ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by Pharmascope Publications Journal Home Page: www.pharmascope.org/ijrps

Pharmacovigilance study of the Penicillin's adverse drug reactions and their seriousness in the Iraqi hospitals

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Article History:

Received on: 15.03.2018
Revised on: 23.08.2018
Accepted on: 27.08.2018

Keywords:

Adverse Drug Reactions, Allergic reactions, Antibiotics, Pharmacovigilance

ABSTRACT

Antibiotics represent one of the most prescribed drugs, antibiotics found to cause about 25% of the entirely reported Adverse Drug Reactions (ADRs), and the ADRs found to be one of the leading causes of morbidity and mortality worldwide. The data collected from the Iraqi Pharmacovigilance database then sorted and analysed, and eventually only 137 reports regarding penicillins included. The data showed that the Penicillins caused 48 severe ADRs and allergic reactions and skin responses were the most reported exceeding the half of the total pool of the ADRs. We concluded that the ADRs were mostly unpredictable or type B which unusual since it should not exceed the 20% of the total ADRs hence this is a new field of study in Iraq, further studies will be required to set the track of achieving the goal of pharmacovigilance.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v9i3.1628

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INTRODUCTION

Fitzgerlad said, 'the safety of drugs is of paramount importance to patients and healthcare professionals.' The repercussions of a new drug having a potentially dangerous side effect profile are enormous for patients, healthcare professionals and the industry" (S. *et al.,* 2013). Pharmacovigilance (PV) was briefly defined as the science and activities that were related to detecting, assessing then understanding and preventing the noxious unwanted drug effects or any other medicine-related problems; that may include herbals, medical devices, vaccines, blood products, biological or biosimilar drugs, drug-related mortality, substandard medications, drug errors and drug poisoning (Ronald and Elizabeth, 2002). As regarded one of the most critical health-related problems, ADRs might have caused very serious and potentially life-threatening conditions (Gomes and Demoly, 2005) and The International Conference of Harmonization (ICH) guidelines for Good Clinical Practice (GCP) had defined Adverse Drug Reactions (ADRs) as "any response to any medicinal product which was noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease or the modification of physiological function which includes the terms out of marketing authorization such as off-label uses, overdose, misuse, abuse and medication errors" (Abdel-Latif and Abdel-Wahab, 2015). Antibiotics represent one of the most prescribed drugs in the USA, around 16% of the emergency cases require the use of these drugs and alone they cost about more than a one billion dollars just for the promotional services (Shehab *et al.,* 2008) and in another study the rate of antibiotic prescription in the hospitals involve at least half the hospitalized patients which represent a (20-50 %) of the total drug expenditure (Geitona *et al.,* 2017), and in Australia the antibiotics found to cause about 25% of the entirely reported ADRs

(Trubiano *et al.,* 2015). The ADRs found to be one of the leading causes of morbidity and mortality worldwide, accounting for around 10 – 20 % of the hospitalization cases (Nagaiah *et al.,* 2017) with collective incidence of 6.7% to be branded as severe ADRs and 0.32% that led to fatality (Shah *et al.,* 2017, Granowitz and Brown, 2008).

Since the most unpredictable common reaction to Penicillin is the allergic reaction, Drug allergy defined as an immune-mediated response to a pharmaceutically active material or formulation additive or excipient agent in a sensitised person (2010). Allergic drug reactions, formerly used in an inappropriate way to describe the incidence of ADRs (Gomes and Kuyucu, 2017) and they are of four types: Type I reactions (the Immediate Hypersensitivity Reaction), which are mainly an IgE-mediated histamine release like anaphylaxis and allergic rhino-conjunctivitis (Pichler, 2003, Ariza *et al.,* 2014). Type II reactions (Cytotoxic Hypersensitivity Reaction) which are mainly related to the cytotoxic effect of immunoglobulins mostly IgG and sometimes IgM usually represented by blood dyscrasias like anaemia's (Pichler, 2003, Ariza *et al.,* 2014). Type III reactions (Immune Complex Reaction), which are the reactions caused by the direct effect of the immune complexes which mostly deposit in the post-capillary venules triggering the complement cascade like serum sickness (Pichler, 2003, Ariza *et al.,* 2014). Type IV reactions and they are called Type D or sometimes the Delayed Hypersensitivity reaction because of their delayed appearance which was mainly attributed to the cell-mediated response of the T- cells of the immune system (Ariza *et al.,* 2014, Aronson and Ferner, 2003). Anaphylaxis formerly has been known as an Ig-E-mediated response while anaphylactoid represent the correspondent event. They were clinically indistinguishable and hard to diagnose as the severity might change from episode to episode considering the causative factor was the same (Kemp *et al.,* 2008).

