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Identification and Assessment of the Severity of the Infusion Related Reactions of Medications

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ABSTRACT

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Objective: To identify infusion related reactions (IRRs) of medications. To establish the causality relationship between the drug and IRRs and to assess the severity of IRRs. **Methodology:** The required data were collected from the various sources such as patients' case reports, treatment charts and through direct patient interview. The obtained data was evaluated for their severity according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).The causal relationship between the drug and the reaction was established by using the Naranjo scale and WHO causality assessment scale.**Results and Discussion:** A total of 75 IRRs were reported in the six months period. Most of the IRRs were developed in the patients receiving anti-cancer agents and antibiotics are next to them. According to Naranjo scale out of 75 IRRs 30% were probably have a causal relationship with the drug and remaining 70% were possibly related to drug given through infusion and according to WHO Severity assessment 3% reactions were certain, 39% were probable, 52% were possible and 6% were unlikely. Based on the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) revealed that the 28% were at grade 1, 57% were at grade 2 and 13% were at grade 3 severity.**Conclusion:** Infusion related reactions monitoring is important as it may prevents the complications which may occur in future. Awareness of infusion-related reactions is necessary, and the risk factors associated with these reactions may have important clinical implications.

Keywords: Infusion related reactions, Causality assessment, Common Terminology Criteria for Adverse Events v4.0.

INTRODUCTION

Infusion related reactions are defined as the signs and symptoms experienced by the patient which occurs during the infusion of any pharmacological or biological substances. The infusion related reactions are classified as acute and delayed type of reactions. Clinical manifestations of these reactions may vary. Anaphylactic or anaphylactoid reactions are the most severe forms of infusion-related reactions and may result in patient death. Death may occur rapidly; thus, in managing severe infusion-related reactions, it is crucial that risks are understood and early signs and symptoms are recognized. All clinicians should be well trained in the management of acute events. Identification of individuals likely to develop severe and sometimes life-threatening infusion-related reactions is challenging. Some proposed risk factors are repeated use of the agent and a personal history of drug allergy[1].

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Infusion medications are associated with high risk of harm which are seeking to improve patient safety, the primary focus should be on preventing errors with the greatest potential for harm. The administration of the drugs through the infusion has the fewest safeguards and fewest support mechanisms, and it often relies on a single healthcare professional for accuracy. A standard approach to IV medications exists in many hospitals. But often the standard is not the same across all areas in a hospital, across hospitals in a system, or across all or even most hospitals in a given region where patients and staff may transfer[2].

Most cancer therapeutics-including cytotoxic agents and biologics-carry a risk for infusion reactions, which vary in symptom severity from mild flushing to potentially life threatening events. Because of the possibility of infusion reactions, medical therapy including epinephrine, corticosteroids, I.V antihistamines, bronchodilators, oxygen, and vasopressors should be readily available. Physicians and nurses working in chemotherapy infusion rooms are certainly prepared to address severe infusion reactions based on their experience with platinum compounds and taxanes of chemotherapy[3].

Infusion reactions may be classified as acute, occurring within the first 24 hours of infusion, or delayed, occurring at least 24 hours after infusion. The majority of acute reactions occur within the first 2 hours of initiating infusion[4].

Grade is an essential element of the assessing severity of IRRs and, in general, relates to severity for the purposes of regulatory reporting to National Cancer Institute as follows:

Grade Description[5]:

- No AE (or within normal limits).
- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Life-threatening consequences; urgent intervention indicated.
- Death related to AE.

Administration of cytotoxic agents should be initiated upon the prescription of an appropriately qualified clinician. Protocols for the administration of cytotoxic agents should be set out in organizational policies and procedures. Prior to administration of chemotherapeutic agents, laboratory data and other relevant investigations should be reviewed and the patient assessed for appropriateness of the prescribed therapy.

Identify high risk patients and rechallenging of the drug[1]:

Identification of individuals likely to develop severe and sometimes life-threatening infusion-related reactions is challenging. Some proposed risk factors are repeated use of the agent, gender, age. Effective oncologic agents are extremely valuable—and oncologists often have few, if any, therapeutic alternatives to their use. Thus, it is not uncommon or unreasonable to rechallenge patients with a drug to which they have reacted adversely. Generally patients experiencing the infusion related reactions of grade 1 or 2 are managed using antihistamines and corticosteroids after complete resolution of the symptoms. To avoid serious infusion-related reactions that may occur despite their best efforts, physicians must accomplish a risk-benefit analysis based upon individual goals of therapy and must accurately assess the severity of infusion-related reaction to manage them appropriately.

