Impact of pharmacovigilance on adverse drug reactions reporting in hospitalized internal medicine patients at Saudi Arabian teaching hospital

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ABSTRACT

الأهداف: دراسة معدل الآثار الجانبية للأدوية وأهمية دور عملية التيقظ الدوائي في مراقبة مخاطرها.

الطريقة: أجريت هذه الدراسة في مستشفى الملك عبدالعزيز التعليمي التابع لجامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من يناير إلى ديسمبر 2011م. شملت هذه الدراسة مرضى قسم الأمراض الباطنية. لقد قمنا بدراسة معدل الآثار الجانبية بطريقتين وهما الطريقة الأولى: دراسة معدل الآثار الجانبية للأدوية المعطاة لعدد 600 مريض من خلال الرجوع إلى السجلات الطبية الخاصة بهؤلاء المرضى. أما الطريقة الأخرى فهي دراسة معدل الآثار الجانبية لعدد 600 مريض من خلال المرضى المنومين في المستشفى من حيث العمر، والجنس، والأعراض الجانبية الأكيدة، والممكنة، والمحتملة، والأدوية المستخدمة، وكذلك أكثر الأجهزة عرضة. وبعد ذلك قمنا بتحليل البيانات ومقارنتها لمعرفة دور التيقظ الدوائي في مراقبة مخاطر الأعراض الجانبية للأدوية.

النتائج: أشارت نتائج الدراسة بأن نسبة الأعراض الجانبية بالنسبة للمرضى المسجلين في السجلات الطبية كانت (3.1%) بينما كانت النسبة في المرضى المنومين (5.5%) وهذا يدل على قلة وعي الأطباء والكادر الطبي بأهمية تسجيل وتقييد الأعراض المصاحبة للأدوية المستخدمة والاحتفاظ بها في سجلات المرضى. كذلك بينت الدراسة أن زيادة عدد الأدوية قد أدى إلى زيادة نسبة الأعراض الجانبية في كلا الحالتين وهما المرضى المسجلين في السجلات (15%) والمرضى المنومين (14.5%). وكانت معظم الأعراض الجانبية للأدوية بسبب المضادات الحيوية بالنسبة للمرضى المسجلين في السجلات (36.9%) والمرضى المنومين (48.5%). وكان الجهاز الهضمي من أكثر أجهزة جسم الإنسان تأثراً بنسبة 47.4% للمرضى المسجلين في السجلات الطبية بالمقارنة مع 57.6% ولكن لم تكن هذه الأعراض الجانبية خطيرة.

خاتمة: أظهرت الدراسة بأن نسبة الأعراض الجانبية في المرضى المنومين قليلة وذلك بسبب عدم وعي الأطباء والكادر الطبي حول أهمية تسجيل وتقييد جميع ما يشوب استخدام الدواء، وتشير هذه الدراسة إلى أهمية ودور التيقظ الدوائي في تسجيل جميع الأعراض الجانبية المصاحبة للدواء.

Objectives: To determine the incidence, diversity of adverse drug reactions (ADRs), and impact of pharmacovigilance on reporting it.

Methods: This prospective and retrospective study was carried out in the Department of Medicine, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia between January to December 2011 in 600 patients of ADR. Data regarding age and gender distribution of the patients, incidence rate, drugs, body systems/organs involved in ADR, time of occurrence of adverse drug reactions, total number of drugs administered, and impact of pharmacovigilance on finding the incidence rate of ADR were recorded. Comparison of the 2 data was carried out to determine the impact of pharmacovigilance.

Results: Incidence rate of ADRs in retrospective study was 3.1% and 5.5% in the prospective study. The highest incidence of ADR (retrospective 15% and prospective 14.5%) was observed in both groups in patients receiving more than 10 drugs. The frequency of ADR in relation to age in both groups was highest in patients of age >60 years; it was 52.7% in retrospective study and 54.5% in prospective study. Antibiotics were the more frequently involved in ADR, (48.5% in prospective study and 36.9% in retrospective study). The system most commonly involved in ADR was gastrointestinal tract 47.4% in retrospective study and 57.6% in prospective study. None of the ADR proved to be fatal.

