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A pharmacovigilance Study on Critically Ill Patients Admitted In Beni-Suef University Teaching Hospital.

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Abstract:

The significance of adverse drug reactions (ADRs) among hospitalized patients particularly fundamentally sick patients conceded in the emergency unit has now turned into a worldwide concern. Albeit numerous clinical preliminaries have been directed on medication treatment in fundamentally sick patients, there are no adequate information on the wellbeing of the medication treatment utilized.

The present work is a prospective observational study that was carried out in the ICU department, Benisuef teaching hospital, between August 2015 to December 2016, in which one hundred patients; admitted to the ICU, were enrolled. Patients who experienced drug related problems in the form of ADRs and/or adverse drug-drug interactions (DDIs) were recorded. The ADRs were analyzed regarding the incidence (88%), factors affecting the incidence, characteristics (most of ADRs were moderate, preventable, probable and type "A"). Clinically relevant adverse DDIs were analyzed regarding the incidence, mechanism, causal drugs and management plans.

Keywords: ADRs, Pharmacovigilance.

1- Introduction:

Adverse drug reactions (ADRs) are a leading cause of death and morbidity in both hospitalized and outpatient patients. ADRs are among the top ten leading causes of death in many countries. As a result, ADRs must be thoroughly investigated in order to raise patient awareness of ADRs and encourage health care providers to report ADRs in order to reduce the risk (1)**.**

ADR is defined according to WHO as "any response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or the modification of physiological function" (2).

ADRs account for about 5% of all hospital admissions, and about 10%–20% of hospitalised patients will encounter at least one ADR during their stay (3).

Age, gender, genetics, polypharmacy, dose accuracy, environmental factors, and other internal factors such as disease conditions all affect the development of ADRs (4).

One of the leading causes of morbidity and mortality is ADRs. To reduce the harm caused by ADRs, it is important to diagnose, assess, treat, and prevent them in critically ill patients (5).

Hence, pharmacovigilance is a key component of effective drug regulation systems, clinical practice and public health programs. World Health Organization defines pharmacovigilance as ''the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems, particularly long term and short term adverse effects of medicines''(6).

Need of pharmacovigilance:

Pharmaceutical companies' aggressive promotion of new drug drugs, as well as the resulting rapid exposure of vast numbers of patients to them within a limited period of time, necessitate the development of a framework for global evaluation of drug safety issues. These activities necessitate an effective and efficient pharmacovigilance scheme, which is now more than ever needed to ensure drug safety (7).

The thalidomide tragedy occurred in 1961, prompting the WHO to establish the Program for International Drug Monitoring. The majority of countries have developed adverse drug reaction (ADR) reporting systems (8). So, The aim of this present study is to investigate adverse drug

reactions ,adverse drug-drug interactions related to the pharmacotherapy used for treatment of ICU patients.

2- Patients and method:

A prospective observational study that was carried out in the Intensive Care Unit department, Beni-Suef University Hospital, between August 2015 and December 2016, after the approval of the ICU departement.

2.1Patients' inclusion criteria Both male and female adult patients with different diseases, older than 18 years of age and not older than 70 years.

2.2Patients' exclusion criteria

- Patients less than 18 years old and older than 70 years old.
- Pregnant or lactating females.

2.3Study design

- One hundred patients were included in the study to detect ADRs and DDI.

Data collection

- Clinical data, data related to the pharmacotherapy, investigations and clinical progress of patients were collected using a data collection form that was especially developed for this study.

- **Data analysis**
- Adverse drug reactions were assessed for the following:
  - **Causality:** The causality of ADRs was verified and ADRs were categorized as definite, probable, possible or doubtful according to the Naranjo algorithm (Table 1) (9).
  - **Predictability:** The predictability potential of ADRs was assessed and ADRs were categorized as Type A (predictable) or Type B (non-predictable) (6).
  - **Preventability:** The preventability of ADRs was assessed and ADRs were categorized as preventable or non-preventable according to the preventability criteria (Table 2) (10).
- **Severity:** The severity of ADRs was assessed and ADRs were categorized as mild, moderate or severe (Table 3) (11).
- Drug drug interactions (DDIs) were identified using ***Epocrates Rx***® online free, an online medical decision support tool that provides current and clinically relevant information concerning drug interactions available at **https://online.epocrates.com/**. Only clinically relevant DDIs that altered the course of treatment and required an intervention of any form will be recorded. According to the ***Epocrates Rx***® online, DDIs are classified as follows:

- According to the **Mechanism of interaction** as:
  - Pharmacokinetic interaction.
  - Pharmacodynamic interaction.
  - Pharmaceutical interaction.
- According to the **Management strategy** as:
  - Contraindicated (life threatening and permanent damage may be induced, they should not be co-administered).
  - Use alternative /Avoid combination (can cause therapeutic problems but may be administered together if the patient is carefully monitored).
  - Modify treatment/Monitor (cause increased or reduced effects but to a lesser extent, effects are mainly expressed in already chronic disease compromised patients).
  - Caution (caution on use, mainly cause unimportant effects and no specific action is required).

Table (1): Adverse drug reactions causality scale (9).

	Yes	**No**	**Do not know**	**Score**
Are there any previous conclusive reports on this reaction?	+ 1	0	0	
Did the adverse event appear after the suspected drug was administered?	+ 2	−1	0	
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+ 1	0	0	
Did the adverse reaction reappear when the drug was readministered?	+ 2	−1	0	

	Yes	**No**	**Do not know**	**Score**
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
Did the reaction reappear when a placebo was given?	−1	+1	0	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have the similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total score: Definite ≥ 9, Probable 5–8, Possible 1–4 and doubtful ≤ 0.

Table (2): Adverse drug reactions preventability criteria (10).

Preventability criteria
• Was the drug involved in the ADR not considered appropriate for the patient's clinical condition? • Were the dose or route and frequency of administration not appropriate for the patient's age, weight and disease state? • Was there a required therapeutic drug monitoring or other necessary lab tests that were not performed? • Was there a history of allergy or previous reaction to the drug (or drug class)? • Was a drug interaction involved in the reaction? • Was a toxic serum drug level (or lab test) documented? • Was poor compliance involved in the reaction?

An answer of 'yes' to one or more of the questions suggests that the ADR might have been preventable.

Table (3): Adverse drug reactions severity scale (11).

	Yes	**No**	**Do not know**	**Score**
Did the adverse drug reaction impair the patient's quality of life?	+ 1	−1	0	
Was the (immediate) discontinuance of the drug necessary or recommended?	+ 1	0	0	

	Yes	**No**	**Do not know**	**Score**
Was the use of a different drug or other therapy necessary or recommended?	+ 1	0	0	
Did the adverse drug reaction prolong or lead to hospitalization?	+ 1	0	0	
Did the adverse drug reaction cause temporary malfunctioning of an organ (system)?	+1	0	0	
Did the adverse drug reaction cause permanent malfunctioning of an organ (system)?	+2	0	0	
Did the adverse drug reaction cause temporary inability to work?	+1	0	0	
Did the adverse drug reaction lead to permanent inability to work?	+2	0	0	
Was the adverse drug reaction: potentially dangerous? (treated in ward)	+1	0	0	
potentially life threatening? (treated in ICU)	+2	0	0	
fatal?	+3	0	0	

Total score: Mild 1-4, Moderate 5-8 and Severe >8.

Statistical analysis:

All collected questionnaires were revised for completeness and consistency. Pre-coded data was entered on the computer using "Microsoft Office Excel Software" program (2010) for windows. Data was then transferred to the Statistical Package of Social Science Software program, version 21 (SPSS) to be statistically analyzed. Chi square or Fissure's exact test square were used for qualitative variables and independent sample t-test for quantitative variables and Spearman correlation coefficient (Rho; ρ) was calculated to get the association between ordinal variables.

3- Results:

1. Adverse drug reactions and drug-drug interactions, Incidence:

Out of the 100 patients, 88 (88%) patients experienced drug related problems in the form of ADRs, adverse DDIs or both. Patients who experienced ADRs only were 35 (35%) patients with both ADRs and adverse DDIs were 47 (47%)patients who experienced adverse DDIs only were 6 (6%), so, total number of patients experienced ADRs with or without DDIs were 82 (82%) (Table 4).

Table (4): Incidence of adverse drug reactions and adverse drug-drug interactions in all patients (n=100).

Patients with drug related problems (ADRs and DDI or both)	88 (88%)
Patients with ADRs only	35 (35%)
Patients with adverse DDI only	6 (6%)
Patients with both adverse DDI&ADRS	47 (47%)

Adverse drug reactions, Factors affecting incidence:

The present study included a total of 47 female patients and 53 male patients. 83% of the females experienced ADRs while 81.1% of the males experienced ADRs. However, using the Chi square test, this difference in the incidence of occurrence of ADRs among the two genders was statistically insignificant ($p>0.05$) (Table 5).