Assessing causality[6]:

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. In eliciting a causality relationship, a temporal or possible association is sufficient for an adverse drug reaction report to be made. The assessment of causality relationship is often highly subjective based upon an individual clinician's assessment. Thus one clinician's-possible may be another clinician's -unlikely.

Using formal algorithms, collected data are subjected and critically assessed by using one or more standard algorithms. Some of the important algorithms (Causality assessment scales) used for assessing the causality relationship include Naranjo scale, WHO , European ABO system, Kramer, Bayesian, Karch and lasagna's, French imputation method.

The assessment and establishment of Causality relationship between suspected drugs and reaction has certain applications they include;

- Patient management
- Signal generation
- Drug regulation
- Scientific publication
- Data exchange

Every suspected ADR should be assessed for its causality and documented in the patient's medical record. This serves as a reference for alerting clinician's to the possibility of a particular drug causing a suspected reaction.

METHODOLOGY

Study design:

It was a prospective, observational study with duration of six months

Study period:

The study was conducted over a period of six months from February 2011to July 2011.

Study Population*:*

Subjects who were receiving infusion therapy of drugs were included in the study.

Study Criteria*:*

Inclusion Criteria:

Both male and female patients receiving infusion therapy of drugs were included in this study.

Exclusion Criteria:

- Pediatric patients are excluded from the study.
- Patients unable to respond to verbal questions.
- Patients those who are receiving IV fluids alone.

Study protocol:

Patients who met the study criteria were included in the study. Patient demographics, past medical and medication history and information about the over the counter drugs etc. were collected through patient's case reports and patient interview and treatment charts. A separate data entry form was prepared and the interview was carried out during the time of infusion and patient reports were thoroughly checked for the presence of any new symptom. They were kept under close observation by nursing staff taught to detect infusion related reactions. Patients were asked about any adverse reaction following their previous infusion on each visit prior to commencement of infusion. The primary objective of the study was to identify the IRRs and the secondary objectives was to assess the severity and establishing causality assessment of the reaction with the drug. Infusion related reactions were identified and the causal relationship was established by using Naranjo scale[7] and WHO causality assessment scales[8]. The severity of each infusion related reactions were assessed by using NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Institutional review board approval and oral informed consent from the patients were obtained for the study. Variables were expressed as percentages.

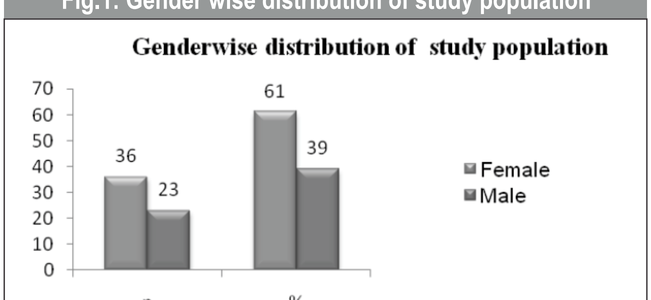
RESULTS

A total of 75 reactions were observed during the study period. Among the study population infusion related reactions were observed mostly in the women consists of about 61% and males were observed as 39%.

Table 1: Infusion related reactions based on gender of patient

Gender	n	%
Male	23	39
Female	36	61

Fig.1: Gender wise distribution of study population

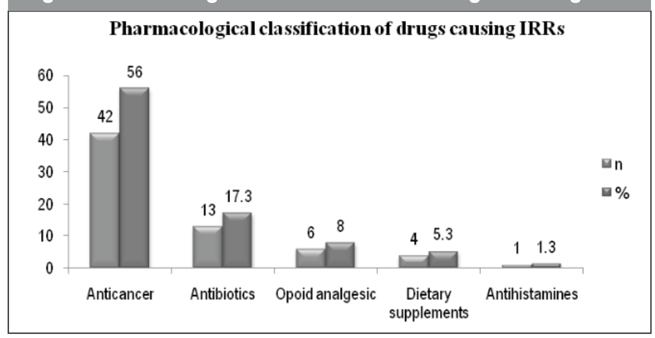


According to the pharmacological classification of the drugs which causes the infusion related reactions most of the drugs were anticancer drugs which constitutes of about 56%, and the next to it antibiotics consists of about 18% and the remaining were opoid analgesic at 8%, dietary supplements were at 6% and only one IRR caused by antihistamine.

