Available online on 15.01.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

The spectrum of adverse drug reactions in a multidisciplinary kidney clinic

Shaima Al-Bader *, Shaikha Al-Bader **, Kamel El-Reshaid ***

* Asad Al-Hamad dermatology center, Ministry of health, Kuwait

** Department of Medicine, Kidney unit, Al-Amiri Hospital, Ministry of health, Kuwait

*** Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

ABSTRACT

Introduction: Data on adverse drug-reactions (ADR) in the medical field are rare. **Objective:** To report on the pattern of such problem in a multidisciplinary kidney clinic **Patients and Methods:** Medical records of patients were reviewed retrospectively for such phenomenon in the past 6 years **Results**: A total of 4834 patients were included for analysis. The unit is responsible for a large proportion of patients with acute and chronic kidney diseases of diverse etiologies and multiple co-morbid conditions. Acute and maintenance dialysis as well as immunosuppressive treatment for idiopathic glomerulopathy and autoimmune systemic diseases were common practice. **Results**: A total of 70044 ADR were diagnosed in 4438 patients. Most patients were adults (39±14) and had median follow up of 38 months. Nearly half of the ADR were due to drug-side effects while idiosyncrasy accounted for 1.2%. The former is due to misuse/abuse of medications while the latter is due to genetic, co-morbid conditions or synergetic between 2 drugs or a drug and disease. Details of drugs ADR are outlined with their respective prevalence. Our study indicates the need for careful auditing of patient's response during follow up to improve their drug-compliance.

Keywords: adverse drug reaction, allergy, medical clinic, kidney disease.

Article Info: Received 10 Nov 2018; Review Completed 20 Dec 2018; Accepted 27 Dec 2018; Available online 15 Jan 2019

Cite this article as:

Al-Bader S, Al-Bader S, El-Reshaid K, The spectrum of adverse drug reactions in a multidisciplinary kidney clinic, Journal of Drug Delivery and Therapeutics. 2019; 9(1):61-67 **DOI: http://dx.doi.org/10.22270/jddt.v9i1.2160**

***Address for Correspondence:**

Dr. Kamel El-Reshaid, Professor, Dept. of Medicine, Faculty of Medicine, Kuwait University, PO Box 24923, 13110 Safat, Kuwait

INTRODUCTION

An adverse drug reaction (ADR) is a harmful and unintended response to a drug. This includes any undesirable patient's effect suspected to be associated with health product use. Unintended effect, health product abuse, overdose, interaction (including drug-drug and drug food interactions) and unusual lack of therapeutic efficacy are all considered to be reportable adverse reactions. A serious ADR is one that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. ADRs are major public health problem in terms of morbidity, mortality, and cost [1]. In USA, their costs exceeded 4.2 billion annually and comprise 3% to 6% of all hospital admissions and complicate 10% to 15% of hospitalized patients [2]. Data from the Arabian Gulf-area, such as Kuwait is limited to a single report on 51 referrals collected over 3 years by Al-Rashid allergy center [3]. The present study was aimed to shed some lights on the extent of the problem in our area.

PATIENTS AND METHODS

Study design:

Medical records of patients attending El-Reshaid kidney clinic from 1st June 2012 to 31st May 2018 were analyzed retrospectively for ADRs. The clinic was established in 1997 in the capital of Kuwait city. It is a referral center and equipped with adequate diagnostic and therapeutic facilities to care for both in- and out-patients with all medical and renal diseases.

Inclusion criteria:

Patients were included if they had developed a reaction (sign and/or symptom) to a given drug that had developed immediately and up to weeks later. A checklist was used to report medications of all patients and to define those with ADR. The latter was further classified into: (a) allergic (b) delayed hypersensitivity reactions (c) intolerance (d) idiosyncrasy (e) misuse/abuse.

Definitions and classification:

ADR were classified according to definitions of the Committee of World Allergy Organization [3].

