International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 8(H); August 2018; Page No. 15082-15087
DOI: http://dx.doi.org/10.24327/ijcar.2018.15087.2753

Research Article

ADVERSE DRUG REACTION PROFILE AT RADIOTHERAPY, PAEDIATRICS AND EAR, NOSE AND THROAT DEPARTMENT OF A TERTIARY CARE TEACHING HOSPITAL: A DESCRIPTIVE CROSS SECTIONAL STUDY

Ganesh Dakhale., Latesh Raghute*., Avinash Turankar., Sonali Pimpalkhute., Viraj Shinde and Piyush Nama

Department of Pharmacology, Govt. Medical College, Nagpur, M.S. 440003

A R T I C L E I N F O

Article History:

Received 11th May, 2018
Received in revised form 7th June, 2018 Accepted 5th July, 2018
Published online 28th August, 2018

Key words:

ADRs, causality analysis, pharmacovigilance.

A B S T R A C T

Objective: To monitor adverse drug reactions (ADRs) in radiotherapy, paediatrics and ear, nose and throat (ENT) department of a tertiary care teaching hospital.
Materials and Methods: This was a descriptive cross sectional study carried out for detection, classification, assessment and causality analysis of ADRs in radiotherapy, paediatrics and ENT department of a tertiary care teaching institute after approval from Institutional Ethics Committee. The study period was of 22 months from December 2014 to September 2016. Suspected ADRs were recorded in Indian Pharmacopoeia Commission Suspected ADR reporting form.
Results: During study period total 298 patients with ADRs to different drugs were detected. Maximum numbers of ADRs were from department of radiotherapy, followed by ENT and paediatrics department. Maximum ADRs were observed in age group of 41– 60 years with more number of ADRs in female than in male. In causality assessment, maximum ADRs were categorized as probable and maximum ADRs were of moderate severity. GIT was most common system affected followed by skin and CNS. Type A ADRs were found to be commonest.
Conclusion: This study has created a database about different ADRs and the drugs causing it which may be useful in identifying and minimizing ADRs. Various pharmacovigilance awareness programs should be conducted to increase the spontaneous reporting of ADRs. This could help physician to give different prescribing options depending on ADR profile of the drugs; which will ultimately alleviate human sufferings and reduce financial burden to the patient and society.

INTRODUCTION

According to World Health Organization (WHO), an adverse drug reaction (ADR) is defined as "a reaction to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function".[1] ADRs are of great concern in therapeutics and the fourth leading cause of death. Thus, they have an economic burden on the patients as well as on the health care establishment.[2] ADRs are negative consequences of drug therapy and common occurrences in a hospital setting, attributed to the severity and complexity of the disease process, use of multiple drugs, drug interactions and possible negligence. An incidence of 5% to 35% of ADRs is observed in all age groups among outpatients.[3] Serious ADRs account for 6.7% of all hospital admissions.[4] It is well known that chemotherapeutic agents are associated with severe adverse effects leading to economic burden and decreased quality of life. The most troublesome classes of drugs contributing to ADR are antibiotics followed by anticancer drugs.[5,6] Various chemotherapeutic agents in single, in combination and in conjunction with surgery, radiotherapy and immunotherapy are used widely for the treatment of variety of neoplastic diseases. One of the characteristics that distinguish anticancer agents from other drugs is the frequency and severity of side effects at therapeutic doses. The antineoplastic agents have the lowest therapeutic indices of any drug and as such they cause frequent and predictable multi system toxicity.[7] There is no extensive published data regarding the adverse effects of anticancer agents in Indian population.

