The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 1698-1706

Evaluation of Adverse Drug Events Relating to Cardiac Disorders in Iraqi Public Sector

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ABSTRACT

Introduction: The cardio-vascular disease is a reason for mortality and morbidity is a serious and expanding issue. Cardiotoxicity is a frequent adverse pharmacological reaction, and the anthracycline class of anticancer medications, in particular, causes significant cardiotoxicity. Oxidative stress, free radical production, and hypoxia are common mechanisms causing cardiotoxicity. **Objective:** The aim of the current study is to determine which pharmaceuticals and adverse drug reaction cardiac problems are detected in Iraqi Public Sector.

Material and methods: By examining the reported adverse medication responses in terms of their seriousness, severity, preventability, and expectedness. Individual case safety records from the Ministry of Health and Pharmacovigilance of Iraq were examined retrospectively in this study.

Results: The study comprised 2453 reports of adverse medication reactions with 1101 individual case safety reports. The medicine with the most adverse drug reactions was tozinameran. Cardiac diseases were the cause of the majority (46.73%) of negative medication responses. In terms of the degree of adverse medication responses, the majority were found to be light [Level 1 (38.4%). Patients under the age of 18 experienced much more severe adverse medication responses than did adults and the elderly. According to a severity evaluation, the majority of adverse medication responses (47.6%) were not severe. The majority of negative drug reactions (97.9%) were likely avoidable.

Conclusion: Most reported cardiac adverse drug reactions were low in intensity, predictable, not life-threatening, and most likely preventable. The lack of information in the Individual Case Safety Report (ICSR) impacted how the reports were evaluated, necessitating the creation of training initiatives to create a stronger reporting system.

Keywords: Cardiotoxicity, Cardiovascular Diseases, Morbidity, Retrospective Studies, Iraq.

INTRODUCTION

Pharmacovigilance refers to the studies and procedures centered on the detection and evaluation, comprehension, and avoidance of any other effects related to drug problems [(1)]. Pharmacovigilance has recently broadened its scope to include vaccines, medical equipment, biologicals, and blood products complementary and alternative medicines. Numerous other issues are also pertinent to science, including subpar medications, medicine mistakes, not being effective data, the use of medications for conditions for which they have not been accepted and for which little scientific evidence exists support, case studies of both acute and long-term toxicity, estimation of drug- associated death, drug misuse, abuse, and unfavorable interactions between medications and foods, chemicals, and other medications.

The objectives of pharmacovigilance are to enhance the use's impact on patient safety of treatments, as well as public safety on the administration of drugs. They also include encouraging safe, logical, and more effective use of medications that is also cost-effective, as well as promoting understanding education and clinical training in pharmacovigilance [(2)].

Activities related to pharmacovigilance include data collection and management on medication safety, analysis of particular case reports to find new "signals," proactive risk management to reduce any potential risks related to medication use, and communication with and education of stakeholders and patients. When a new pharmaceutical product initially enters the market, the Marketing Authorization Holder (MAH) must give the Summary Product Characteristics (SPC), may be changed by CAs (Controlling Authorities) based on recently discovered signals as part of this smooth after-sales monitoring, which is essentially intended to protect the public [(3)].

The proliferation of fake medications, which causes significant morbidity and mortality, the happening of preventable unfavorable effects of drugs, a rise in the cost of healthcare due to adverse drug events, an increase in the inappropriate use of medications, the development of drug resistance, treatment failures necessitating the switch to more expensive medications, and ultimate death are all effects of ineffective pharmacovigilance systems (weak or absent pharmacovigilance systems) [(4)].

Adverse effects of drugs "A response to a substance that is noxious and undesired and occurs at dosages usually employed in man for the prophylaxis, diagnosis, or therapy of disease, or alteration of physiological function" is how the WHO defines an adverse drug reaction [(5)]. Alternative phrases like "toxic impact" or "side effect" should be avoided in favor of "adverse effect." A toxic effect is uncommon at normal levels and arises as an exaggeration of the desired therapeutic Effect.

Received: 27/07/2022
Accepted: 29/09/2022

There is always a dose-related harmful impact. On the other hand, a negative side effect happens through a different mechanism and may or may not be dose-related.