Table (5): The incidence of adverse drug reactions in relation to the gender of patients (n=100).

Gender	Total patients	Patients with ADRs	Patients with no ADRs	p value
Male	53	43 (81.0%)	10 (18.9%)	0.810 (Chi square)
Female	47	39 (83.0%)	8 (17.0%)	

The Mean age (± SD) for patients who experienced ADRs was 53.8±12.1 years, while the mean age (± SD) for patients who didn't experience ADRs was 47.8±8.7 years. Using the t-test, this showed a significant statistical difference ($p<0.05$) between the ages of patients who experienced ADRs compared to the ages of patients who did not experience any ADRs (Table 6).

To estimate the age range which was more predisposed to ADRs, patients were divided into 3 age groups according to their statistical distribution in the study; patients less than 20 years, 20-40 years and more than 40 years. Using the Chi square test, the occurrence of ADRs insignificantly increased with increasing age. Using the Fisher exact test, ADRs were insignificantly higher ($p>0.05$) in patients aging 20-40 years and patients aging more than 40 years compared to patients aging less than 20 years (Table 6).

Table (7): The incidence of adverse drug reactions in relation to the age of patients (n=100).

Age	**Total patients**	**Patients with ADRs**	**Patients with no ADRs**	**p value**
Mean±SD	100	53.8±12.1	47.8±8.7	0.047 ** (t-test)
18-20 years	13	9(69.2%)	4 (30.8%)	0.07 (Chi square)
20-40 years	71	57(80.3%)	14 (19.7%)	
40-70 years	16	16(100.0)	0 (0.0%)	

** **p<0.05 comparing mean age ± SD of patients with ADRs to patients with no ADRs.**

p>0.05 comparing number of patients with ADRs to patients with no ADRs among age groups

The mean (± SD) of length of hospital stay for patients who experienced ADRs was 10.3±2.1 days, while the mean (± SD) of length of hospital stay for patients who did not experience any ADRs was 1.6±0.4 days. This difference in the length of hospital stay was statistically significant (p<0.05) (Table 7).

The present study included 60 patients who were admitted to hospital for 10 days

(or less), 73.3% of which experienced ADRs during their hospital stay. On the other hand, 40 patients were admitted for more than 10 days. 95% of which experienced ADRs during their hospital stay. Using the Chi square test, this increase in the incidence of ADRs among patients admitted for more than 10 days compared to patients admitted for only 10 days or less was found to be statistically significant ($p<0.05$) (Table 7).

Table (7): The incidence of adverse drug reactions in relation to the length of hospital stay.

Length of hospital stay (days)	**Total patients**	**Patients with ADRs**	**Patients with no ADRs**	**p value**
Mean (±SD*)*	100	10.3±2.1	1.6±0.4	0.001* (t-test)
≤ 10 days	60	44(73.3%)	16(26.7%)	0.006** (Fisher's test)
> 10 days	40	38(95%)	2(5%)	

*** p<0.05 comparing mean length of hospital stay of patients with ADRs to patients with no ADRs.**

****P<0.05 comparing number of patients with ADRs to number without ADRs in relation to hospital stay.**

The prescriptions for patients during their hospital stay varied from 7 to 15 drugs. Using the Spearman correlation coefficient (Rho; ρ), there was a positive correlation between the number of drugs and the incidence rate of ADRs (R or ρ = 1); the incidence of ADRs increased significantly ($p<0.05$) with increasing the number of drugs prescribed for the patient (Table 8).

Table (8): The incidence of adverse drug reactions in relation to the number of drugs prescribed to the patient (n=100).

Factors	Total patients	Patients with ADRs	Patients with no ADRs	Correlation coefficient
7 drugs	19	9(11 %)	10(55.6%)	
8 drugs	20	17(20.7%)	3(16.7%)	
9 drugs	24	23(28%)	1(5.6%)	
10 drugs	25	22(26.8%)	3(16.7%)	ρ =0.002**
11 drugs	5	4(4.9%)	1(5.6%)	
12 drugs	6	6(7.3%)	0(0%)	
13 drugs	1	1(1.2%)	0(0%)	
Total	100	82	18	

[#] Positive correlation by Spearman correlation coefficient (Rho; ρ).