Adverse drug reactions are common clinical problems in both paediatric and adult medicine. Over 9% of hospitalized children have adverse reactions to therapy and up to 4% of all hospital admissions are the consequence of ADRs.[8,9] The toxicity of many medicines in children is different to that seen in adults. Essentially, children cannot be regarded as small adults; they are afflicted with many conditions and disease

Corresponding author:* **Latesh Raghute
Department of Pharmacology, Govt. Medical College, Nagpur, M.S. 440003

processes that are different from those in adults, particularly neonates and infants. Drugs may behave differently in children (different pharmacokinetics) compared to adults and also may cause different effects (different pharmacodynamics) in children.[5,6,9] It can be difficult to evaluate drug toxicity in children. Studies of drug-induced toxicity are generally comprised of retrospective reviews and isolated case reports. It is difficult to be certain about the association between drug exposure and possible toxicity in the majority of cases. Thus, it is critical to maintain a high index of suspicion for the occurrence of drug toxicity in infants and children.[8]

Infections are one of the most important causes of patients visit in the hospital and ENT department is one of those where consumption of antibiotics are higher. Therefore, it is necessary to study the ADR profile associated with them. The reason being is the massive use of antimicrobial agents in the hospitals.[10]

Pharmacovigilance as per WHO is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse drugs reactions or any other drug related problems".[11] Though Pharmacovigilance Programme of India (PvPI) was started in 2005, it is still in its development phase in our country. Monitoring the ADRs in any setting can be undertaken by several methods. Passive surveillance by voluntary reporting or stimulated reporting by physicians, active surveillance by prescription event monitoring and patient registries, epidemiological studies such as cohort and case control studies form some of the important methodologies used globally.[12] Causality assessment of ADRs is the structured and standardized assessment of individual patients/case reports of the likelihood of involvement of suspected drug in causing particular event in a given patient. Various methods in use for causality assessment include WHO-UMC scale, Naranjo scale, European scale and many others.

Our study centre is a tertiary care teaching hospital which is recognized as one of the ADR monitoring centre under the PvPI. With such an enormous number of patients being treated here and health services being provided from resident doctors to unit in-charge, it is obvious that ADRs must be occurring frequently. Probably, because of lack of awareness and overall hectic schedule of the treating physicians, many of the ADRs are not reported at all or are underreported. There is also scarcity of Indian database of ADRs. Taking this view in mind, the present study is undertaken for detection, assessment, classification and causality assessment of ADRs in the radiotherapy, paediatrics and ENT department of tertiary care teaching hospital.

MATERIALS AND METHODS

This was a descriptive cross sectional study carried out for detection, classification, assessment and causality analysis of ADRs. The study was conducted in the patients attending the out patient department (OPD) and those admitted in the wards of radiotherapy, paediatrics and ENT department of a tertiary care teaching institute after approval from the Institutional Ethics Committee. The study period was of 22 months from December 2014 to September 2016. Daily round of the respective wards/OPD was taken and information about adverse events was obtained from doctors & nursing staff. All the in-patients were assessed for ADRs during the study period. In the suspected cases, past medical/medication history of patients were collected. Patients were interviewed, monitored daily throughout their hospital stay and their medical records were reviewed. The suspected ADRs were carefully analyzed and documented. All relevant data including all drugs the patients received prior to the onset of the reaction, their respective dosage, route of administration with frequency, date of onset of reaction were recorded.

Study details

On reporting of ADRs either by physicians, nurse or collecting them personally, patient's data about ADRs was recorded in the Indian Pharmacopoeia Commission Suspected Adverse Drug Reaction reporting form. The form contains the patient details, drug details, the description of the reaction, name of the suspected drug causing the reaction, duration of reaction, concomitant medication, co-existing illness, etc. Every attempt was made to personally interview and examine the patients presenting with ADRs. All suspected adverse events were documented and analyzed.

Classification of ADRs was done as per type, severity and organ /system involvement**,** pharmacological group of the causative drug.[13-15]

The causality relationship with the drug will be established using the Naranjo scale. Accordingly the causality will be categorized as definite, probable, possible and unclassified.

Statistical analysis

The results were analyzed using descriptive statistics.

RESULTS

During the study period, total 298 ADRs were reported. Maximum ADRs were seen with radiotherapy 253 (84.90%) followed by ENT 32 (10.74%) and paediatrics 13 (04.36 %) department. Maximum ADRs i.e. 132 (44.29%) were observed in age group of 41-60 years followed by 77 (25.84%) ADRs in age group of 19 - 40 years. Forty-five (15.10%) ADRs were observed in age group ≥ 61 years and lowest ADRs i.e. 44 (14.76%) were observed in age group 7 months-18 years (Figure 1).