A side effect "is connected to the pharmacological features of the medicine," according to the WHO definition, which is vague [6]. One advantageous side effect of using a B-blocker to treat hypertension is that it may, through B-blockade, also help the patient's angina. Although "adverse effect" and "adverse response" are synonymous, an adverse impact is viewed from the perspective of the medication, whereas a negative reaction is viewed from the patient's perspective. However, "adverse incident" must be separated from "adverse effect" and "adverse reaction." An adverse event is a negative outcome that happens while a patient takes medication but is not always related to it. An adverse effect is a negative outcome linked to a drug's activity.

Everywhere in the globe, cardiovascular disease (CVD), the major cause of morbidity and mortality, is a serious and expanding issue [7]. More individuals are surviving the beginning CVD occurrences due to improvements in the investigations and therapeutics of CVD and rising expectation of life. The main goal for patients with existing CVD is to avoid another CVD episode or early mortality. As a result of incident CVD events, current secondary prevention strategies have significantly decreased the incidence of cardiovascular events and mortality [8] major adverse cardiovascular events (MACE). a majority pertinent the consequences of secondary prevention is MACE, an endpoint often utilized in cardiovascular research since it continues to be the leading source of morbidity and mortality in patients with CVD [9]. The term "MACE" is widely used to refer to a combination of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death [10,11]. It is occasionally broadened to encompass heart failure, coronary revascularization, and ischemic cardiovascular events [12]. Cardiotoxicity is a frequent adverse pharmacological reaction [13] and the anthracycline class of anticancer medications, in particular, causes significant cardiotoxicity [14]. Amphetamine, mitomycin, paclitaxel, and zidovudine are more medications that induce cardiotoxicity [15,16]. Oxidative stress, free radical production, and hypoxia are common mechanisms causing cardiotoxicity [17]. Apoptosis and myocontractility dysregulation are further caused by long-term exposure to cardiotoxic medications.

The aim of the current study is to determine which pharmaceuticals and adverse drug reaction cardiac problems are detected in Iraqi Public Sector.

MATERIAL AND METHODS

Retrospective analysis of the Individual Case Safety Reports (ICSRs) from the database of the Iraqi Pharmacovigilance Center and Ministry of Health was conducted in this study (Sent from the 1st of January 2010 to the 31st of December 2021). Before the study began, the National Center for Training and Human Resources of Iraq, the College of Pharmacy in Iraq and the Ministry of Health in Iraq received the approval of the scientific ethical committee.

Vigiflow - Iraq is the data source. Vigiflow is a database for adverse drug reactions (ADRs) from numerous national hubs all throughout the world that is run and maintained by UMC, a WHO collaborating center. In the analysis for this study, 1101 ICSRs with 2453 ADRs were used.

A group of drugs used in Iraqi hospitals is selected, and the reported cardiac ADRs collected from the IPVC Data Center are investigated. Twenty-four drugs (Tozinameran, Salbutamol, Aminophylline, Azithromycin, Ceftriaxone, (Favipiravir, Azithromycin), Hyoscine butyl bromide, Dexamethasone, Thyroxin, AstraZeneca COVID-19 vaccine, Isosorbide dinitrate, Metoprolol, Theophylline, Vancomycin, Ciprofloxacin Hydrocortisone, Doxorubicin, Sinopharm, Trastuzumab, Bisoprolol, Amlodipine, Favipiravir, Nilotinib, Oxytocin) were included in the research. The demographics, classification of ADRs, severity, predictability, and seriousness, result, and actions taken were examined in their reports. Vigiflow - Iraq is the information source. The Vigiflow database is located at the Uppsala Monitoring Center (UMC), a center for ADRs from several national institutions that collaborates with WHO worldwide [18].

The inclusion criteria for all the IPhvC reports of cardiac adverse reactions for adult Iraqi patients (≥18 years) were found in the Vigiflow. Exclusion criteria were non-cardiac ADR reports. Initially, 1101 reports were extracted from the database containing 2453 ADRs. 1303 non-cardiac adverse effects were subsequently excluded. The study looked at the ICSRs' demography, adverse drug events Categorization, intensity, entrepreneurship and business, prevention and treatment, and severity. The age categories included a newborn (4 weeks), a child (1–12 years), an adolescent (13–18 years), an adult (over 18 years), and an elderly person (over 65 years) [19].