[*] p<0.05 (calculated for the correlation between number of drugs and the occurrence of ADRs).

3. Adverse drug reactions, Characteristics:

In the present study out of the 100 patients included in the study, 82 patients experienced ADRs. Patients who experienced only 1 ADR were 33 (40.2%), while patients who experienced 2 ADRs were 34 (41.5%) and patients who experienced 3 ADRs were 15 (18.3%).

Regarding the probability score by **Naranjo**, 24.3% of ADRs were possible, 57.3% were probable and 18.4% were definite (Table 9).

According to **Rawlins and Thompson** classification, the majority (89.2%) of ADRs

were Type A, whereas only 10.8% of ADRs were Type B (Table 9).

When ADRs were analyzed according to **Schumock and Thornton** preventability criteria, 75.7% of ADRs were preventable and 24.3% of ADRs were non preventable (Table 9).

According to **Dormann's** criteria for classification of severity of ADRs, 43.2% of ADRs were mild, 51.4% of ADRs were moderate and & 5.4% of ADRs were severe (Table 9).

Table (9): Characteristics of adverse drug reactions (n=82).

Characteristics of ADRs	**Frequency**	**Percentage**
Causality		
Doubtful	Zero	zero
Possible	20	24.3
Probable	47	57.3
Definite	15	18.4
Predictability		
Predictable (Type A)	73	89.2
Non-predictable (Type B)	9	10.8
Preventability		
Preventable	62	75.7
Non-Preventable	20	24.3
Severity		
Mild	36	43.2

Moderate	42	51.4
Severe	4	5.4

4. Adverse drug reactions, Body systems involved

The blood was the most system affected by ADRs followed by the cardiovascular system, musculoskeletal system, the gastrointestinal system, the respiratory system, the nervous system while immune system ,the eye and the skin were the least affected by ADRs. The most commonly occurring ADRs were hypomagnesemia, tachycardia, hyperglycemia, tremors and dry cough (table 10).

Table (10): Adverse drug reactions encountered and body systems involved.

System involved in ADRs	**Frequency of ADRs**	**ADRs**	**Percentage of total ADRs (n=82)**	**Percentage of patients affected (Incidence) (n=100)**
Hypersenstivity	2	Skin rash	1.2%	1%
		Flushing	1.2%	1%
GIT	9	Abdominal pain	3.7%	3%
		Diarrhea	1.2%	1%
		Xerostomia	1.2%	1%
		Constipation	2.4%	2%
		Nausea and/or vomiting	2.4%	2%

CVS system	47	Tachycardia	34.1%	28%
		Arrythmia	2.4%	2%
		Hypertension	3.7%	3%
		Bleeding	3.7%	3%
		Thrombosis	1.2%	1%
		Bilateral lower limb. oedema	2.4%	2%
		Hypotension	7.3%	6%
		Palpitation	1.2%	1%
		Bradycardia	1.2%	1%
Nervous system	4	Psychosis	1.2%	1%
		Anorexia	1.2%	1%
		Irritability	1.2%	1%
		Sedation	1.2%	1%
Blood	63	Hypoglycemia	4.9%	4%
		Hyperglycemia	14.6%	12%
		Hypocalcemia	1.2%	1%
		Elevated hepatic transaminases	2.4%	2%
		Hyperbilirubinemia	6.1%	5%
		Hypoalbuminemia	1.2%	1%

		Hypomagnesemia	46.3%	38%
Skin (Muco-cutaneous)	1	Facial erythema	1.2%	1%
Musculo-skeletal	15	Tremors	8.5%	7%
		Muscle cramps	1.2%	1%
		Musculoskeletal pain	3.7%	3%
		Asthenia	2.4%	2%
		Myositis	2.4%	2%
Respiratory system	6	Dry.Cough	6.1%	5%
		Bronchospasm	1.2%	1%
Eye	1	Glaucoma	1.2%	1%

5. Adverse drug reactions, Causal drugs:

The present study included 52 drugs, 28 were involved in causing ADRs with variable degrees of certainty (according to the ***Naranjo's*** probability scoring). These drugs were: Pantoprazole, hydrocortisone, salbutamol, ipratropium bromide, frusemide, nitroglycerin, theophylline, ampicillin/sulbactam, cefoperazone, imipenem/cilstatin, budesonide, ranitidine, insulin, heparin, nifedipine, levofloxacin, atorvastatin, atenolol, phenytoin, metronidazol, captopril, losartan, enoxaparin, ca.gluconate, bisoprolol, meropenem, allopurinol and spironolactone (Table 11).