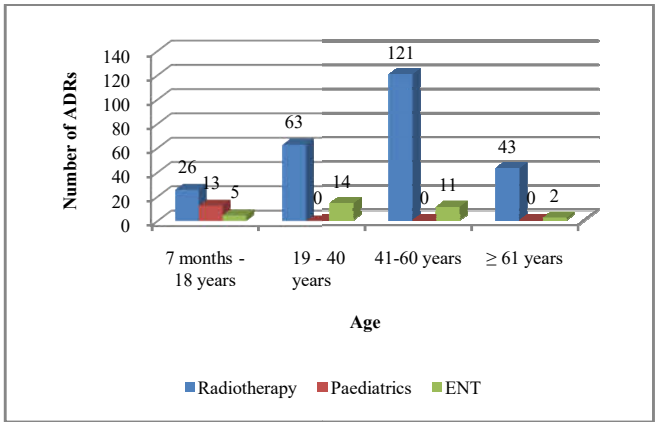

Figure 1 Age-wise distribution of ADRs

ADRs- Adverse drug reactions, (n=298), ENT – Ear, Nose and Throat

Out of the 298 patients presenting with ADRs, 136 (45.64%) were male and 162 (54.36%) were female. Table 1 shows top ten individual drugs causing ADRs in descending order. Maximum percentage of ADRs was observed with cispaltin i.e. (13.42%), followed by paclitaxel (4.70%) and oxaliplatin (3.35%).

Table 1 Top ten individual drugs causing ADRs in descending order

Sr. No	Drug	No. of ADRs (%)
1	Cisplatin	40 (13.42)
2	Paclitaxel	14 (4.70)
3	Oxaliplatin	10 (3.35)
4	Doxorubicin	09 (3.02)
5	Amoxicillin	08 (2.68)
6	Vinblastin	08 (2.68)
7	Cefotaxime	07 (2.35)
8	5 Flurouracil	06 (2.01)
9	Gemcitabine	06 (2.01)
10	Ceftazidime	06 (2.01)

ADRs- Adverse drug reactions, n = 298, ENT – Ear, Nose and Throat

Lowest percentage of ADRs among top ten drugs was due to gemcitabine and ceftazidime. Table 2 shows top ten drug combinations causing ADRs in descending order. Maximum percentage of ADRs was observed with cispaltin + 5 flurouracil combination i.e. (09.39%), followed by carboplatin + paclitaxel combination (07.38%) and cyclophosphamide + doxorubicin combination (05.03%). Lowest percentage of ADRs among top ten combination of drugs was due to amoxicillin + clavulanic acid and oxaliplatin + capecitabine combination.

Table 2 Top ten drug combinations causing ADRs in descending order

Sr. no	Drug combination	No. of ADRs(%)
1	Cisplatin + 5 Flurouracil	28 (09.39)
2	Carboplatin + Paclitaxel	22 (07.38)
3	Cyclophosphamide + Doxorubicin	15 (05.03)
4	Cisplatin + Paclitaxel	10 (03.35)
5	Cyclophosphamide + Doxorubicin + 5 Flurouracil	08 (02.68)
6	Cisplatin + Gemcitabine	08 (02.68)
7	Cyclophosphamide + Doxorubicin + Gemcitabine	06 (02.01)
8	Oxaliplatin + Leucovorin	05 (01.68)
9	Amoxicillin + Clavulanic acid	03 (01.00)
10	Oxaliplatin + Capecitabine	03 (01.00)