Conclusion: Low incidence of hospitalized ADR in our study (5.5%) is due to lack of awareness in healthcare professionals in reporting ADR. Undoubtedly, pharmacovigilance brought more patients with ADR to record.

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Adverse drug reactions (ADRs) are the downbeat outlay of drug therapy.[1] Detection of ADRs in hospitals provides an important measure of the burden of drug related morbidity on the healthcare system. Seriousness of ADR can be gauged from the report that it is between the fourth and sixth leading cause of death in the USA to the fore of pneumonia and diabetes.[2] Hospital acquire ADR shows wide variation in the incidence between 3.5% and 7.3%[3] and 19.2%.[4] It is noteworthy that in developing countries, hospitalized patients have shown quite low incidence of ADR, like in the middle east region 4.4%,[3] India 5.42%,[5] South Africa 6.3%,[6] and Iran 10%.[7] Pharmacovigilance acknowledge, estimate, realize and avoid ADR. In addition it also endorse the notion of reporting serious and unpredicted adverse reactions, eventually to ensure safety and cogent application of medicine.[8-10] It also provide an imperative gauge of morbidity induced by drugs which can be avoided with improved heed to drug therapy.[11] Contemporary means of pharmacovigilance have limitation of under reporting, incidence rate cannot be determined and prejudiced assortment of medication contact.[12-15] In order to reduce the incidence of ADR, it is imperative to recognize the risk of ADRs, common drugs involved in ADR, its therapeutic category and demographic records of patients experienced ADR and associated drugs utilized. In addition, ADR unambiguous information like type of drug reaction, systems involved and causality will be of immense help to minimize the ADRs.[16] Three local studies related to hospital admissions associated with ADRs and clinical pharmacist intervention in the intensive care unit were reported,[17,18] and no study was found related to ADR in hospitalized patients.

In this study, the aim was to identify and characterize the pattern of ADRs due to commonly used drugs, and analyze them on the basis of various parameters in King Abdulaziz University Hospital, which is a 761 bedded tertiary teaching hospital, and provide healthcare for residents of Jeddah. This information may also be useful in identifying and minimizing preventable ADRs, at the same time it may help clinicians to tackle with ADRs more efficiently.

Methods. This prospective study spread over one year duration from January to December 2011. The study was carried out in the Department of Medicine, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Concurrently, a retrospective analysis of ADR in patients admitted during the last one year was undertaken by reviewing patient's files. A sample size of 600 patients was taken to conduct both retrospective and prospective studies. This sample size of 600 patients was intended for detecting an incidence rate of 6.7% found in an international systematic review.[3] Approval for the study was obtained from the University Ethics Committee prior to data collection. Confidentiality of the information obtained was assured throughout the study. Appropriate study format for monitoring ADR was developed for data collection and authenticated by performing a pilot study in 20 patients.

The exclusion criteria were patients not receiving drug therapy, patients referred by or transferred from other departments, patients discharged or transferred to other departments within 48 hours of admission. The inclusion criteria were all patients of either gender admitted in medical wards during the study period, and who did not fall in any of the above-mentioned categories. Any untoward event was labeled as ADR only after the agreement of the treating physician.

Data were then further analyzed to determine the age and gender distribution of the patients, incidence rate, drugs, body systems/organs involved in ADR, time of occurrence of adverse drug reactions, total number of drugs administered and impact of pharmacovigilance on finding the incidence rate of adverse drug reaction. Comparison of percentage of total ADRs of both studies was made to determine any significant difference in the incidence rate. Causality evaluation of ADR was carried out by Naranjo's algorithm scale.[19]

Statistical analysis. Results are expressed in absolute number and percentages. Comparisons between incidences of ADR in different age groups were performed using Chi-square test. $P<0.05$ was considered significant.