Concerning the drugs that were involved in causing ADRs, pantoprazole was the drug that caused the largest number of ADRs compared to other drugs involved. ADRs due to pantoprazole were 25.7% of the total ADRs recorded in the present study.

Table (11): Adverse drug reactions reported with their causal drugs

Drug	**ATC**	**Frequency of ADRs (patients affected)**	**Percentage from total ADRs**	**Frequency**
Nitroglycerine	C01DA02	7	4.7%	Tachycardia(5) Hypotension(1) Flushing(1)
Ca.gluconate	A12AA03	4	2.7%	Tachycardia(4)
Ampicillin/Sulbactam	J01CR01	3	2.0%	Hypoalbuminemia (1) Skin rash(1) Diarrhea(1)
Ipratropium bromide	R03BB01	8	5.4%	Tachycardia(4) Xerostomia(1) Constipation (2) Glaucoma (1)
Captopril	C09AA01	4	2.7%	Dry cough(4)
Nifedipine	C08CA05	5	3.4%	Tachycardia(4) Hypotension(1)
Cefoperazone	J01DD04	2	1.4%	Bleeding(1) Elevated

				transaminases(1)
Levofloxacin	J01MA12	2	1.4%	Irritability(1) Arrythmia(1)
Atenolol	C07AB03	1	0.7%	Bradycardia(1)
Atorvastatin	C10BX03	2	1. 4%	Myositis(2)
Spironolactone	C03DA01	2	1.4%	Abdominal pain(1) Nausea&vomiting(1)
Phenytoin	N03AB02	1	0.7%	Bleeding(1)
Heparine	B01AB01	1	0.7%	Bleeding(1)
Imipenem.Cilastatine	J01DH51	1	0.7%	Abdominal pain(1)
Hydrocortisone	H02AB09	21	14.2%	Hyperglycemia (9) Hypocalcemia(2) Hypertension (3) Bilateral l. l. oedema(2) Psychosis (1) Musculoskeletal pain (2) Facial erythema (2)
Salbutamol	R03AC02	19	12.8%	Tachycardia (9) Palpitation(1)

				Tremors (7) Cough (1) Bronchospasm(1)
Frusemide	C03CA01	9	6.1%	Thrombosis (1) Hypotension (4) Muscle cramps(1) Hyperglycemia(3)
Enoxaparin	B01AB05	2	1.4%	Elevated transaminases(2)
Ranitidine	A02BA02	1	0.7%	Dizziness (1)
Losartan	C09CA01	2	1.4%	Asthenia(2)
Metronidazol	G01AF01	1	0.7%	Anorexia(1)
Pantoprazole	A02BC02	38	25.7%	Hypomagnesemia(38)
Insulin	A10AB A10AD	3	2.0%	Hypoglycemia(3)
Bisoprolol	C07AB07	3	2.0%	Hypoglycemia(1) Hyperkalemia(2)
Theophylline	R03DA04	1	0.7%	Arrhythmia (1)
Meropenem	J01DH02	1	0.7%	Hyperkalemia(1)
Budesonide	R01AD05	1	0.7%	Hyperglycemia(1)

Allopurinol	M04AA01	1	0.7%	Nausea&Vomiting(1)

6. Adverse drug-drug interactions:

In the present study 53% of patients experienced clinically relevant adverse DDIs (out of all patients included in the study). According to the mechanism of DDIs, 100% were pharmacodynamic, no pharmacokinetic or pharmaceutical DDIs (Table 12).

According to ***Epocrates Rx***® online, DDIs were classified according to the management plan. In the present study the majority (81.2 %) of adverse DDIs; were classified as "**Modify treatment / Monitor"** (cause increased or reduced effects but to a lesser extent, effects are mainly expressed in already chronic disease compromised patients), while 18.8 % of adverse DDIs were classified as **"Use alternative / Avoid combination"** (can cause therapeutic problems but may be administered together if the patient is carefully monitored). There were Zero DDIs classified as "**Contraindicated**" (life threatening and permanent damage may be induced, they should not be co-administered) and zero as "**Caution"** (caution on use, mainly cause unimportant effects and no specific action is required) (Table 13).