While Gastrointestinal side effects are the most common Predictable ADRs, diarrhoea is the most frequently reported ADR, and medically defined as the passage of more than 200 gram of stool per day or changing the stool consistency such as watery, bloody or mushy with more than three times per day and may be caused by the direct organic or toxic effect of the antibiotics on the intestine or by altering the normal flora causing overgrowth of certain bacteria like the opportunistic *Clostridium disciple* or what was called the infectious origin of Antibiotic-related diarrhoea although it accounts for only 10-20% of the total diarrhoea cases with minor cases another organism could cause diarrhoea as Antibiotic-Resistant Salmonella and Candida species (Hogenauer *et al.,* 1998). Penicillin rarely cause a serious case of colitis known as "Acute Segmental Haemorrhage- Associated Penicillin Colitis" in which the endoscopic and macroscopic appearance showed several layers that have been lost or eroded from the duodenal and terminal ileac segments mostly affecting the epithelial layer with Goblet and Paneth cells where observable without any sign of viral infections finally the lamina properia have shown some dense appearance, and T- cells were higher (Hogenauer *et al.,* 1998, Wurm *et al.,* 2017). All these ADRs could be serious or not thus; the seriousness which was usually studied based on the clinical experience of the experts or based on certain criteria, the seriousness has been investigated for the reason that during drug development processes, ADRs have emerged and these ADRs may range in their severity to those who require a tangible change in drug development; including changing the dose, apply TDM rules or apply some consent forms this is especially imperative if the ADR was severe enough that may threaten life or impair a certain function (Scavone *et al.,* 2017). The current study aims to understand the pattern of ADRs those are happening after giving the penicillin group drugs to the patients and comparing the results with the global results to achieve the goal of the pharmacovigilance that relies on promoting and communicating safety of the drugs.

Methods

This descriptive, retrospective study has been conducted in Iraq using the database of the Iraqi Pharmacovigilance Center in which more than a thousand reports reviewed, and the reports with which Penicillins included have been selected while the others eliminated, thus; 137 reports studied in which the ADRs classified according to Rawlings and Thompson classification, and The seriousness was assessed based on the criteria previously applied by the staff of the Pharmacovigilance center or the Iraqi regional centers found in the health directorates in all Iraqi provinces, these criteria are available in the Individual Case Safety Report (ICSR), which is the paper reporting form of the encountered ADRs in all Iraqi hospitals. The seriousness was assessed based on the criteria included in the ICSR paper below (Rawlins, 1981, 2018). Discrete variables presented using there number and percentage, while mean and standard deviation used for continues data presentation, Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA) used to carry out the results.

RESULTS

Male had a similar ratio to female (50.4% to 44.5%, respectively) with 7 with unknown gender (lost

data) as illustrated in figure 1. 44 cases had an age group between 18 – 44 years, followed by 29 cases 2 – 11 years, 26 cases 1 – 23 months, 16 cases 45 – 64 years, 9 cases 1 – 28 days, 6 cases 12 – 17 years, 5 cases ≥65 years and 2 cases with unknown age as illustrate in figure 2.

The majority of cases reported from Nineveh 47 cases, followed by 32 cases from Aldewaniah, 19 cases from Baghdad, 4 cases from Kirkuk and one case from each of Najaf, Babylon and Basra, 30 cases from unknown governorate, as illustrated in figure 3. The most common adverse reaction is an allergic reaction and skin rash with 74 cases (54.0%), followed by 36 cases (26.3%) GIT side effect, 17 cases (12.4%) anaphylactic reaction, the rest illustrated in figure 4. The frequency of serious ADRs was 35.0% (48 cases), as illustrated in figure 5.