Results. The incidence of ADR in retrospective study was 3.2% while in prospective study it was found to be 5.5% (**Table 1**). The causality assessment in prospective study reveals that most of the ADR were probable in 23 (69.7%), followed by possible in 5 (15.1%) and definite in 5 (15.1%). Moreover, similar pattern was revealed in retrospective study: probable 13 (68%), possible 4 (21.5%) and definite 2 (10.5%) (**Table 1**). Regarding the type of ADR, in prospective study 25 patients out of 33 developed type A reactions (augmented) and only 8 patient developed type B reactions (Bizarre), whereas in retrospective study they were 13 and 6, respectively (**Table 1**).

In both retrospective and prospective studies, all patients were divided into 4 groups according to the number of drugs received by the patients (**Table 2**). It was observed that patients receiving more than 10 drugs

in both retrospective and prospective studies developed highest incidence of ADR (retrospective study 14.5% and prospective study 15%). In both retrospective and prospective studies, all patients were divided into 5 age groups (**Figure 1**). The incidence of ADR was seen to be highest in patients of age more than 60 years in both prospective (55.5%) and retrospective studies (52.6%), and it was found to be statistically significant in both groups. In prospective and retrospective studies within group analysis, comparing the frequency of ADR between patients more than 60 years and patients less than 60 years of age ($p<0.001$ and $p<0.05$). As regards to the organ and systems involved in ADR, gastrointestinal tract was most frequently implicated in both retrospective study (47.4%) and prospective study (57.6%), the second commonly observed ADR was related to skin. Incidence of skin ADR in both retrospective study was 31.6% and prospective study it was 24.3% (**Table 3**).

In both retrospective and prospective studies, the highest incidence of ADR were induced by antibiotics, in retrospective study it was 36.8% while in prospective study it was 48.5%. Drug class involved in ADR such as cardiovascular drugs, glucocorticoids, NSAIDs, and diuretics in both groups are summarized in **Table 4**.

Discussion. In the present study, the incidence rate of ADR in prospective sstudy was 5.5% and retrospective study 3.1%. Epidemiology of hospital acquired ADR were comprehensively studied from 1990s, and it demonstrates a broad variation, a recent systematic review in 2002, suggested that the figure was lower, between 3.5% and 7.3 %.[3] Consequently, another extensive study of adverse drug reactions in hospitalized patients had revealed that ADRs occurred in 19.2% of patients.[4] These conflicting records are perhaps suggestive of diverse methodologies used in the different studies. When compared with these studies,

Table 2 - Relationship of number of drugs intake and adverse drug reaction in retrospective and prospective studies.

Group of patients	Number of drugs	Number (%) of ADRs in retrospective study	Number (%) of ADRs in prospective study
A	1 to 2	0 (0.0)	0 (0.0)
B	3 to 5	3 (1.7)	5 (2.9)
C	6 to 10	6 (1.8)	7 (2.1)
D	>10	10 (14.5)*	11 (15.0)*

*In both retrospective and prospective studies within group analysis of less than 10 and more than 10 drugs $p>0.0001$

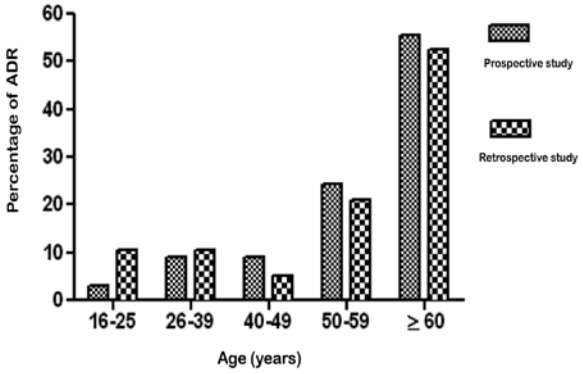

Figure 1 - Adverse drug reaction (ADR) in relation to age in the retrospective and prospective studies.