(a) Allergic ADR refer to IgE-mediated hypersensitivity reactions which include urticaria, angioedema and anaphylaxis. (b) Delayed hypersensitivity reactions include T-cell mediated immunity viz. drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiformis, Stevens-Johnson syndrome, toxic epidermal necrolysis. (c) Drug intolerance is an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. (d) Drug idiosyncrasy is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug. It is not mediated by a humoral or cellular immune response but is reproducible on readministration. Unlike drug intolerance, it is usually due to underlying abnormalities of metabolism, excretion, or bioavailability. (e) Misuse/abuse of a drug refers to toxicity to a drug which has been inadvertently administered at a higher dose or for a prolonged period

Statistical analysis:

The mean and ± standard deviation were used to describe the normally distributed variables viz. age. However, since the duration of follow up was not normally distributed, they were expressed as a median and (interquartile range).

RESULTS

Over the past 6 years, a total of 4438 patients fulfilled the above mentioned criteria and hence were included in the study. The demographical data on the patients are summarized in (Table 1). Patients with different age groups were included (range: 6-78 years) yet mostly they were adults (mean: 39±14) years. Gender distribution was almost equal (Male/Female: 0.9). Average follow up of those patients was (38±18) months. The initial cause of screening, including their co-morbid conditions and the in-patient activity are summarized in table 1.

Table 1: Epidemiological profile of the patients screened

Category		No.
Demographical data:		
	age (years)	39±14
	Sex (Male/Female)	0.9
	Duration of follow up (months)	38(18)
Initial cause of screening:		
Renal-related:		
	Acute renal failure:	538
	Chronic renal failure	827
	Nephrotic syndrome	432
	Electrolytes abnormalities	159
	Active autoimmune state	276
Co-morbid conditions:		
	Coronary artery disease	557
	Infection	340
	Uncontrolled diabetes mellitus	458
	Uncontrolled hypertension	206
	GI-related	437
	Autoimmune disease (without renal involvement)	97
	Peripheral vascular disease	68
	Miscellaneous	43
Grand total:		**4438**
In-patient activity:		
	Admissions	283
	Observation room	395
	Access placement	420
	Access complications:	366
	Kidney biopsy	136
	Skin biopsy	16

Miscellaneous conditons included fractures, malignancy, psychiatric disorders, DVT/PE

* Age expressed in mean+SD while duration of follow up in meadian (interquartile range)

Specific ADR:

Antibiotics:

A- Lactam antibiotics: Penicillin allergies were rare for 2 reasons: (a) rarely used (b) all patients were tested by a skin test before its use. Amoxicillin & cephalosporins reactions were rare. (None with EBV had received it). However, gastritis was common.

B- Non-Lactam:

1- Sulphonamide with/without trimethoprime: gastritis was common and 2 cases of EM were associated with it. Overall, they were rarely used in chest and urinary tract infections because of high incidence of resistance.

2- Vancomycin: No reaction except for 1 patient who had developed red-man syndrome (erythema, pruritis and flushing especially in the neck area). The latter is due to non-IgE-mediated histamine release. He improved after slowing the infusion rate and antihistaminics.

3- Aminoglycosides rarely caused ADR except for misuse by not adjusting the dose leading to acute tubular necrosis (ATN) and deafness with streptomycin after 2 weeks treatment for drug-resistant Brucella endocarditis.

4- Quinolones: gastritis was common if the dose in > 250 mg X2. Drug allergy was rare with oral and IV Ciprofloxacillin compared to multiple incidents with acute interstitial nephritis in other quinolones.

5- Anti-mycobacterial drugs were well tolerated except for gastritis. However, Rifampicin and INH had major problems with:

(a) Pruritis indicating discontinuation in % of patients.

(b) Abnormal liver functions in %

6- Diflucan and ampizone: no allergy was reported with their use yet the Ampizone has to be given slowly to avoid hypotension due to Non-IgE-mediated histamine release.

7- Acyclovir allergy was common despite dose adjustment (3/197) compared to 0/65 with gancyclover.