Characteristics of adverse DDIs	**Frequency**	**Percentage (%n)**
Mechanism		
Pharmaceutical	Zero	Zero
Pharmacokinetic	Zero	Zero
Pharmacodynamic	53	100%

Management		
Caution	Zero	Zero
Modify treatment / Monitor	43	81.2%
Monitor / Avoid combination	10	18.8%
Contraindicated	Zero	Zero

Table (12): Characteristics of adverse drug-drug interactions (n=53).

DDI (Mechanism) (Management)	**Drug combinations**	**Patients developing (DDIs)**	**Percentage of total DDI (n=53)**
Decreased insulin effect (PharmacoDynamic) (Monitor)	Insulin + Hydrocrtisone	**1**	**1.9%**
Augmented hypokalemia (PharmacoDynamic) (use alternative or avoid)	Hydrocortisone +Salbutamol or hydrocortisone + salbutamol Frusemide	**5**	**9.4%**

Augmented hyperkalemia (PharmacoDynamic) (use alternatives or avoid)	Captopril +Levofloxacin +Bisoprolol or Enoxaparin+Meropenem or Heparin +Spironolactone	**5**	**9.4%**
Decreased hypotensive effect (PharmacoDynamic) (Monitor)	Captopril +hydrocortisone +Losartan or Captopril+Hydrocortisone	**4**	**7.5%**
Bleeding (PharmacoDynamic) (Monitor)	Heparin + Phenytoin +Asprin.small.dose	**3**	**5.7%**
Increase effect of hypotensive (PharmacoDynamic) (Monitor)	Nitroglycerine +Frusemide +Nifedipine	**2**	**3.8%**
Hypomagnesemia	Pantoprazole	**33**	**62.3%**

(PharmacoDynamic) (Monitor)	+Frusemide		

Table (13): Adverse drug-drug interactions and their causal drugs

4- Discussion:

ADRs are global problems of major concern. They affect both children and adults with varying magnitudes, causing both morbidity and mortality (12). Adverse drug reaction reporting helps the drug monitoring system to detect the unwanted effects of those drugs which are already in the market (13).

In the present work, out of the 100 patients, 88 (88%) patients experienced drug related problems in the form of ADRs and/or adverse DDIs. Patients who experienced ADRs and DDI were 82 (82%), patients who experienced adverse DDIs only were 6 (6%).

In accordance to the current study a prospective observational study reported that a total of 100 ADRs of different types were observed in 77 patients out of total 177 patients included in the study, with an overall prevalence of about 43.5% (14).

On the contrary, a prospective observational study reported that, a total of 947 Patients were studied and out of which 57 Patients experienced ADRs with the incidence rate of 6% to develop ADRs (15).

The high incidence of ADRs reported in the current work may be due to variations in age, sex, genetic, polypharmacy, dose accuracy, environmental and other internal factors like disease conditions.

In the current study, there was a statistically insignificant increase in the incidence of ADRs in females (83%) compared to that in males (81.1%).

In accordance an open, prospective study, reported that the prevelance of ADRs in females was insignificant high (53.6%) as compared to males (46.4%) (16).

In contrast a prospective observational, showed that, a total of 57 ADRs were identified out of which 32(56.1%) were Male Patients and 25(43.9%) were Female Patients. Male patients showed the higher affected gender with ADRs but insignificant (17).

However, the pharmacokinetic factors are not the only ones accounting for the sex differences in drug response. For instance, female steroid hormones are likely to contribute to pharmacodynamic changes to a great extent. First of all, steroid hormones are well known to influence target tissues, such as cardiac channel density and thiazide receptor density in the kidneys (18). Second, besides direct effects on drug metabolizing enzyme activity and drug transporters, steroid hormones also modulate gene expression. Sex differences in patterns of growth hormone secretion by the hypothalamus result in different expression patterns (19).

Concerning patient's age, the present study reports an insignificant increase of ADRs incidence in patients aging more than 40 years compared to younger adults. ADRs were highest (100%) in patients older than 40 years.

A comparable retrospective study, revealed that majority of the patients data that showed the ADRs were in the age group of 37-54 years (n = 35, 48.61%), The mean age of the patients who developed ADR was 39.26 years (20).

However, in opposite to the present study, reported a higher incidence of ADRs in patients less than 35 years (54.5%) than patients more than 35 years (45.5%) (21).

