ejpmr, 2018,5(9), 290-296

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ASSESSMENT OF KNOWLEDGE OF MEDICAL UNDERGRADUATE STUDENTS BY ALLOTTING THEM ADR REPORTING ACTIVITY AND BY QUESTIONNAIRE METHOD

Rashmi Singla*[1], Dr. Rangeel Singh Raina[2] and Dr. Dev Chaudhary[3]

[1]Assist professor, GDMC.
[2]Prof. GDMC.
[3]Tutor, GDMC.

***Corresponding Author: Rashmi Singla**

Assist professor, GDMC.

Article Received on 06/07/2018 **Article Revised on 27/07/2018** **Article Accepted on 17/08/2018**

ABSTRACT

Introduction: Drug is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment /cure of a disease. Adverse effect is any undesirable or unintended consequence of drug administration. **Objectives**: To assess the knowledge of students about the pharmacovigilance programme and adverse drug reactions from clinical postings acquired knowledge and ADR reports submission. **Material and methods**: A conclusive summary was made by assessing the performance in written questionnaire based on information provided to them about ADRs in practical lectures and based on knowledge from ADR reports submitted by 50 11nd year MBBS students who did the clinical postings and and ADR submission activity and among 50 students who did not do the ADR activity. **Results**: 50 students who submitted their reports, out of them 50% ADR reports were from cases related to Dermatology Deptt. and rest 50% from cases related to other depts. like Medicine, Opthalmology, Surgery, Gynecology etc The ADRs of drugs reported were mostly of steroidal creams like clobetasol cream as topical ointment, betamethsone cream, mometasone of antifungals like fluconazole ,antibiotics like cortimoxazole, cefuroxime, ofloxacin, ofantileprotic drug like clofazimine and ATT, of antiamoebics like metronidazole ,antivirals like tenofovir and eyes drops like carboxymethylcellulose. Out of 25 questions in the questionnaire, most of the students responded correctly for common 14 questions. Among 50 students who did not do the ADR exercise, 11 questions were responded differently by students. In the first question, the category of ADR to be reported was responded differently. 40 responded that only confirmed reactions should be reported, I0 students said suspected reactions and 10 said all. The kind of ADR to be reported was known and unknown by 20, serious and non serious by 10, rare and frequent by 10, rest said all should be reported.Re -challenge test definition was answered wrongly by 40 students. Most of the students said reporting ADR is not a professional obligation. Also, by whom the ADR should be reported was answered wrongly by 45 students. Mostly all the students had no knowledge of Adverse drug reaction monitoring centre(NDDTC), ADR monitoring regulatory body(CDSCO,) and national coordination centre for ADR monitoring in India(IPC, Indian pharmacovigilance centre, Gaziabad). Among rest 50 students who did the ADR reporting exercise, mostly responded correctly. The relevant medical history to be taken after the ADR was reported wrongly by most of the students. The students had varied opinion about factors which discourage them from reporting ADRs. **Conclusion**: The knowledge of ADR reports prepared by collecting information from clinical postings made the student aware of various aspects of ADRs and their contribution and knowledge of the pharmacovigilance program me.

KEYWORDS: Adverse drug reaction, undergraduate students, WHO UMC causality scale.

INTRODUCTION

Pharmacovigilance also known as **drug safety**, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. As such, pharmacovigilance heavily focuses on adverse drug reactions, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy.[1] Adverse drug reaction is any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug.[2] Adverse drug reactions can be considered a form of toxicity; however, toxicity is most commonly applied to effects of over ingestion(accidental or intentional) or to elevated blood levels or enhanced drug effects that occur during appropriate use (eg, when drug metabolism is temporarily inhibited by a disorder or another drug. Side effect is a term often used to refer to a drug's

unintended effects that occur within the therapeutic range.[3]

All drugs are capable of producing adverse effects and whenever a drug is given, a risk is taken. The magnitude of the risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient eg even risk of bone marrow suppression may be justified in treating cancer, while mild drowsiness caused by an antihistaminic in treating cold may be unacceptable. Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug.[3] In the US, 3 to 7% of all hospitalizations are due to adverse drug reactions. ADRs occur during 10 to 20% of hospitalizations; about 10 to 20% of these ADRs are severe.[3]

Adverse drug reactions are classified into six types: dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Timing, the pattern of illness, the results of investigations, and recalling can help attribute causality to a suspected adverse drug reaction. Management includes withdrawal of the drug if possible and specific treatment of its effects. Suspected adverse drug reactions should be reported. Surveillance methods can detect reactions and prove associations.[4] Hence is the importance of doing a study on ADR reporting by medical students in a medical college.