Diuretics:

No allergy was noted with Furosamide despite its common use for patients with renal and heart failure (0/3031) compared to 279/438 with thiazides. The latter were used for prophylaxis in nephrolithiasis & an adjuvant treatment, with Furosamide, in refractory edema states. Aldactone-use was associated with significant allergy (133/672) which was mainly pruritis.

Antihypertensive:

1- Allergy was rare except for cough/throat irritation, shortness of breath with ACEI 237/2014 and 25/1896 with ARB compared to none in hundreds to thousands treated by others.

2- Intolerance to antihypertensive leading to drug-discontinuation was a common problem. Headache with Nifidipine, dependent-edema with Amlodopine, constipation with Verapmil. The latter, was associated with major bradycardia with misuse combination with betablockers. Overall, the most tolerated was Diltiazem. Oversedation was a major problem with 2 potent drugs viz. Aldomet and Clonidine. Autoimmune hemolytic anemia, lupus nephritis and hepatitis were rarely reported despite the extensive use of Aldomet.

3- Hyperkalemia was a major problem in those treated with Spiranolactone, beta-blockers and ACEI/ARB drugs.

4- Precipitation of an asthma or heart failure was a common problem with beta-blockers. On the other hand, direct vasodilators-use was limited in the elderly due to sinus tachycardia limiting its use in ischemic heart disease patients.

Anti-platelets:

Aspirin was responsible for 2/2064 cases of chest allergy compared to 166/976 cases of severe pruritis with plavix.

Statins: No reported allergy with the drugs yet significant intolerance of muscle aches with/without rabdomyelisis was noted. Rusovastatin was the least culprit yet the dose cannot be increased safely above 40 mg daily for fear of rhabdomyelisis. Evolocumab (Repatha) is an inhibitor antibody of proprotein convertase subtilisin kexin type 9. It is a promising drug and in the cases used it was effective and without allergy, liver injury and rhabdomyelisis side effects.

Oral hypoglycemia agents:

No major allergic phenomenon except for severe metabolic acidosis in 2 patients who, by mistake, did not discontinue their Metformin at a GFR < 30%. Metformin was discontinued in % of patients for intolerable gastritis and DDP-4 for pancreatitis.

Disease-modifying agents (DMRARDs):

1- Aspirin/salazopyrines were rarely used.

2- Methotrexate: no case of interstitial pulmonary fibrosis was reported with dose < 6 tab/week.

Blood products and blood transfusions:

With erythropoietin blood transfusions were rarely used for treatment of anemia of chronic renal failure. However, patients with life-threatening acute bleeds had received blood transfusions. All patients were screened for blood groups and rheusus types as well cross match was done prior to blood transfusions. Routine testing for IgA-deficiency and IgA antibodies were not done. Fortunately, transfusional anaphylaxis was not recorded. For short-term treatment of leucopenia; Filgrastim (Nepogen) was an effective and safe agent. Similar experience was noted with Romiplostin (Nplate) for severe thrombocytopenia. Protamine sulphate was rarely used for correction of overzealous heparinization due to its previous experience with allergic reactions and misuse with exaggeration of bleeding. Our approach was to simply use infusions of few bags of fresh frozen plasma to correct for overzealous anticoagulation.

Table 2. The pattern of adverse drug reactions (ADR) encountered with the common drugs