The SOC, or System Organ Classification classifies adverse responses depending on the organ or system involved, was used to compile a list of the ADRs [20]. The updated Seligel and Hartwig severity scale was used to evaluate the severity (**Table 1**) [21].

ADRs were categorized into seven severity levels. Levels 1 and 2 are regarded as low severity, 3 and 4 as moderate, and 5, 6, and 7 as severe [22]. Assessing the expectedness of ADRs involves consulting the SmPC for medicinal medications. This primary reference manual offers guidance to healthcare practitioners about how to use the drug successfully and safely [23]. As a result, ADRs were categorized as "anticipated" if they appeared in the

SmPC and "unexpected" otherwise weren't [24]. Schumock and Thornton's standards (**Table 2**) were utilized to assess if ADRs could be prevented. In its current form, this criterion is broken down into three categories: preventable, probably preventable, and non-preventable. There are five questions in section A and four in section B. Each response has two categories: "Yes" and "No." If "yes" was given to any one or more of the section questions, ADRs were "definitely preventable.

" If all of the responses were negative, we moved on to section B. If "yes" was given to any one or more of the section B questions, ADRs were considered "probably preventable." We moved on to section C if all of the responses were negative. The ADRs in Section C were non-preventable and hence could not be avoided [25].

Using criteria defined by national or regional centers headquartered in Iraqi health directorates, the Seriousness was determined. These requirements are contained for all ADRs observed in Iraqi hospitals, a paper reporting format is used in the ICSR. The Seriousness was selected if the information in the ICSR was accurate; if not, the researcher assessed the Seriousness (**Figure 1**) [26].

Table 1. Shows the scale of severity as described by Hartwig and Seigel [21].

Level of severity	The criteria
1	Despite the adverse effect, the suspected drug's therapy did not need to be altered.
2	The unfavorable consequence necessitated delaying, stopping, or altering the suspected drug's course of therapy. No antidote or other form of therapy was necessary. No lengthening of the stay (LOS)
3	Due to the adverse effect, the suspected drug's course of therapy had to be postponed, stopped, or otherwise altered. AND/ OR A countermeasure or alternative therapy was necessary. LOS did not rise
4	The duration of stay is extended by at least one day for each adverse consequence of Level 3. OR The acknowledgment was made because of the negative impact.
5	Any Level 4 adverse impact requiring immediate medical attention
6	The patient suffered lifelong injury as a result of the unfavorable response.
7	Patient 2 died as a result of the unfavorable response, either directly or indirectly.

ADR: adverse drug reaction; LOS: length of stay

Table 2. Measures of preventability by Schumock and Thornton [25].

N	Question	Yes	No
1	Had the person ever had an allergy or an adverse medication reaction?		
2	Was the medicine used inappropriate given the clinical condition of the patient?		
3	Was the delivery method, frequency, or dose inappropriate given age, weight of the patient's, or condition?		
4	Any necessary therapeutic drug detection tests or other lab checks weren't carried out?		
5	Was the negative effect a result of a drug interaction?		
6	Was there a link between poor compliance and the negative medication effect?		
7	Was it a lab or a dangerous serum concentration? The monitoring test was it recorded?		

ADR: Adverse drug reaction.

