condition.

Table 3. Specific Incidence Rates for Gender and Age Profiles

Selected Profile	Categories	Exposed Population (Consumers)	Number of Events	Specific Incidence Ratio (%)
Gender	Females	112.325	17.188	15,3
	Males	74.591	11.258	15,1
Age	Under 15	22.063	4.815	21,8
	15 to 64	111.749	12.148	10,9
	Over 64	53.104	11.483	21,6

The importance of drug-drug interactions (50.38 % over the total adverse events), clearly shows that indiscriminate polypharmacy plays a very important role in the occurrence of drug adverse reactions. This polypharmacy shows very serious deficiencies in the understanding of the nature of the drugs, of its indications, adverse effects and interactions, for both prescribers and dispensers, as a result of an insufficient academic education, continuing education, non or under use of drug information tools and technologies or, due to marketing pressures. These may also originate the drug-pediatrics events (16.50 %).

The importance of the high rate of drug-pregnancy adverse events (15.80 %) should also be stressed. However, the causes for the rest of the events may be multiple. For instance, the high incidence of controlled substance abuse checks (31.29 %) and acknowledges stress and psychiatric diseases as a main cause in this present crisis time, as well as the existence of addictive conducts. On the other hand, drug-gender events (1.84 %) clearly indicate possible frauds such as card misuse by unauthorized people.

This leaves out of our study several of the direct costs; and all indirect ones such as the provoked cost of morbidity and mortality and the required ones to mend damages caused by the events i.e. pregnancy.

There is a clear bidimensional problem on the use of drugs, since the utilization of resources is involved and, on the other hand, it may generate an increase of risk among the population, which could easily cause a raise in the cost of morbidity and mortality [8,10,12,13].

CONCLUSION

Finally, the importance of the problem that we have studied, presents the need of a management program working in real time, and with the capacity of generating preventive actions to stop fraud or non-rational use of the drugs. Thus,

avoiding occurrence of drug adverse reactions and additional costs, which no health care system can afford today.

ACKNOWLEDGEMENT

Any founding provided for conduct of this study and preparation of the paper.

REFERENCES

[1] Alban A, Gyldmark M, Pedersen AV, Sogaard J. The Danish approach to standards for economic evaluation methodologies. Pharmacoeconomics 1997; 12: 627-36.
[2] Barro RJ. Macroeconomics. Mexico: McGraw-Hill, 1986.
[3] Bloom B, Wierz D, Pauly M. Cost and price of comparable branded and generic pharmaceutical. JAMA 1986; 256: 18-21.
[4] Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. How to perform a decision analysis. Med Decis Making 1997; 17: 123-59.
[5] Dombusch R, Fischer S. Macroeconomics (6th ed.). Madrid: McGraw-Hill, 1994.
[6] Hennessy S, Bilker W, Zhou L, *et al.* Retrospective drug utilization review, prescribing errors and clinical outcomes. JAMA 2003; 290: 1494-9.
[7] Neri A. Health and social politics. Buenos Aires: Hachette, 1982.
[8] Sackett DL *et al*. Evidence-based medicine: what it is and what it isn't. BMJ 1996; 312: 71-2.
[9] Siegel JE, Torrance GW, Luce BR. Guidelines for pharmaco-economic studies. Recommendations from the Panel on cost effectiveness in health and medicine. Pharmacoeconomics 1997; 11: 159-68.
[10] Laupacis A. Economic evaluations in the Canadian Common Drug Review. Pharmacoeconomics 2006; 24: 1157-62.
[11] Glassman PA, Belpeiro P, Lanto A, *et al*. The utility of adding restrospective medications profiling to computerized provider entry in a ambulatory care population. J Am Med Inform Assoc 2007; 14: 424-31.
[12] Yeon JH, Park JS, Oh OH, Shin HT, Oh JM. Identification of inapropiate drug prescribing by computerized, restrospective DUR screening in Korea. Ann Pharmacother 2005; 39: 1918-23.
[13] Van Eimeren W, Horisberger B. Socioeconomic evaluation of drug therapy. Berlin-Heidelberg: Springer-Verlag, 1988.
[14] Varo J. Strategic management of the quality of the health services. Madrid: Díaz de Santos, 1996.

Received: December 11, 2008 Revised: January 25, 2009 Accepted: February 1, 2009