Class / Drug	ADR (No. & % of total)					Total cases
	Allergic	Cytotoxic	Intolerance	Idiosyncrasy	Misuse/abuse	
Antibiotics:						
Klacid		1	86			693
Azithromycin		1	11			64
Clindamycin			65		24	862
Amoxicilin	3		69		13	995
Keflex	1		23			186
Zinnat			47			612
Rocephine	2					735
Tazocin	4				1	261
Meropenum	1				1	1892
Vancomycin					2	1892
Amikacin					5	753
Ciprofloxacin		1	56			863
Other quinolones	5	1	27			92
Metronidazole			213(33%)			644
Rifampicin	42(11%)	2	10	27	26	376
Isoniazide	73(17%)		37	13	35	431
Ethambutol			187(71%)			263
Pyrazinamide	2		57			263
Streptomycin					1	2
Diflucan			13			473
Ampizone					3	357
Acyclover	3		2		35	197
Gancyclover					2	65
Diuretics & Antihypertensives:						
Furosemide					643(21%)	3031
Thiazides	279(64%)				223(51%)	438
Spiranolactone	133(20%)				289(43%)	672
Adalat LA			298(30%			784
Amlodopine			882(55%)			1608
Lercandipine			67			386
Diltiazem			3		8	1276
Verapmil			132(36%)		32	372
ACEI	43				622(31%)	2014
ARB	12				562(30%)	1896
Beta blockers			257		342	1896
Minipress/Doxazocin					26	185
Minoxidil			38(88%)		12	43
Hydralazine			92		60	293
Clonidine			309(53%)		27	582
methyldopa			605(62%)		2	974
Labetolol			3		12	483
Dilatrend			21		33	861

Continuation of table 2. The pattern of adverse drug reactions (ADR) encountered with the common drugs

Class / Drug	ADR (No. & % of total) Allergic elayed hypersensetivi		Intolerance	Idiosyncrasy	Misuse/abuse	Total cases
Anti-platelets:						
Aspirin	2		5		449	2059
Plavix	166(17%)					976
Anticoagulants:						
Heparin	217(12%)				64	1849
LMWH					33	694
Warfarin	4				648(50%)	1286
Xarleto					12	253
Statins:						
Simvastatin			144	83(9%)		892
Atrovostatin			231	34		1107
Rusovastatin			26	17		973
Evolocumab						162
Oral anti-diabetic agents:						
Biguanides			326		228	1821
Thiazolidinediones			6			2737
2nd G Sulphonylurea					665(40%)	1652
Meglitinides					65	649
Insulin:						
Short-acting					328	1728
Long-acting					669(34%)	1978
Mixtard					792(68%)	1159
GLP:						
DPP-4:			233		213	376
SGLT-2 inhibitors:			36		62	189
Antiepileptics:						
Phenytoin	3	2	32		6	271
Carbamazepine	6	4	12		5	187
Others			3			163
Opiates:	3		5		238(36%)	664
Local anesthetics:	5		136		2	2895
Corticosteroids:			829(40%)		325	2071
Radio-contrast media:	4		47		334(37%)	893
NSAIDs:	529(81%)		253(39%)	42	378(58%)	649
H2-blockers & PPI:						4761
Miscellaneous agents:						
Rituximab	26(8%)	1		5		327
Adalimumb		1				29
d-Penicillamine:			2			46
Allopuronol	228(22%)				103	1029
Pregabalin (Lyrica)			247(38%)		61	649
Vitamin D					87	338
Oral iron	83		447(41%)		258	1092
IV iron (Ferinject)	3		1		26	662
Gum Arabia	5				8	8
Grand total:	1887 (2.7%)	14 (0.02%)	6631 (9.5%)	221 (0.3%)	9100 (13 %)	70044

Anti-coagulants:

Hypersensitivity reactions to unfractionated heparin were common. Skin allergy and fever were rare except for purpura due to severe thrombocytopenia. The latter was noted with and ½ of the cases were associated with spontaneous thrombosis i.e. Heparin-induced thrombocytopenia and thrombosis (HITT). The latter was a major practical challenge in management of the acute thrombosis and subsequent long-term anti-coagulation. Recently, and for unknown reasons, HITT is a major problem for our hemodialysis patients. It may have been related to new manufacturing technique which is currently being investigated in Kuwait. Overall, it is our practice to avoid Heparin and Warfarin in these patients in the acute phase and to use adjusted dose of Fondaparinux since Argatroban in not available yet in Kuwait. Warfarin use was associated rarely with skin-necrosis but frequent if used early in HIT cases.