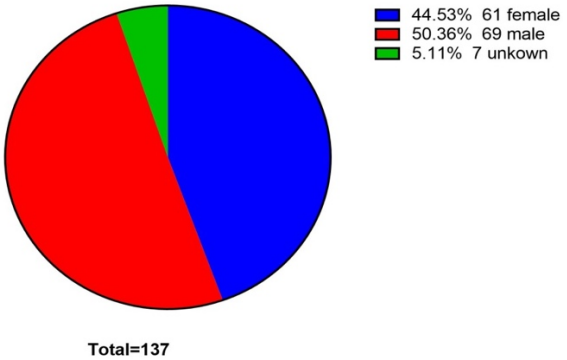

Figure 1: The distribution of genders in the reports sent to the IPVC in which some of the reports contained insufficient demographic data

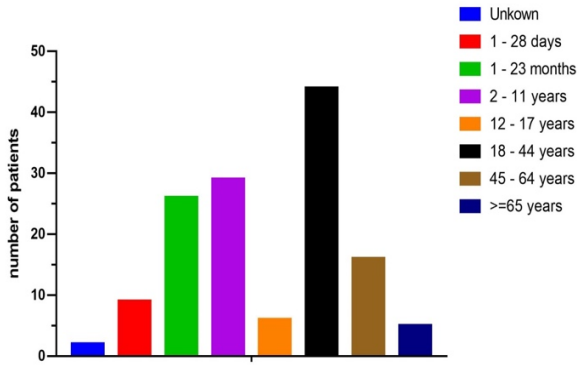

Figure 2: The reports distribution regarding the age groups of the patients who had encountered antibiotics related to ADRs.

DISCUSSION

The results in the current study show similarity between male (69 reports) and females (61 reports) in the incidence of ADRs which may suggest the idea that the gender is not a risk factor for ADRs incidence. The results in current study regarding the age groups of the patients in the reports which had been sent to the center, shows that the age group of adult effective working age which is between (18-44) is the most affected with 44 cases has been reported to have Penicillin- related ADRs, and this may reflect the fact that this age group bears the burden of work and the occupational hazards which may lead to hospitalization and the need for such antibiotics thus the appearance of such ADRs.

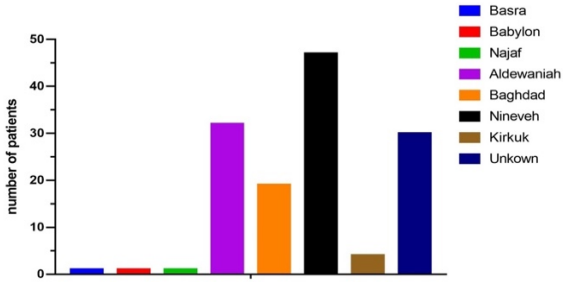

Figure 3: The demographic data of the reports numbers which had been sent by each governorate.

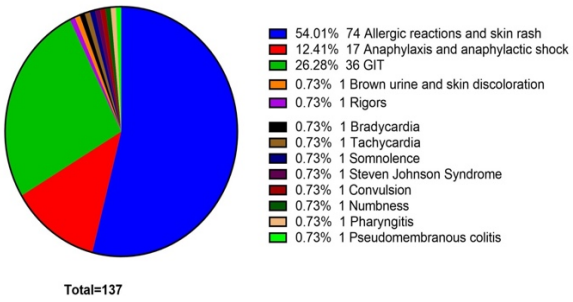

Figure 4: The count of different ADRs who reported to the Iraqi Pharmacovigilance Center in which the hypersensitivity reactions were the most abundant

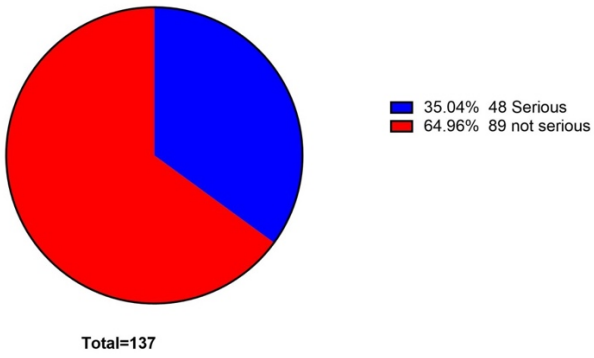

Figure 5: The seriousness of the ADRs in the reports which sent to the centre was about two-thirds were not serious

Nineveh, despite the war is still the governorate which sent the majority of the reports compared to other provinces in which they are safe yet made little or null contribution to the drug safety global efforts, the second most senders were the not available or unknown which is a very common practice in the reports which reviewed in this study which may be caused by the lack of value of these data in the perspective of the reporters.