ADRs- Adverse drug reactions, n = 298, ENT – Ear, Nose and Throat

Causality assessment was performed by Naranjo scale. Definite relationship was established between the drugs and ADR in 01 (0.33%) patient, while 247 (82.89%) and 50 (16.78%) ADRs were categorized as probable and possible respectively. In the department of radiotherapy, among various classes of drugs, maximum ADRs of nausea (19) and vomiting (10) were noted in platinum coordination complexes group. Alopecia (06) and nausea (04) were common with microtubule damaging agents group. The most frequently observed ADRs were due to platinum coordination complexes which included (cisplatin, carboplatin and oxaliplatin) in 54 (21.34%) patients followed by microtubule damaging agents (Paclitaxel, Vincristine and Docetaxel) in 24 (09.49%) patients. Third common received group of drugs with antimetabolites (5 Flurouracil, Gemcitabine, Methotrexate and Capecitabine) in 17 (06.72%) patients. Among various combination of class of drugs in department of Radiotherapy, maximum ADRs of nausea (11), headache (11) and abdominal pain (05) were noted in platinum coordination complexes and antimetabolites combination group. Abdominal pain (08) and nausea (07) were common with platinum coordination complexes and microtubule damaging agents combination group. The most frequently observed ADRs were due to platinum coordination complexes and antimetabolites combination (Cisplatin + 5 Flurouracil, Cisplatin + Gemcitabine and Oxaliplatin + Capecitabine) in 39 (15.41%) patients followed by platinum coordination complexes and microtubule damaging agents combination (Carboplatin + Paclitaxel, Cisplatin + Paclitaxel and Cisplatin + Vincristine) in 33 (13.04%) patients. Third common received group of drugs with alkylating agents and antibiotics combination (Cyclophosphamide + Doxorubicin, Epirubicin + Cyclophosphamide and Ifosfamide + Doxorubicin) in 17 (06.72 %) patients.

In department of paediatrics, the most frequently observed ADRs were due to antibiotics (Ceftriaxone, Cefotaxime, Amoxicilline, etc) in 11 (84.61 %) patients followed by antiepileptic (Carbamazepine) in 01 (07.69 %) patient and vaccine (DPT vaccine) in 01 (07.69 %) patient.

In the ENT department, the most frequently observed ADRs were due to antibiotics (Amoxicilline, Cefotaxime, Ceftriaxone etc) in 22 (68.75%) patients followed by antihistaminics (cetrizine, rupatidine, etc) in 06 (18.75%) patients. Single drug was received by 68 (22.82%) patients and 230 (77.18%) patients received more than one drug.

Gastrointestinal system (GIT) was involved in 164 (55.03%) patients and GIT symptoms were nausea, vomiting, diarrhea, abdominal pain, anorexia, throat irritation, stomatitis and gastritis. Skin manifestations like alopecia, rash, pruritic rash, itching, erythema and mucositis were seen in 61 (20.47%) patients. CNS manifestations like sedation, headache, dizziness, convulsions and vertigo were seen in 35 (11.74%) patients. Cardiovascular system (CVS) was involved in 03 (01%) patients and CVS manifestations were hypotension and tachycardia. Haematopoetic ADRs like febrile neutropenia was seen in 02 (0.67%) patients. Other ADRs like fever, fever with chills, weakness, edema, tinnitus, weight loss and dry mouth were seen in 33 (11.07 %) patients.(Table 3)

In severity assessment, maximum patients were reported in moderate group i.e. 166 (55.70%) and mild group included 128 (42.95%) patients. Four (01.34%) patients were labeled as suffering from severe ADRs.

Type-A ADR were found to be the commonest i.e. 277 (92.95 %). Type C ADR were 11 (03.69%) followed by Type- B ADR 07 (02.35%) and Type-D ADR 03 (01.00%) (Figure 2).

Table 3 ADRs according to organ system involvement

Department	No. of ADRs (%)	GIT	CNS	Skin	CVS	Haemat	Others
Radiotherapy	253 (84.90)	141 (47.31)	27 (09.06)	52 (17.45)	00	02 (0.67)	31 (10.39)
Paediatrics	13 (04.36)	03 (01.01)	02 (0.67)	06 (02.01)	01 (0.34)	00	01 (0.34)
ENT	32 (10.74)	20 (06.71)	06 (02.01)	03 (01.01)	02 (0.67)	00	01 (0.34)
Total no. of ADRs (%)	298 (100)	164 (55.03)	35(11.74)	61(20.47)	03(1.01)	02(0.67)	33(11.07)

ADRs- Adverse drug reactions, n = 298, GIT - gastrointestinal system, CNS - central nervous system, CVS – cardiovascular system, Haemat – haematopoetic system