As regard to hospital stay, the current work reported that patients admitted for more than 10 days (95%) recorded a statistically high incidence of ADRs as compared to patients admitted for less than 10 days (73.3%).

In a comparable study, out of the 3695 patient episodes assessed for ADRs in twelve wards for six months. The median length of stay for patient episodes that resulted in an ADR was 20 days, compared to 8 days without ADRs (22). data obttained from patients admitted to six wards of Internal Medicine, revealed that the duration of hospital stay was longer in patients who experienced ADRs during hospitalization, compared to patients without ADRs median days were 12 (23)**.**

The present work revealed that there was a significant increase between the incidence of ADRs and the increased number of drugs received by the patients.

The risk of ADRs increases from 13% in a person taking two medicines to 58% when taking five and 82% when taking seven or more (24). The risk of ADRs was higher in patients who were using more than 6 medications (25). There was increase in

incidence of ADRs with increased medications (26).

On the contrary, ADRs increased with increasing the number of drugs up to 5 drugs, but when drugs were more than 10 in number, there was no increase or decrease in ADRs in the patients (27). Poly-pharmacy may cause ADRs due to the drug additive effect, synergism, duplication, drug interactions, discontinuation of treatment and physiological antagonism (28).

In the current work Patients who experienced only 1 ADR were 33 (40.2%), while patients who experienced 2 ADRs were 34 (41.5%) and patients who experienced 3 ADRs were 15 (18.3%). In accordance, multiple ADRs were identified in 27.4% of patients with ADRs, 22.5% experienced two ADRs and 4.9% experienced 3 ADRs (29).

Regarding the causality score reported in the present study (using **Naranjo algorithm**), 24.3% of ADRs were possible, 57.3% were probable and 18.4% were definite.

In contrast, a retrospective study reported that, 29 (28.71%) of cases were probable and 72 (71.28%) of cases were possible in Naranjo scale respectively (23). Also, a prospective observational study showed ADRs as possible [(30) 52.63%], followed by probable [(22) 38.59%] and definite [(5) 8.77%] (15).

According to **Rawlins and Thompson** classification, the majority (89.2%) of ADRs reported in the present study, were Type A (predictable), whereas only 10.8% of ADRs were Type B (non predictable).

In accordance**,** the ADRs, 75.5% were of type A reactions (predictable type) and 24.5% were of type B reactions (unpredictable type) (32). Another study reported that. type A (77.55%) was the most common compared to Type B (22.44%) reactions according to the ADR classification by Rawlin and Thomson (30).

In the present study, ADRs were analyzed according to **Schumock and Thornton** preventability criteria, 75.7% of ADRs were preventable and 24.3% of ADRs were non preventable.

A study on 100 patients with cutaneous ADRs 34% cutaneous ADRs were definitely preventable, 12% were probably preventable and 54% were not preventable (31). Another study conducted on sychatric patients reported that, about 91 (90.09%) of total ADRs were non preventable (22).

In the present study, according to **Dormann's** criteria for classification of severity of ADRs, 43.2% of ADRs were

mild, 51.4% of ADRs were moderate and & 5.4% of ADRs were severe.

Accordingly, (58.5%) of ADRs were moderate in severity while (41.5%) were mild (32). The most of the ADR reported were moderate (51%) severe (31%) and mild (9%) (33).

Another study, reported that (44.7%) of ADRs were moderate, followed by mild (42.5%), and severe (12.8%) (28).

The blood was the most system affected by ADRs followed by the cardiovascular system, musculoskeletal system, the gastrointestinal system, the respiratory system, the nervous system while immune system, the eye and the skin were the least affected by ADRs.

A number of studies proved that the most system affected by ADRs was the skin (25, 27, 28). Some studies detected that the most affected system by ADRs was the gastrointestinal system (34, 35, 36).

The current work included 52 drugs, 28 were involved in causing ADRs with variable degrees of certainty (according to the ***Naranjo's*** probability scoring). These drugs were: Pantoprazole, hydrocortisone, salbutamol, ipratropium bromide, frusemide, nitroglycerin, theophylline, ampicillin/sulbactam, cefoperazone, imipenem/cilstatin, budesonide, ranitidine, insulin, heparin, nifedipine, levofloxacin, atorvastatin, atenolol, phenytoin, metronidazol, captopril, losartan, enoxaparin, ca.gluconate, bisoprolol, meropenem, allopurinol and spironolactone. Pantoprazole was the most involved drug in causing ADRs as it was prescriped for all patient included in the study for prophylaxis of stress ulcers. ADRs due to pantoprazole were 25.7% of the total ADRs recorded in the present study followed by hydrocortisone (14.2%) salbutamol (12.8%).