Table2: Classification of drugs associated with infusion related reactions

Category	n	%
Anticancer drugs	42	56
Antibiotics	13	17.3
Opioid analgesic	6	8
Dietary supplements	4	5.3
Antihistamine	1	1.3

Fig.2:Pharmacological classification of drugs causing IRRs

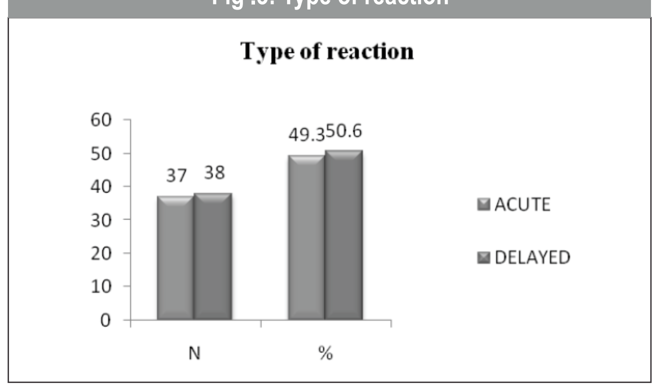


Among the 75 Infusion related reactions observed acute reactions were 49.3% (which occurs within 24 hours after the infusion) and the delayed reactions were at 50.6% (which occurs 24 hours after the infusion)

Table 3: Type of infusion related reactions

Reactions	n	%
Acute	37	49.3
Delayed	38	50.6

Fig .3: Type of reaction

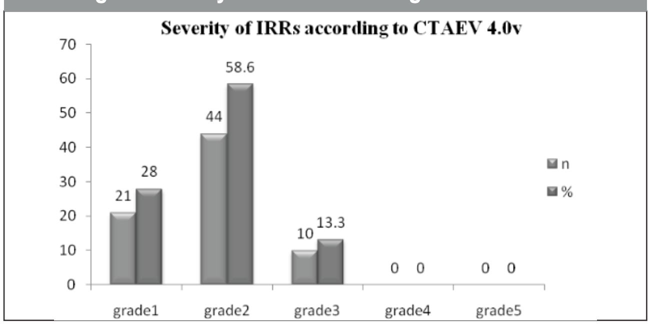


Severity of the Infusion related reactions has been performed according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) in which 28% were found to be grade1, 59% were grade 2 and the remaining 13.3% were at grade 3.

Table 4: Severity according to ctcae4.0 version (common terminology criteria for adverse events)

Severity	n	%
Grade1	22	29.3
Grade2	43	62.6
Grade3	10	13.3
Grade4	0	0
Grade5	0	0

Fig. 4:Severity of IRRs according to CTAEV 4.0v

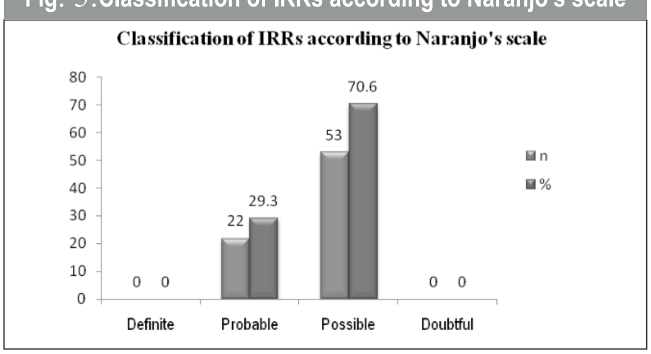


For the observed Infusion related reactions causality assessment was carried out by Naranjo scale in which 29.3% reactions were found to be probably associated and 70.6% reactions were found to possibly associated with the drug.