Opiates: are rarely used in our patients except for a combination of Paracetamol and Codiene to avoid the use of NSAIDs for osteoarthrosis and Short course of Tramadol with/without Paracetamol in severe preoperative pain. Constipation is a major side effect of Codiene and drug-dependence with Tramadol if misused.

Local anesthetics: vasovagal attacks were common. It was difficult to discriminate between anxiety and true pseudoallergic mechanisms. All were benign and responded to conservative management and the procedure was accomplished. Rarely true allergic reactions or misuse of inadvertent intravenous leak of an adrenaline has used dysarrythmias.

Radiocontrast media: is a major cause of concern with regards the subsequent high incidence of

ATN in patients with renal impairment. The use of non-ionized dye did not decrease incidence of allergy or vomiting if proper pre-medication with an antihistaminic is given. Our protocol of hydration with N-acetylcystine for those with GFR > 50% was adequate. Those with GFR < 50% were treated with CVVHF 6-12 hours immediately after the dye study and did not have significant deterioration of the poor kidney function.

Many patients by mistake did not discontinue their Metformin, 3 days prior to the procedure and did not have any side effect.

All patients with history of atopy and hyper-reactive air way disease or allergy to radiocontrasts were safe with prior antihistaminics and corticosteroids.

Aspirin allergy: (asthma, rhinitis, sinusitis, urtecaria, angioedema) was not encountered. Major concern was misuse by combining Aspirin and Warfarin with 2 peptic bleeding of which 1 was fatal. However, combining other anti-platelets with anticoagulants was seldom a problem if dose of the

NSAIDs: are major concerns for our patients. They were rarely used in our patients for fear of their deleterious effects on the kidney. Acute interstitial nephritis had developed in 529

of the 649 patients who had used them. Acute deterioration of dehydrated patients and those with chronic renal disease was noted in 253. Forty two patients had developed acute papillary necrosis with them. A total of 378 patients those drugs should not have been used and had resulted in the previous side effects as well as gastritis and peptic disease if were not pre-medicated with PPI.

H2-blockers and PPI: were safe drugs and were not associated with higher incidence of aspiration pneumonia.

Miscellaneous group of drugs:

A- Immunomodulatory agents: Rituximab was used extensively in our patients with nephrotic syndrome and lupus nephritis as well as patients with severe chronic urticaria, pemphigoid and skin vasculitis. It was tolerated in given over 4-6 hours. Twenty six (8%) had severe allergic manifestations that had prevented its use. Adalimumb was used rarely for rheumatoid arthritis and inflammatory bowel disease. One patient had developed severe systemic vasculitis 2 weeks after its treatment.

B- d-Pencillamine was used in 46 patients intolerance was observed in 2 patients only.

C- Allopuronol was used for gout which was common in our patients due to their renal disease and diuretic-use. Moreover, it was used to decrease stone formation. It was associated with high incidence of complications viz. acute skin allergy in 228 of the 1029 patients who had used it. Twenty four cases of pancytopenia was reported due to its misuse with Azathioprime and 79 had developed chronic renal deterioration due to it and had improved after it discontinuation. Febuxostat was used in 173 patients and had similar pattern of side effects.

D- Pregabalin was used in our patients to control neuropathic pains of diabetic peripheral neuropathy, cervical and lumber disc disease as well as pain due to herpes zoster. Thirty eight % could not tolerate it for drowsiness for severe drowsiness. Sixty one patients had misused or abused it for.

E- Vitamin D is essential treatment for osteoporosis. However, overzealous use, in correcting low levels or during pregnancy, was associated with nephrolithiasis.

F- Oral iron was a major cause of pruritis in 83 of the 1092 who had use it compared only to 2 with iron carboxymaltose (Ferinject). The latter had less incidence of allergic manifestations compared with the previous iron-dextran or sucrose. Moreover, gastritis and constipation was a common side effect.

G- Gum Arabia was associated with chronic interstitial nephritis with fibrosis was noted in 5 of the 8 patients who admitted its use to prolong kidney survival.