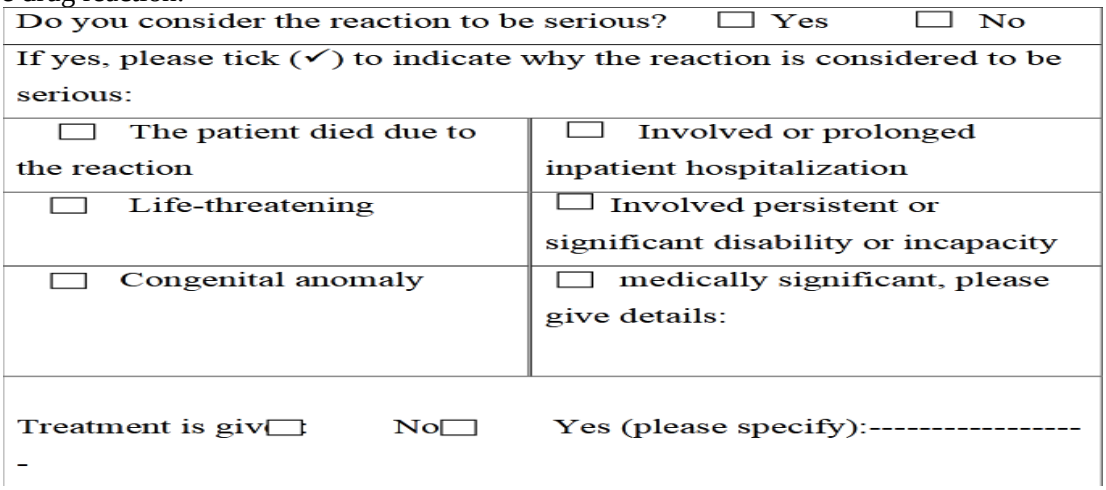

Figure 1: The Individual Case Safety Report's seriousness evaluation [26].

Ethical Approval:

Approval was obtained from the Scientific Science Ethics Committees at the Department of Clinical Pharmacy, Baghdad, Iraq's University of Baghdad College of Pharmacy.

Statistical analysis

The retrieved data from the ICSR reports was arranged in Excel spreadsheets, the parameters' requirements were then applied, and the outcomes were displayed in bar charts. Quantifying the frequency and proportion of each reported cardiac adverse response was done using descriptive statistics.

RESULTS

During the study period, 2453 ADRs were reported corresponding to 24 drugs identified throughout the research period, causing 8 cardiac ADRs. The ICSRs research revealed that there were more reports for women are more prevalent than for men. (56% of female reports compared to 41% of male reports, and 3% of the reports had no gender information). The ICSRs were evaluated in the following categories based on age groupings. Neonates, child, adolescent, adult, elderly, and unknown were with 4.36, 4.45, 2.27, 72.39, 11.53, and 5%, respectively. The distribution showed that most of the ICSRs reports were associated with adults (72.39% of total reports). The majority of the reports were written by pharmacists, with 960(87.19% of total reports) (**Table 3**).

For each of the 24 medications, the frequency of cardiac ADRs and ICSRs was highest for cardiac ADRs was for Tozinameran, with 100 reports (7.8%) to the lowest with 10 reports (0.9 %) for Oxytocin (**Table 4**). The number and percent of cardiac ADRs are arranged in **Table 5**, from Tachycardia with the highest cardiac ADRs of 595 (51.7%) to Cardiac arrest with the lowest 6 Cardiac ADRs (0.5%).

Based on the SOC system's assessment of undesirable effects with 1150 adverse effects (46.73%), cardiac disorders were found to be the most frequent reason of ADRs, followed by general disorders and conditions at the administration site (281 ADRs (11.42%), diseases of the lungs, thorax, and mediastinum (178 ADRs), gastrointestinal disorders (172 ADRs), diseases of the (172 ADRs), and nervous system disorders (149 ADRs). Other ADRs were less common and only seldom manifested (**Table 6**).

Table 3. Distribution of ICSRs by age group, gender, and reporter qualification.

Variable	Number of Individual Case Safety Reports	% of Individual Case Safety Report (ICSRs)
Gender		
Female	618	56%
Male	449	41%
Not Available	34	3%
Age Group	**% of ICSRs**	
Neonate	48	4.36%
Child	49	4.45%
Adolescent	25	2.27%
Adult	797	72.39%
Elderly	127	11.53%
Unknown	55	5%
Reporter qualification	**% ICSRs**	
Pharmacist	960	87.19%
Not Available,	45	4.09%
Other health professional	36	3.27%
Consumer or other non-health professional	36	3.27%
Physician	24	2.18%

Table 4. The number and percent of drugs that cause cardiac ADRs.

Drug name	Frequencies	Percent
Tozinameran	100	8.7
Salbutamol	92	8
Aminophylline	79	6.9
Azithromycin	56	4.9
Ceftriaxone	50	4.3
Favipiravir, Azithromycin	34	3
Hyoscine butyl bromide	25	2.2
Dexamethasone	22	1.9
Thyroxine	17	1.5
AstraZeneca COVID-19 vaccine	16	1.4
Isosorbide di nitrate	15	1.3
Metoprolol	15	1.3
Theophylline	15	1.3
Vancomycin	15	1.3
Ciprofloxacin	14	1.2
Hydrocortisone	14	1.2
Doxorubicin	13	1.1
Sino pharm	13	1.1
Trastuzumab	13	1.1
Bisoprolol	12	1
Amlodipine	11	1
Favipiravir	11	1
Nilotinib	10	0.9
Oxytocin	10	0.9

Table 5. Cardiac ADRs numbers and percent.