ADRs revealed a very strange pattern in which the number of the unexpected ADRs (Allergic reaction are an example) exceeds the recognized ratio of

not more than 20% of the total reports while the rest is predictable (74 reports were unpredictable which means not mentioned in the leaflets when the drug first marketed, and the remaining 63 were predictable) which may reflect a real problem in the reporting pattern as the staff may miss reporting the minor or predictable type A reactions which may usually confuse the staff with the normal conditions that the patient may encounter in the hospitals which may mislead the staff to ignore them thinking that those may not have a relevant connection with the drugs taken and ADRs that may be caused by Penicillin such as the GIT side effects which could be precipitated by many of the drugs which are being given concomitantly during the inpatient settings.

The serious ADRs reported in 48 out of 137 (35%) reports were serious reports which required hospitalisation and patients receive some management according to the criteria stated in the Iraqi Pharmacovigilance Centre's reporting paper form or the Individual Case Safety Report (ICSR).

Reviewing and comparing the data with the results found in other studies which had been conducted in several countries like in South Korea, in one multicentre study in 2009 the number of serious ADRs found to be 17.7% while in a newer study conducted in the same country, but in 2017 the ratio of the serious ADRs found to be only 3.4% which is considered a huge improvement for this country (Jung *et al.,* 2017, Shin *et al.,* 2009).

Another study which conducted in Uganda 2017 and India 2017 found that the percentage of the serious ADRs caused by the antibiotics use is about 32% and 23% respectively, which is very high yet not as high as the results of our study and the reason after this high incidence is not clear if the underreporting is the problem, the fact that the staff did not see the benefit of reporting simple ADRs (maybe they could not see the actual value of such reports) or they were not aware of such reactions, and the only ADRs they saw were serious, and they reported it (Kiguba *et al.,* 2017, Vijaishri and Andhuvan, 2017).

CONCLUSION

The data above suggest that the Penicillin caused 137 reported ADRs to the centre with one third of these reports were recognized as serious ADRs and the remaining were not serious and more than half the reports contained unpredictable or type B ADRs which suggest a real problem in the reporting system more than issues in the drugs themselves as it is globally known that the predictable ADRs account for 80% which was not the case in our study which highlights an underreporting issue in the staff that may lack the experience due to the fact that this field is relatively new to the Iraqi medical field and thus promoting such responsibility and sharing the efforts with the proper training programs to all staffs will allow us to obtain the optimal goal of promoting and communicating and safety to the patients.

Conflicts of interests

All authors have none to declare

Author contributions

All author contributed equally

REFERENCES

2010. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol,* 105**,** 259-273.

2018. *Individual Case Safety Report* [Online]. Iraqi Pharmacovigilance center Available: http://www.tecmoh.com/mypages/books/hvLunzPpY0.doc [Accessed].

Abdel-Latif, MM. & Abdel-Wahab, B.A. 2015. Knowledge and awareness of adverse drug reactions and pharmacovigilance practices among healthcare professionals in Al-Madinah Al-Munawwarah, Kingdom of Saudi Arabia. *Saudi Pharm J,* 23**,** 154-61.

Ariza, A., Fernandez, T. D., Dona, I., Aranda, A., Blanca-Lopez, N., Melendez, L., Canto, G., Blanca, M., Torres, M. J. & Mayorga, C. 2014. Basophil activation after nonsteroidal anti-inflammatory drugs stimulation in patients with immediate hypersensitivity reactions to these drugs. *Cytometry A,* 85**,** 400-7.

Aronson, J. K. & Ferner, R. E. 2003. Joining the DoTS: a new approach to classifying adverse drug reactions. *BMJ,* 327**,** 1222-5.

Geitona, M., Toska, A., Latour, D., Sardi, M., Evripidou, A. & Evripidou, I. 2017. Antibiotics' Prescribing and Pharmacovigilance Attitudes among Pediatricians and Pediatric Residents in Cyprus. *Pharmacology & Pharmacy,* 8**,** 75-84.

Gomes, E. R. & Demoly, P. 2005. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol,* 5**,** 309-16.

Gomes, E. R. & Kuyucu, S. 2017. Epidemiology and Risk Factors in Drug Hypersensitivity Reactions. *Current Treatment Options in Allergy,* 4**,** 239-257.