AIM AND OBJECTIVES

1. To assess the understanding of adverse drug reaction and knowledge of filling of ADR reporting form information.
2. To assess the knowledge of ADRs with various drugs and to manage them.

MATERIAL AND METHOD

The students were given practical lectures on adverse drug reaction exercise. 50 students out of 100 students were asked to submit ADR report files after attending clinical postings in their respective departments for one month. They were asked to fill an ADR reporting Performa. The ADR reporting files submitted by the students contained information about the patients age, sex, residence, chief complaints on presentation in the hospital, history of past illness, photograph of prescription containing treatment of ADR ,mechanism of drug action causing ADR, WHO causality scale and the conclusion report and references. A 25 objective answer questions based questionnaire was given to half the students before the activity and to half after the activity. (Annexure 2).

Inclusion criteria: 100 students who were first enrolled for ADR reporting.

Exclusion criteria: Incompletely filled ADRs.

RESULTS

Table 1: Assessment of no. of adverse drug reactions in different clinical depts.

Dermatology	25
Medicine	15
Surgery	5
Gynecology	3
Ophthalmology	2

These adverse effects with each drug were seen differently in different cases reported. The **causality was assessed according to WHO UMC causality scale. Annexure 1.**

Table 2: Type of adverse drug events with drugs and number of patients.

Drug	Type of adverse events	Number of patients
Topical clobetasol	Seborrhea dermatitis over face and scalp, tine incognito on forearm and face, telangiectasia	10
Tenofovir	Multiple maculopapular rash over upper limb & face	3
Isotretinoin	Angular cheilitis, rash on forearm, dryness of eyes, nose, hyperpigmentation, loss of appetite, blurring of vision at night	6
Clofazimine	Icthyosis on hands and legs	2
Sail cyclic acid	Itching, severe irritation & burning sensation	2
Carboxymethylcellulose	Redness in eyes	2
ATT	Fever & vomiting	2
Metronidazole	fixed drug eruption ,itchy erythematous lesion over right arm	2
Pantoprazole	Itching during blood transfusion	1
Cortimoxazole	Nausea & vomiting, erythema multiforme	3
Betamethasone	Telangiectasia(reddish lines), itching and acne on the face	7
Ofloxacin	Urticaria and maculopapular rash all over body	2
Mometasone	Irritant contact dermatitis, hyperpigmemtation, stria, telengiectasia	5
Amoxyclav	Diarrhea	2
Salicyclic acid	Red rashes	1

Table 3: Not done the activity n =50 11 questions which students found difficult were answered as.

Questionnaire	Correct answer	Wrong answer	Opinion
1. Which factor discourages from reporting ADRs.			8-Difficult to decide whether ADR has occurred or not 12-A single unreported case may not affect database 10-no answer 8-No remuneration for reporting 12-Lack of time to report ADR
2&3. Which category and type of ADRs should be reported?	10	40	
4. The healthcare professional responsible for reporting ADR are?	25	25	
5. The national coordination centre for ADR monitoring centre is located in?	10	40	
6. What relevant history is taken after ADR?	12	38	
7. Is reporting ADR a professional obligation for you?	5	45	
8. What kind of adrs should be reported?	17	33	
9. In India which regulatory body is responsible for monitoring ADRs?	10	40	
10. Rechallenge test reflects?	12	38	
11. What are mandatory fields for suspected ADR reporting form?	10	40	

Table 4: Knowledge in % age (n=100).