Reaction/event	Frequency	Percent
Tachycardia	595	51.7
Palpitation	268	23.3
Bradycardia	112	9.7
Arrhythmia	62	5.4
Atrial fibrillation	12	1
Heart failure	9	0.8
Heart attack	7	0.6
Cardiac arrest	6	0.5

Table 6. ADRs classification based on the SOC system.

SOC	N	%
Cardiac disorders	1150	46.73%
Conditions at the administration site and general problems	281	11.42%
Diseases of the respiratory, thoracic, and mediastinum	178	7.23%
Digestive system issues	172	6.99%
Diseases of the skin and subcutaneous tissues	151	6.14%
Nervous system disorders	149	6.05%
Vascular disorders	90	3.66%
Diseases of the muscles, bones, and connective tissues	53	2.15%
Renal and urological conditions	36	1.46%
Investigations	34	1.38%
Problems of metabolism and nutrition	33	1.34%
Psychiatric conditions	32	1.30%
Infections and infestations	23	0.93%
Eye disorders	18	0.73%
Breast and reproductive system problems	17	0.69%
Immune system conditions	10	0.41%
Blood and lymphatic system disorders	10	0.41%
Labyrinth and ear diseases	5	0.20%
Injury, toxicity, and procedural issues	5	0.20%
Hepatobiliary disorders	3	0.12%
Procedures in medicine and surgery	1	0.04%
Prenatal, perinatal, and pregnancy conditions	1	0.04%
Product issues	1	0.04%

ADRs: adverse drug reactions; SOC: System Organ Classification

Regarding the severity of cardiac ADRs, the majority of cardiac ADRs were observed in Level 1 (38.4%), Level 3 (20.1%), and Level 6 (19.7%). The cardiac ADRs, which were evaluated as Level 6, are serious and cause permanent harm to the patient. Level 4 (9.4%) requires intensive treatment and hospitalization. The last level 7 is serious, and they immediately endanger the lives of (1.7%) of the patients. The expectedness of the cardiac ADRs was investigated, and it was found that 0.2% of the cardiac ADRs weren't a part of the SmPCs. They are therefore regarded as surprising. About 31.7% of all cardiac adverse drug reactions were unexpected. The expected cardiac ADRs represented 68.1% of total cardiac ADRs. Concerning preventability, an assessment of the reported cardiac ADR cases showed that about (97.9%) of the cardiac ADRs among patients are probably preventable, whereas the proportion of non-preventable cardiac ADRs was (2.1%). According to a seriousness evaluation of the cardiac adverse drug reactions for the chosen medications, serious cardiac ADRs make up 45.6% of the ADRs, while non-serious cardiac ADRs make up 47.6% of the ADRs for the pharmaceuticals that were encountered. Only 6.9% of cardiac ADRs lacked sufficient information to determine how serious they were, and these cases are listed in the N/A category (**Table 7**).

Table 7. Reports of the severity, expectancy, preventability, and seriousness of cardiac adverse drug reactions.

Severity evaluation	Frequency	Percent
Level 1	442	38.4
Level 2	123	10.7
Level 3	231	20.1
Level 4	108	9.4
Level 6	226	19.7
Level 7	19	1.7
Expectedness	Frequency	Percent
N/A	2	0.2
Unexpected	365	31.7
Expected	783	68.1
Preventability	Frequency	Percent
Probably Preventable	1126	97.9
Not Preventable	24	2.1
Seriousness	Frequency	Percent
N/A	79	6.9
Not serious	547	47.6
Serious	524	45.6

N/A: Not Available.