Granowitz, E. V. & Brown, R. B. 2008. Antibiotic adverse reactions and drug interactions. *Crit Care Clin,* 24**,** 421-42, xi.

Hogenauer, C., Hammer, H. F., Krejs, G. J. & Reisinger, E. C. 1998. Mechanisms and management of antibiotic-associated diarrhoea. *Clin Infect Dis,* 27**,** 702-10.

Jung, I. Y., Kim, J. J., Lee, S. J., Kim, J., Seong, H., Jeong, W., Choi, H., Jeong, S. J., Ku, N. S., Han, S. H., Choi, J. Y., Song, Y. G., Park, J. W. & Kim, J. M. 2017. Antibiotic-Related Adverse Drug Reactions at a Tertiary Care Hospital in South Korea. *Biomed Res Int,* 2017**,** 4304973.

Kemp, S. F., Lockey, R. F. & Simons, F. E. 2008. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy,* 63**,** 1061-70.

Kiguba, R., Karamagi, C. & Bird, S. M. 2017. Antibiotic-associated suspected adverse drug reactions among hospitalized patients in Uganda: a prospective cohort study. *Pharmacol Res Perspect,* 5**,** e00298.

Nagaiah, B. H., Patil, S. B., Vahila, N., Venkata Rao, Y., Raikar, S. R. & Sajid, M. 2017. Analysis of adverse drug reactions of antimicrobial agents reported to ADR monitoring centre of a rural tertiary care teaching hospital. *International Journal of Basic & Clinical Pharmacology,* 6**,** 1151-1154.

Pichler, W. J. 2003. Delayed drug hypersensitivity reactions. *Ann Intern Med,* 139**,** 683-93.

Rawlins, M. D. 1981. Clinical pharmacology. Adverse reactions to drugs. *Br Med J (Clin Res Ed),* 282**,** 974-6.

Ronald, D. & Elizabeth, B. 2002. *Pharmacovigilance,* New York, USA, John Wiley & Sons, Ltd.

S., P., K, M. & S, A. 2013. Causality, severity and preventability assessment of adverse cutaneous drug reaction: a prospective observational study in a tertiary care hospital. *J Clin Diagn Res,* 7**,** 2765-7.

Scavone, C., Sportiello, L., Sullo, M. G., Ferrajolo, C., Ruggiero, R., Sessa, M., Berrino, P. M., Di Mauro, G., Berrino, L., Rossi, F., Rafaniello, C. & Capuano, A. 2017. Safety Profile of Anticancer and Immune-Modulating Biotech Drugs Used in a Real World Setting in Campania Region (Italy): BIO-Cam Observational Study. *Front Pharmacol,* 8**,** 607.

Shah, R. C., Karki, S., Parajuli, S. B., Bhattarai, P. & Chowdhary, P. K. 2017. Pharmacovigilance by World Health Organisation Uppsala Monitoring Center Causality Assessment Algorithm in Medicine Ward of Tertiary Care Hospital of New Delhi. *Birat Journal of Health Sciences,* 1**,** 61-64.

Shehab, N., Patel, P. R., Srinivasan, A. & Budnitz, D. S. 2008. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis,* 47**,** 735-43.

Shin, Y. S., Lee, Y. W., Choi, Y. H., Park, B., Jee, Y. K., Choi, S. K., Kim, E. G., Park, J. W. & Hong, C. S. 2009. Spontaneous reporting of adverse drug events by Korean regional pharmacovigilance centers. *Pharmacoepidemiol Drug Saf,* 18**,** 910-5.

Trubiano, J. A., Cairns, K. A., Evans, J. A., Ding, A., Nguyen, T., Dooley, M. J. & Cheng, A. C. 2015. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. *BMC Infect Dis,* 15**,** 572.

Vijaishri, R. & Andhuvan, G. 2017. A prospective study on antibiotics-associated spontaneous adverse drug reaction monitoring and reporting in a tertiary care hospital. *Asian J Pharm* 11**,** S834-S840.

Wurm, P., Spindelboeck, W., Krause, R., Plank, J., Fuchs, G., Bashir, M., Petritsch, W., Halwachs, B., Langner, C., Hogenauer, C. & Gorkiewicz, G. 2017. Antibiotic-Associated Apoptotic Enterocolitis in the Absence of a Defined Pathogen: The Role of Intestinal Microbiota Depletion. *Crit Care Med,* 45**,** e600-e606.