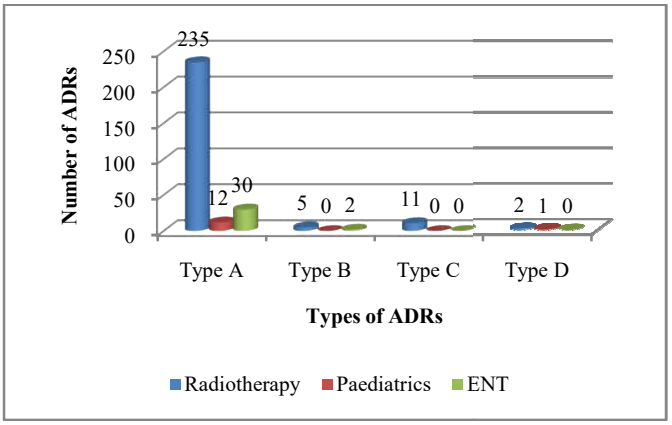

Figure 2 Types of ADR

ADRs- Adverse drug reactions, (n=298), ENT – Ear, Nose and Throat

Outcome of maximum ADRs was recovered in 124 (41.61%), followed by recovering 91 (30.54%) and continuing 47 (15.77%).

In the present study, out of 298 patients, 285 (95.64%) patients received drugs causing ADRs by parenteral route (intravenous, intramuscular) and 13 (04.36%) patients received drugs causing ADRs by oral route.

DISCUSSION

Adverse drug reactions remain a significant concern in drug development and clinical use. Due to increase in the number of pharmacotherapeutics and other chemical entities, the general population is exposed to increase risk of ADRs. So, every health care professional must have knowledge about the importance of adverse drug reaction reporting, monitoring and pharmacovigilance.

In the present study, out of total 298 ADRs, maximum ADR were seen with radiotherapy (84.90%) followed by ENT (10.74%) and paediatrics (04.36%) department. The reason for maximum number of ADRs in the department of radiotherapy may be due to ability of anticancer drugs to cause side effects even at therapeutic doses and also the reporting of ADRs could be more from this department. It may be possible that there is less willingness and awareness about ADR reporting in ENT and paediatrics department and hence less number of ADRs are reported from these departments.

In the present study, maximum ADRs were observed in age group of 41- 60 years. It is likely that this age group is attending hospital more repeatedly and is a major population receiving drug therapy. This finding is comparable to the results obtained from the study conducted by Poddar *et al*. and Khan F A *et al*. [10,16]

In the present study, there was female gender predominance over males. This is consistent with other studies and the fact that women experience more adverse reactions to therapeutic dose of drugs than men because of different pharmacokinetic and pharmacodynamic responses to drugs.[17-20]

Maximum percentage of ADRs among top ten individual drug was observed with cisplatin while lowest percentage of ADRs was due to gemcitabine and ceftazidime. Maximum percentage of ADRs among top ten drug combinations was due to cispaltin + 5 flurouracil combination. Lowest percentage of ADRs among top ten combination of drugs was due to amoxicillin + clavulanic acid and oxaliplatin + capecitabine combination.

In the present study, causality assessment showed that maximum ADRs were in the probable category followed by possible and definite. In a study conducted by R. Arulmani *et al*, Saini V. *et al* and Sharma A. *et al* showed maximum number of probable followed by possible and definite ADRs,[2,21,22] while study conducted by S. Palanisamy *et al* and Khan M. *et al* showed maximum number of possible followed by probable and definite ADRs.[23,24]

In our radiotherapy department, among various classes of drugs, the most common class causing ADRs was platinum coordination complexes. Most common platinum compound to cause ADRs was cisplatin followed by oxaliplatin and carboplatin. In this department, platinum compounds are more frequently prescribed, so maximum ADRs could have occurred due to cisplatin. Similar findings were reported in previous studies where cisplatin was the most common drug causing ADRs. [19,25,26] In the study conducted by Poddar *et al*, antimetabolites was the most common group of drug causing ADRs.[16] Among various combinations of drugs causing ADRs, the most frequently observed ADRs were due to platinum coordination complexes and antimetabolites combination. In the study conducted by Kirthi C. *et al*, the most common combination causing ADRs was 5- fluorouracil + adriamycin + cyclophosphamide combination followed by adriamycin + cyclophosphamide combination.[17]