Table 3 - Systems involved in adverse drug reaction (ADR) in the retrospective and prospective studies.

Systems involved in ADR	Number (%) of ADRs in retrospective study	Number (%) of ADRs in prospective study
Gastrointestinal	9 (47.4)	19 (57.6)
Respiratory	2 (10.5)	2 (6.1)
Skin and appendages	6 (31.6)	8 (24.3)
Metabolic	2 (10.5)	0
Multi-system	0	4 (12.0)

Table 1 - Incidence, causality and type of adverse drug reactions (ADR) in 600 patients in both retrospective and prospective studies.

Characters	Retrospective Study				Prospective Study			
	Male n (%)	Female n (%)	Total n (%)	*P*-value	Male n (%)	Female n (%)	Total n (%)	*P*-value
Incidence	7 (36.9)	12 (63.1)	19 (3.1)†	0.51‡	15 (45.5)	18 (54.5)	33 (5.5)**	0.83‡
Definite*	2 (100)	0	2 (10.5)	0.75‡	3 (60.0)	2 (40.0)	5 (15.1)	0.71‡
Probable*	4 (30.8)	9 (69.2)	13 (68.0)	0.42‡	10 (43.5)	13 (56.5)	23 (69.8)	0.79‡
Possible*	1 (37.5)	3 (62.0)	4 (21.5)	0.83‡	2 (40.0)	3 (60.0)	5 (15.1)	0.71‡
ADR type A	4 (30.8)	9 (69.2)	13 (68.4)	0.42‡	14 (56.0)	11 (44.0)	25 (75.8)	0.80‡
ADR type B	3 (50.0)	3 (50.0)	6 (31.6)	1.0‡	1 (12.5)	7 (87.5)	8 (24.2)	0.17‡

*Causality evaluation of ADR, †the difference of ADR incidence between 2 studies is significant (Chi-square -3.613, the one-tailed $p<0.05$), ‡No statistically significant influence of gender was observed on ADR

Table 4 - Drug class involved in ADR in retrospective and prospective studies.

Drug class involved in ADRs	Number (%) of ADRs in retrospective study	Number (%) of ADRs in prospective study
Antibiotics	7 (36.8)	16(48.5)
Anticancer drugs	1 (5.3)	1 (3.0)
Glucocorticoids	2 (10.5)	4(12.1)
NSAIDS	2 (10.5)	2 (6.1)
Cardiovascular drugs	3 (15.8)	6(18.2)
Anti-epileptic drugs	1 (5.3)	1 (3.0)
Immunomodulators	0 (00.0)	2 (6.1)
Antidiabetic drugs	1 (5.3)	0 (0.0)
Hormonal preparations	0 (00.0)	1 (3.0)
Diuretics	2 (10.5)	0 (0.0)
Total	**19 (100)**	**33 (100)**

the incidence rate in our study appears to be low. Interestingly in developing countries the incidence, pattern and severity of ADR may differ markedly because of various factors which may account for this apparently low rate of ADR, this may include genetic factors, ethnic factors, dietary, healthcare infrastructure, detection methods, differing disease entities, culture, medical educational programs, national economic status, and regional pharmaceutical company marketing.[20-22] Nevertheless, other possibilities may include the use of computerized physician order entry (CPOE) systems being implemented in our hospital, which reduces the medication error rates.[23] A randomized study at Brigham and Women's and Massachusetts General Hospitals in Boston demonstrated that the introduction of CPOE reduced the serious medication error rate by 55%, and the preventable ADE rate by 17%.[23] The other reason could be that the present study was carried out over small number of patients.

It is a well-established fact that the important predictor of ADR risk is the number of drugs taken by an individual patient, as the number of drugs increases; the chance of developing ADR also increases.[24] This was confirmed in our study, we observed that as the number of drugs intake by the patient was increased, there was a significant increase in the rate of ADR. When the number of drugs were 2 or less, then there was no ADR. On the other hand, the rate of ADR increased in retrospective and prospective studies when more than 10 drugs were administered. There was a significant association between the number of drugs and the rate of ADR (p>0.001).