DISCUSSION

The study of ADR and its monitoring is the concern of the field known as “pharmacovigilance”. In a recent study, nearly 80% of physicians were aware of the importance of such program for safe practice yet only 15% had reported ADR to the concerned centers leading to limited reports on this field [4]. In our study, a large number of patients, attending a dedicated clinic, were screened and for years in an attempt to improve the results of the study. A total of 70044 drug-usage that has been recorded in a 4438 patients who attended the clinic in the past 6 years. In those patients ADR were 17853 (25.5%). Nearly half (51%) of which, were due to drug side-effects while idiosyncrasy accounted only for 1.2%. The former is due to misuse/abuse of medications while the latter is due to genetic, co-morbid condition or synergetic between 2 drugs or a drug and disease. The high incidence of misuse/abuse emphasizes the value of proper training and experience in medicine to avoid such iatrogenic disorders. Moreover, it emphasizes the need for proper reporting of ARD for sack of improving health standards and patient’s care. In our study, the most misused/abused drugs were diuretics (Furosamide, Thiazides and Spirolactone) with or without ACEI and ARB leading to acute renal failure. The next group of misused drugs was Warfarin, second generation sulphonylurea, Insulins, Opiates, Radiocontrast media and NSAIDs. The latter 2 were a major cause of acute renal failure in patients with underlying kidney disease [5]. The first 4 drugs need proper monitoring of their dosage by a experienced physician since their therapeutic window is narrow [6]. On the other hand, drug allergy was relatively uncommon, accounting for 10.6% of ADR and delayed hypersensitivity reactions were rare (0.08%). Our results are in harmony with that reported from UK indicating that drug allergy accounts for 10% of all ADR and occurs in 1-2% of all admissions and 3-5% of hospitalized patients, respectively [2]. However, in our practice, such phenomenon was very common with certain drugs viz. NSAIDS with their serious side effects on kidney function with acute interstitial nephritis [7]. It is followed by thiazide (64%) and Aldactone (20%). Both drugs have renewed interest as first line treatment of hypertension, management of refractory fluid overload to Furosamide and in cardiac protection protocol [8-11]. In our study, the second cause of ADR was drug-intolerance and had a prevalence of 9.5% of and accounted for 37% of ADR. The latter indicates the need for carful auditing of the different patient’s response during follow up in an attempt to improve drug-compliance [12]. Moreover, alternative management plans should be laid out for different diseases to overcome such incidents.

REFERENCES

1- Lazarou J, Pomperanz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. JAMA 1998; 279:1200-1205.

2- Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011; 71:684-700.

3- Al-Ahmad M, Rodrigues-Bouza T. Pattern of inpatient referrals to a drug allergy unit in Kuwait. Eur Ann Allergy Clin Immunol 2017; 49:276-280.

4- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832–836.

5- El-Reshaid K, Kapoor M, Johny KV and Sugathan TN. Acute renal failure in Kuwait, a prospective study. J Trop Med Hygiene 1993; 96:323-329.

6- Muller PY, Milton MN. "The determination and interpretation of the therapeutic index in drug development". Nature Reviews. Drug Discovery 2012; **11**:751–61.

7- Dixit M, Doan T, Kirschner R, Dixit N. Significant kidney injury due to non-steroidal anti-inflammatory drugs: Inpatient setting. Pharmaceuticals 2010; 3:1279-1285.

8- Jentzer JC, Dewald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. JACC 2010; 56:1527-1534.

9- Sinha AD, Agawal R. Thiazide diuretics in chronic kidney disease. Curr Hypertens Rep 2015; 17:1-6.

10- Pitt B, Pierard LA, Bilge A et al. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldosterone Evaluation Study (RALES). *Am J Cardiol*. 1996; 78:902-907.

11- James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8) JAMA. 2014; 311:507–20.

12- Omer HM, Hodson J, Thomas SK, Coleman JJ. Multiple drug intolerance syndromes: a large-scale retrospective study. Drug Saf 2014; 37:1037-45.