Knowledge before clinical posting	Knowledge after ADR submission after clinical posting
20%	70%

DISCUSSION

Out of 100 students, 50 students performed the ADR reporting exercise. The maximum ad verse reactions reported were from dermatology deptt, rest from medicine, surgery, gynecology and ophthalmology. The adverse drug reaction was reported as probable, possible and unlikely with different drugs, according to WHO UMC causality report. The knowledge was assessed by written questionnaire taking 50 students before the activity and taking other 50 students who had done the activity. The knowledge gained was as:

1. The students came to know of different adverse drug events with drugs and their mechanism of action in causation of ADR and their management. The ADRs reported were

Clobetasol application on face caused seborrhoeic dermatitis over face and scalp, tinea incognito on forearm and face and telengiectasia after 5 days. Topical steroids when applied on the skin cross the cell membrane and bind to receptors in cytoplasm to form steroid receptor complex. This complex enters the nucleus and binds to DNA .This can either stimulate or inhibit the synthesis of specific proteins through m-RNA .These topical steroids inhibit m-RNA responsible for IL1 formation. It also stimulates synthesis of lipocortin which inhibits the activity of phospholipase A2, which releases arachidonic acid. These actions produce anti-inflammatory and immunosuppressive effects.

Isotretinoin: Patients after taking isotretinoin tablets 60 mg /day for two months for acne vulgaris presented with angular cheilitis, rash on forearm, dryness of arm, nose and in some cases hyperpigmentation and loss of appetite and in some blurring of vision at night. Isotretinoin amplifies production of neutrophil gelatinase associated lipocalin in the skin. –which reduce sebum production by inducing apoptosis in sebaceous gland cells. –leading to decrease in sebaceous gland secretion attributing to alteration in skin surface lipids which leads to poor barrier function due to alteration in epidermis –leads to dryness in lips and shedding.

Clofazimine: Patient took clofazimine along with antileprotic treatment for 4 months for multibacillary leprosy and developed blackish discoloration of skin, itching and excessive drying of skin.The proposed mechanism is that clofazimine has anticholinergic effect and stops the secretions from sweat glands—causes extensive drying &itching of skin called icythyosis. Clofazimine is highly lipid soluble drug and its accumulation in lipids is responsible for hyperpigmentation.

Salicyclic acid: Patient used debroin ointment for red rashes on his face followed by patches of small raised bumps. Debroin ointment composition contains salicyclic acid topical 5% w/w, dithranol and coal tar.

The patient had itching, severe irritation & burning sensation. Salicyclic acid acts as a irritant –causes direct cytotoxic skin damage –leads to skin barrier disruption, cellular changes and release of proinflammatory mediators.

Cortimoxazole: Patient took a week ago cortimoxazole for diarrhea and after use for one week developed rashes and red spots on leg. The etiology of erythema multiform appears to be an immunological hypersensitivity reaction with the CD8 +T lymphocytes in the epithelium which induce apoptosis of scattered keratinocytes & leading to satellite cell necrosis. A range of exogenous factors trigger an immunologically related reaction which appears as a sub & intraepithelial vesiculation. Patient may experience itching & burning at the site of eruption. In another case nausea & vomiting were reported on taking Septran DS.-Trimethoprim (80mg)+sulfamethoxazole(400mg).

Mometasone –patient was applying mometasone cream on face for a week after which she developed rash along with itching on face. Topical steroids cause the synthesis of lipocortin which inhibit the enzyme phospholipase A2. Phospholipase A2 acts the cell membrane phospholipids to release arachidonic acid which causes the inflammation. Topical steroids have inhibitory effect on keratinocyte proliferation in the epidermis. They cause inhibition of collagen 1&3 synthesis in dermis. Also there is inhibition of fibroblasts and hyaluronan synthetase 3 leading to decrease synthesis of hyaluronic acid causing skin atrophy.

Betamethasone ---The patient developed eruption of face after injecting betamethasone. The proposed mechanism of action was T cell mediated hypersensitivity reaction – drug penetrates the skin producing complexes with epidermal carrier proteins which produce a complete allergen by altering self proteins ,including MHC molecules (neoantigens) - recognized by T cell as foreign antigens – lead to cytokine production & inflammation. Also in another cases after application of betamethasone cream for one year for psoriasis, the patient complained of reddish lines (telangiectasia), brown patches on face(melasma). Betamethasone reduces inflammation by reversing the activation of inflammatory proteins for treatment of psoriasis. Improvement in scaly patches lead to its overuse and there were degenerative changes seen in the skin of epithelial cells .On further use, it reduces the stimulation of dermal vessel endothelial cells and release of NO from them causes abnormal dilation of capillaries and formation of whorl like pattern (telengiectasia). Also in induces proliferation of propionobacterium acnes leading to redness like condition within 6 months, known as steroid damaged face.