In our study, there was no influence of gender on the occurrence rate of ADR. But it was found that the incidence of ADR in relation to age in both prospective and retrospective groups was higher, and statistically significant in patients more than 60 years. The high rate of ADR among elderly patients is compatible with most of the other studies, which have documented that polypharmacy, poor health status including compromised renal and liver function and the frequent use of drugs with narrow therapeutic indices may play an important role.[3,25] Other evidences of ADR in the elderly are common in various settings.[26-28] The higher proportion of augmented ADR was observed in our study, 68.4% in retrospective study and 75.8% in prospective study, this was in accordance to that reported in other studies.[29,30] Further, these proportions are similar to the median preventability rate of 35.2% (range 18.7-73.2%) reported in a recent international literature review.[31] As this category, ADRs is predictable and can be prevented, this needs to be prioritized by hospitals and clinicians, which could reduce the burden and cost of managing these illnesses.[30] We should be able to develop strategies to prevent these ADRs, and drug monitoring may be improved with a narrow therapeutic window.

In our studies, causality assessment revealed that most of the ADRs belonged to "possible" followed by "probable" categories, similar to that reported in other studies.[32,33] "Definite" grade of ADR recorded in prospective and retrospective have developed cough following the administration of enalapril or developed anaphylactoid reaction following intravenous drug administration, they did not require any specific therapy and recovered following withdrawal of offending drug. It is noteworthy that no patient died as a sequel of ADR. More recent studies have shown that antibiotics were the most common causative drugs of ADR.[5,33,34] Antibiotics accounted for one-third of all ADRs.[35] Several other studies have shown similar results.[36,37] Our observation of ADR due to antibiotics in both studies is consistent with these findings.

Our study identified gastrointestinal system as the most frequently affected system by ADRs in both studies, patients who developed ADR, have symptoms relating to the gastrointestinal tract and this is in accordance with the findings of other studies.[38,39] This is followed by involvement of skin, almost all the skin reactions in our both studies were related to antibiotics, and they were mild ertythematous macular rash and self limited in nature. This is in accordance with studies showing similar observations of exanthematous eruptions in the range of 34.1% to 68.8%, and mostly related to use of antibiotics in developing countries.[6,40-42] In contrast, studies from developed countries shows that only 2-23% of hospitalized patients are reported to have cutaneous ADRs.[36,39,40] This disparity could be due to

different patterns of prescription, prevalence of disease and genetic factors. The present study was carried out to examine the impact of pharmacovigilance on finding the incidence rate of ADR. The prospective study shows the incidence rate of ADR to be 5.5%, while the incidence rate of ADR is found to be only 3.1% in the retrospective analysis. The difference between these 2 studies is significant (Chi-square -3.613, the one-tailed $p<0.05$). The intensive prospective collection of ADRs as selected in this study have shown that spontaneous reporting of ADRs by clinicians, even with routine reminders, has not been effective in detecting ADR as evident from the results. It is obvious that when one looks for the occurrence of ADR more intentionally, more patients with ADR can be brought to record. The clinicians imparting the treatment must be aware of the importance of observation for ADR, recording them meticulously and reporting them to the concerned authority. This appliance will make the drug therapy safer and more rational. Notwithstanding some limitations like small sample size, short study period, inevitable bias associated with execution of historical data and study limited to one department, our study has provided baseline data for further larger studies and has established the importance of prospective ADR monitoring in pharmacovigilance studies.

The automatic computerized laboratory data signals and adverse drug event trigger tool are recommended for reducing the incidence of hospitalized acquired ADR.

In conclusion, this study can be useful as a preliminary data in initiating a culture of ADR reporting among health care professionals in the hospital under study and to obtain information on the incidence rate of ADRs in the local population. A systematically planned exhaustive and scrutinized move can augment ADR detection. Undoubtedly, pharmacovigilance brought more patients with ADR to record.

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