A prospective cohort study, reported that the most common drugs in causing ADRs were antibiotics (27.5%), antiepileptics (12.1%), antihypertensives (7.8%) (2).

A retrospective study reported that the most common drugs causing ADRs were, antibiotics (35,9%), NSAID (12,4%), antihypertensives (11,5%) (36).

In the present study 53% of patients experienced clinically relevant adverse DDIs (out of all patients included in the study). According to the mechanism of DDIs, 100% were pharmacodynamic, no pharmacokinetic or pharmaceutical DDIs.

According to **Epocrates Rx®** online free, DDIs were classified according to the management plan. In the present study the majority (81.2 %) of adverse DDIs; were classified as "**Modify treatment / Monitor"** , while 18.8 % of adverse DDIs

were classified as **"Use alternative / Avoid combination"** ,there were Zero DDIs classified as "**Contraindicated**" and zero as "**Caution"**.

There were 7 different adverse DDIs recorded in the present study, the most frequently occurring of which was the hypomagnesemia, caused by combination of (pantoprazol + frusemide). This interaction represented 62.3% of all encountered interactions in the study. Other encountered DDIs were, decreased hypoglycemic effect of insulin, caused by combination of (insulin + hydrocortisone), augmented hypokalemia caused by combination of (salbutamol + hydrocortisone) or (salbutamol + hydrocortisone + frusemid), augmented hyperkalemia caused by combination of (spironolactone + heparin) or (captopril + levofloxacin+ Bisoprolol) or (enoxaparin + meropenem), Decreased hypotensive effect of antihypertensive drug caused by combination of (captopril or losartan + hydrocortisone), augmented hypotensive effect of antihypertensive drug caused by combination of (nifedipine + nitroglycerin + frusemid) and Increased bleeding effect of anticoagulants caused by combination of (heparin +aspirin small dose +pheyntoin).

A prospective observational study, 138 patients were included; 360 interactions were detected in 94 patients, The prevalence of DDIs was 68.11%, the most common one was Aspirin/Clopedogril (12.22%), Aspirin/Heparin (8.33%), and Furosemide/Spironolactone(5.83%). Most of these interactions were pharmacokinetic 77.78% and pharmacodynamic were 22.22% (37). a cross-sectional study operated by reviewing charts of 448 hospitalized patients, the overall prevalence of potential DDIs (86.2%) and also major potential DDIs was higher as Aspirin + heparin increased bleeding with high frequency (51). The most important is the DDI between aspirin with other antiplatelet or anticoagulant drugs (such as heparin, warfarin, enoxaparin, and clopidogrel) which may increase the risk of bleeding (38).

5- Conclusion:

The pharmacotherapy used for management of patients admitted to the ICU department Beni-suef teaching hospital, meets to a great extent the latest up-to-date international guidelines. However, the occurrence of adverse drug reactions, drug-drug interactions are still a significant problem. Hence, the present study provided a baseline information about these drug related problems, that would be useful in future, long term and more extensive drug

related problems monitoring in the hospital and in framing policies towards rational use of drugs.

6- Recommendations:

The task of developing better preventive and treatment strategies for drug related problems should not be underestimated. Therefore the following is recommended:

- Multidisciplinary approach involving physicians, clinical pharmacologists, clinical pharmacists and nursing staff should be applied for patient care.
- The construction of a pharmacovigilance centre and a clinical pharmacology committee in every hospital is a must.
- Improving the performance of the systems particularly in linking or merging the databases and making it accessible to healthcare professionals among multidisciplinary healthcare networks.
- The guidelines recommended by the hospital's clinical pharmacology committee should be strictly followed by the patient care team, including physicians, pharmacists and nurses.
- Information technology can be used to assist the pharmacovigilance process in a variety of ways, including computerised physician order entry, clinical decision support systems, electronic dispensing, bar coding of medications and patients, and computerization of medical records as well as discharge prescriptions and instructions.

• Drug safety and pharmacovigilance should be taught in medical school and postgraduate programmes, and undergraduates and postgraduates should be trained in the most effective ways to communicate drug safety concerns to patients.

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