Pantoprazole induced irritation during blood transfusion –The patient had history of abdominal pain &increased frequency of micturition .The patient was later diagnosed with bulky uterus &ovarian cyst. Hystercetomy was performed. Postoperative surgery IV Pantoprazole was administered to reduce gastric acid secretion to prevent acid reflux from the stomach to the esophagus. After administration, she experienced severe itching during routine blood transfusion. Pantoprazole is a proton pump inhibitor and causes acute drug induced hypersensitivity reaction.

The adverse drug reactions were mostly managed by discontinuing the drug (dechallenge test) and giving symptomatic treatment for the symptoms.Dechallenge refers to the stopping of the drug generally after the adverse event or at the termination of the planned treatment. Rechallenge refers to the recommencement of the similar drug after its usage has been stopped because of adverse event.[5] Diarrhea and vomiting were treated by antidiarrhoeals and antiemetics and dermatological reactions like urticaria were treated by calamine lotion and antihistaminics and steroids and dryness of skin was treated by moisturizing lotions and the fungal infections were treated by antifungal drugs. However, the treatment for leprosy was continued and humiderm lotion was applied to the skin. It is an ultra short acting lightweight moisturizing cream which reinforces skin instantly into soft supple and hydrated skin. It consists of cyclo tetrasiloxane, dimethicone, cetyl alcohol, vitE acetate, propyl paraben, methyl paraben. In case of isotretinoin, the drug was withdrawn and alograce cream was applied for rashes, refresh eyedrops for eye dryness, nasoclear drops for nose dryness.

A similar prospective study on adverse drug reaction with antibiotics was done in tertiary care hospital by Shamna, Plip et al.[6] A cross-sectional study was done on adverse drug reactions in tertiary care in northeast India for causality assessment and severity assessment.[7]

11. The students come to know how to fill the ADR Performa form: It includes particulars of the patient like name, sage, sex, weight and relevant medical history (allergy, hepatic, renal disorder), reason for reporting and suspected drug details like – date of occurrence of event &duration of event start of date of medication and route of medication and discontinuation of the drug information. The performa has to be signed by the doctor with the name of the institution.

11.1. The students answered correctly to 70% in the questionnaire after the ADR activity: They understood that all type of ADRs should be reported. They learnt that ADRs can be reported by all healthcare professionals and also that reporting of ADR is a professional obligation. They also came to know that The Upasala Monitoring Centre (Sweden) is the international collaborating centre. The Central Drugs Standard Control Organization is coordinating the pharmacovigilance program me. And national coordination centre for ADR monitoring in India is (IPC, Indian pharmacovigilance centre, Gaziabad. They also came to know about the

relevant medical history to be taken after an ADR. The dechallenge and rechallenge tests were clearly understood.[8]

CONCLUSION

The students had clear conception about adverse drug reaction reporting after the activity. The study concludes that the students have acquired knowledge from clinical postings about the adverse drug reactions and causality assessment and filling of ADR reporting form. The student's knowledge improved from 20 % to 70% after clinical postings and ADR files report submission. They understood that voluntary reporting of ADR is a professional obligation. This has also helped in the Pharmacovigilance programme which is the science and activities relating to the prevention of adverse effects, understanding & prevention of adverse effects or any other drug related problems.

ACKNOWLEDGEMENT

I owe my thanks to Govt. Doon Medical college 11nd year students in contributing to the study.

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ANNEXURE 1

WHO-UMC Causality Categories Causality term Assessment criteria*[5]

Certain • Event or laboratory test abnormality, with plausible time relationship to drug intake • cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary.

Probable / Likely • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required.

Possible • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear Unlikely • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations **Conditional / Unclassified** • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination Unassessable / Unclassifiable • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified * All points should be reasonably complied with.