In the study, the most frequently observed ADRs in department of paediatrics were due to antibiotics followed by antiepileptics and vaccine. Our study findings are similar with the study conducted by M. Inocencia *et al*. which shows more number of ADRs due to antibiotics, whereas Digra *et al*. reported anticonvulsants as the most common drug implicated in maximum patients. [27,28] Most common antibiotic group to cause ADRs was cefalosporin followed by semisynthetic penicillin group and the most common ADRs reported with these antibiotics were rash and headache. Among antiepileptics, carbamazepine caused the ADR while the vaccine responsible for ADR was DPT (diphtheria, pertusis, tetanus) vaccine. The possible explanation for the above results could be that in our paediatrics department, antibiotics are used more frequently, so maximum ADRs could have occurred due to antibiotics.

In our study, the most frequently observed ADRs in department of ENT were due to antibiotics followed by antihistaminics and miscellaneous group of drugs. The most common antibiotic to cause ADRs was amoxicillin followed by cefotaxime and ciprofloxacin. This may be due to the fact that above drugs are frequently prescribed for common ENT related disorders. These findings are consistent with similar prospective study conducted by Khan F A. *et al* which showed β lactams as most common antibiotics causing ADRs.[10] Among antihistaminics, commonly used drugs that caused ADRs were cetrizine, rupatidine and olopatadine. Among miscellaneous group, most frequent ADRs were due to adrenaline followed by tramadol and dexamethasone.

In our study, maximum ADRs were developed in patients who received who received more than one drug. In the study conducted by Dilip C. *et al* and D. Patidar *et al*, majority of ADRs were developed in patients receiving multiple drugs which is consistent with our findings.[29,30] Variation in

pharmacokinetic properties of drug and drug-drug interaction are the key factors for developing ADRs in the patients receiving multiple drugs.

In the present study, most common system affected due to ADRs was GIT. Most common ADRs of GIT system may be due to the fact that more number of ADRs were found in department of radiotherapy and anticancer drugs commonly cause ADRs of GIT system. These results are comparable with study done by Khan F A. *et al*, Chopra *et al* and Jire *et al*.[10,19,26] In the study conducted by Richa *et al* it was seen that skin related ADRs were more common than GIT system ADRs.[31]

In our study, according to severity of ADRs, maximum patients were reported in moderate group. This finding is parallel with study conducted by Sharma A. *et al* and Digra *et al*.[22,27] While study conducted by Jire *et al* reported maximum number of ADRs in mild category which is in contrast to our study.[26] This may be due to different prescribing preferences in our hospital as compared to other hospitals.

In our study, type A reactions was seen in maximum patients followed by type C and type B reactions. Similarly, study conducted by Khan FA *et al*. and Richa *et al*. showed that type A reactions accounted for majority of the reports.[10,31] This was in agreement with the definition of type A reactions that are more common and predictable whereas type B reactions are uncommon. But study conducted by Roy *et. al* showed majority of ADRs were due to type B which is different to our study.[32]

In the present study, outcome of majority of ADRs was recovered. In the study conducted by Lihite *et al*. showed that outcome of majority of ADRs was also recovered.[33] ADRs were maximum in patients receiving drugs by parenteral route (intravenous, intramuscular). This could be due to the fact that majority of ADRs were from department of radiotherapy, where parenteral route is preferred.

The limitation of this study is that it was carried out only in three departments. Also, as the study was based on spontaneous ADR reporting system, under-reporting could not be ruled out.

CONCLUSION

In conclusion, it was found that this study has created a database about different ADRs and the drugs causing it which may be useful in identifying and minimizing ADRs. Various pharmacovigilance awareness programs should be conducted to increase the spontaneous reporting of ADRs. This could help physician to give different prescribing options depending on ADR profile of the drugs; which will ultimately alleviate human sufferings and reduce financial burden to the patient and society.

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How to cite this article:

Ganesh Dakhale *et al* (2018) 'Adverse drug Reaction Profile At Radiotherapy, Paediatrics and ear, Nose and Throat Department of A Tertiary Care Teaching Hospital: A descriptive Cross Sectional Study', *International Journal of Current Advanced Research,* 07(8), pp. 15082-15087. DOI: http://dx.doi.org/10.24327/ijcar.2018.15087.2753

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