DISCUSSION

The current study revealed that cardiac ADRs were more common in female patients; 56% of all ICSRs were linked to female patients. While only 3% of the reports did not specify gender, 41% were related to men. Previous studies, like one that examined 10 years (1986–1996) of ADR in a Canadian facility, found a similar tendency in the outcomes, with more than 70% of the 2367 patients evaluated being female [(27)]. Regardless of age group or amount of medications used, Botiger observed more adverse effects in females than in males using spontaneous reports to the Swedish Drug Reaction Committee. Similar findings were reached in a comprehensive prospective monitoring study of 1920 patients conducted in Chile [(28,29)].

In terms of architecture, physiology, and aging, the cardiovascular systems of men and women are different in certain ways [(30)]. As an illustration, women's hearts are smaller, their resting heart rates are three to five beats faster than men's, and their cardiac cycles are longer during menstruation [(31)].

Women have been found to have smaller Left main and left anterior descending arteries in the heart than males, regardless of their body size [(32)]. Due to their lower blood artery diameter, Women can be more susceptible to coronary blockage than males. Additionally, intriguing early epidemiological data shows that men's and women's inflammatory mechanisms related with plaque development may be different. It's interesting to note that recent hormone replacement therapy (HRT) clinical trials have revealed that C reactive protein (CRP) seems to be raised in the presence of greater estrogen levels [(33,34)]. These results collectively imply that estrogens may influence by using inflammatory pathways, plaque stability. According to recent statistics, plaque erosion happens more frequently when compared to men, more women experience plaque rupture [(35)].

While the age of the patients was taken into account when analyzing the cardiac ADRs, it was discovered that adults, who made up the majority of reports (72.39%), were followed by the elderly (11.53%), who made up the remainder of the reports. Dyslipidemia may also put women at a higher risk than men in women over the age of 65.

Our patients' average age was higher than in previous publications, and older patients were more likely to experience ADEs. This can be due to our inclusion criteria since patients using cardiovascular medications had rather high average ages.

Baghdad had the highest percentage of ICSRs among reporting provinces (40.6%), while Al-Kut had the lowest (0.36%). 17.98% of the stories omitted to mention the province. Baghdad has more hospitals and specialist clinics than other regions, which may help to explain this outcome.

The findings also showed that pharmacists reported the majority of cases (87.19%), followed by cases with uncertain reporter qualifications (4.09%), consumers, or other non-health professionals (3.27%), other health professionals (3.27%), and physicians (2.18%). The fact that pharmacists were more likely than other healthcare professionals to record ADRs and demonstrated a greater awareness of Pharmacovigilance suggests that they are

more in charge of "pharmacovigilance" in healthcare facilities.

The severity of the reported cardiac ADRs was assessed using the Hartwig-Siegel severity assessment scale. Most of the cardiac ADRs in this study were rated as minor by the Modified Hartwig and Siegel Severity Scale and did not need therapy. 20.1% of cardiac ADRs are of Level 3 severity, while 19.7% are of Level 6. With this level of severity, the ADR necessitated delaying, stopping, or altering the course of the suspected drug's treatment (Level 3), and the patient suffered a lasting injury (Level 6) [(21)].

The majority of cardiac ADRs in the current study were low in severity due to intervention. This may be because they can be fully resolved, or they may consider it a normal side effect of therapy. A total of 108 cardiac ADRs at level 4 on the Hartwig's severity scale led to an increase in length of stay by at least one day, OR the ADR was the reason for the admission. A total of 226 cardiac ADRs at level 6 on the Hartwig's severity scale were sufficiently serious to cause permanent harm to the patient. Assessing whether a cardiac adverse impact has lengthened a patient's stay or resulted in death, and specifically whether it is the result of the underlying illness or an adverse consequence, may be incredibly challenging.

CONCLUSION

Tachycardia was the cardiac ADR for which the most reports were made. Most reported cardiac ADRs were low in intensity, predictable, not life-threatening, and most likely preventable. The lack of information in the ICSR reports impacted how the reports were evaluated, necessitating the creation of training initiatives to create a stronger reporting system. Giving clinicians and entire healthcare systems the resources they require to improve and strengthen pharmacovigilance programs through greater reporting of adverse events is essential. Decision-makers can benefit from this kind of study in discussions regarding patient safety and interaction with healthcare systems.

Conflict of interest: The authors say they have none.
Funding sources: Did not get any special grants from for-profit industries.
Equal contributions from all authors were made to the study.

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