ANNEXURE 2

QUESTIONNARE WORKSHOP ...PRESENTED ADR 1.YES 2.NO

Name

Q1. Adverse drug reaction is defined as….*

a) Noxious, Unintended and harmful effects of drug
b) Pharmacological effects of drug
c) Beneficial effects of drug
d) Therapeutic effects of drug

Q2. Pharmacovigilance deals with*

a) Physiology
b) Chemistry
c) Genetics
d) Adverse drug reactions

Q3. These adverse drug reactions should be reported*

a) Confirmed ADR's
b) Suspected ADR's
c) Not confirmed
d) All

Q4.What kind of adverse drug reactions should be reported *

a) Known and Unknown
b) Serious and non Serious
c) Rare and Frequent
d) All

Q5. Rechallenge in Suspected Adverse Drug Reaction (ADR) report reflects *
a) Reintroduction of drug leading to reappearance of ADR
b) Reintroduction of drug will cure the ADR
c) Reintroduction will not effect the individual
d) None

Q6. Is reporting adverse drug reaction a professional obligation for you? *
a) Yes
b) No
c) Don't know

Q7. Have you ever come across an adverse drug reaction? *
a) Yes
b) No

Q8. Have you ever reported an adverse drug reaction?
a) Yes
b) No

Q9. Do you think reporting of adverse drug reactions are necessary.*
a) Yes
b) No
c) Don't know

Q10. Is NDDTC an Adverse Drug Reaction Monitoring Centre (AMC) of Pharmacovigilance Programme of India (PvPI)?*
a) Yes
b) No

Q11. Define Pharmacovigilance
a) The process of improving the safety of drugs
b) The detection, assessment, understanding & prevention of adverse drug effects
c) The science detecting the type & incidence of ADR after drug is marketed
d) The science of monitoring ADR's occurring in a Hospital

Q12. The healthcare professionals responsible for reporting ADR in a hospital is/are
a) Doctor
b) Pharmacist
c) Nurses
d) All of the above

Q13. Have you been given training on reporting of adverse drug reactions (ADRs)?
a) Yes
b) No

Q14. Which among the following factors discourage you from reporting ADRs?
a) No remuneration for reporting
b) A single unreported case may not affect ADR database
c) Lack of time to report ADR
d) Difficult to decide whether ADR has occurred or not.

Q15. In India which regulatory body is responsible for monitoring ADRs?
a) Central Drugs Standard Control Organization
b) Indian Council of Medical Research
c) Indian Clinical Research Institute
d) Medical Council of India

Q16. The National Coordination Centre (NCC) for ADR monitoring is located in?
a) AIIMS-New Delhi
b) IPC-Ghaziabad
c) KEM-Bombay
d) IISC-Banglore

Q17. What is your opinion about establishing ADR monitoring centre in every hospital?
a) Should be in every hospital
b) Not necessary in every hospital
c) One in a city is sufficient
d) Depends on number of bed size in the hospital.

Q18. Is there any ADR monitoring centre under PvPI nearby your Hospital/College affiliated Hospital?
a) Yes (If Yes specify the name of the centre----------
b) No
c) don't know

Q19. What is your opinion on periodic publication of PvPI Newsletter?
a) Excellent
b) Good
c) Average
d) Poor

Q20. Which classification we use to classify ADR?
a) WHO UMC Causality scale
b) Naranjo scale
c) Both
d) None

Q21. What relevant medical histoty is taken after ADR?
a) Allergy
b) Race
c) Pregnancy
d) alcoholism
e) hepatic/renal dysfunction

Q22. Dechallenge Test is:
a) Reintroduce the drug
b) Withdraw the drug
c) Both
d) None

Q23. What are mandatory fields for suspected ADR reporting form?

a) Patient initials
b) Age at the onset of reaction
c) Reaction term
d) Date of onset
e) Suspected medication
f) Reporter information
g) All

Q24. Maximum number of ADRS is usually reported from which deptt?

a) Medicine deptt
b) Dermatology deptt
c) surgery deptt
d) ophthalmology

Q25. What is the use of pharmacoviogilance?

a) Patient safety
b) Adverse drug reoorting
c) Signal reporting
d) All