Table 5: Classification of infusion related reactions according to Naranjo scale

Category	n	%
Definite	0	0
Probable	22	29.3
Possible	53	70.6
Doubtful	0	0

Fig. 5:Classification of IRRs according to Naranjo's scale

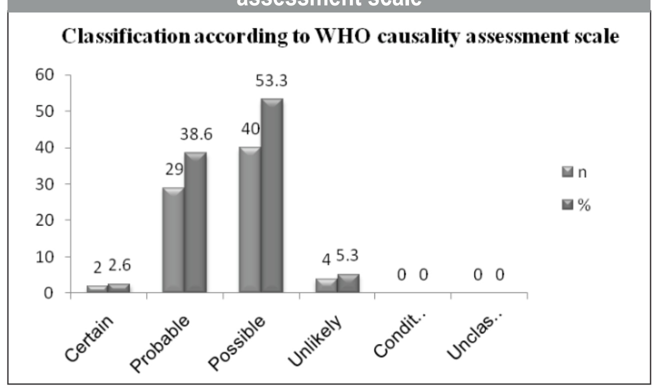


By another method named WHO causality assessment scale was performed in which 53.3% reactions were possibly related to the drug, 38.6% of IRRs were probably related to the drug, 5.3% were treated as unlikely and 2.6% were under certain category.

Table.6: Classification of infusion related reactions according to who causality assessment scale

Categoryn%		
Certain	2	2.6
Probable	29	38.6
Possible	40	53.3
Unlikely	4	5.3
Conditiona	l0	0
Unclassified	0	0

Fig.6 :Classification according to WHO causality assessment scale



DISCUSSION

From the literature survey the IRRs can be treated as a category of adverse events. According to the product label the IRRs can be managed by protocol-special guidelines and prophylactic medications. Patients were provided with the prophylactic medication according to the protocol for different types of medications in which both corticosteroids as well as the antihistamines were used which results in the decreased incidence of infusion reactions among the patients[9].

Anaphylactic reactions are the reactions that occur soon after the administration of the therapeutic agent that are potentially life-threatening. Some of the patients in the present study who were treated with the anticancer drugs were given prophylactic medications with both antihistamines and they were more likely to receive corticosteroids for nausea prophylaxis. The studies showed that the patients with history of prior significant allergy history were significantly more likely to experience the anaphylactic reactions. In our study there were medical records available in which no data was present regarding the previous allergic history of the patients[10].

One of the limitations of the present study is that the acute reaction for some patients would not have been captured and the post infusion monitoring was not done in the patients administering anticancer drugs because of reduced time spent in the hospital. The studies suggesting that no increase in the infusion reactions associated with rapid infusion times and no stopping of infusions and did not warrant any hospitalization if the protocols were strictly followed. The study can be further carried out in order to develop successful desensitization protocols to prevent infusion related reactions for all the drugs which are giving through the infusion[4].

The studies suggest that the test dosing will reduces the incidence of infusion related reactions. In our hospital settings test dosing is provided for the patients in whom a detailed history of the medication and allergies are not available. There have been numerous studies for the patients with a history of allergy to penicillin or cephalosporin may be at increased risk for a reaction to cephalosporin's. For the patients who are considered as high-risk successful desensitization should be performed[11]. Some of the literatures conducted causality assessment between the specific drug and a clinical event. When a suspected reaction occurs in a clinical practice it may be helpful to assess the reaction. In the present study Naranjo probability scale were used to perform causality assessment and also we have utilized the World Health Organization-Uppsala Monitoring Centre criteria for standardized case causality assessment[12].

Studies concluded that the IRR-related hospitalization was occurred mainly because of the antineoplastic agents and immunosuppressive agent's results in the increases the cost associated with the mortality and morbidity and treatment of IRRs. Our study has a limitation that the cost related to IRRs-related hospitalization because of the underreporting of these reactions in the hospital environment as they are not noted in the discharge reports of the patients[13].

CONCLUSION

IRRs are a significant public health problem that is associated with prolonged hospitalization, morbidity and mortality. Infusion-related reactions, including deaths following the administration of drugs through infusion have been reported rarely. More research to identify risk factors for severe infusion-related reactions is needed; however, some infusion-related reactions are unavoidable. The incidence of IRRs may be reduced by giving premedication. The data suggested that the premedication is associated with decreased incidence of IRRs. But some severe IRRs lead to death which requires estimation of risk factors to prevent IRRs. The present study determines that the females are more prone to IRRs when compared to males. The premedication protocol was available for the specific category of drugs like anticancer agents and monoclonal antibodies etc, Incorporation of test dosing of antibiotics with close monitoring provide a safe and effective of administration of the drugs. Further more research is needed to avoid IRRs produced because of antibiotics and other drugs giving through infusion. To reduce the IRRs most effective interventions need to developed like premedication protocol for certain category of drugs and risk assessment of IRRs.

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REFERENCES

1. Peter KS, Saif WM. Infusion-Related and Hypersensitivity Reactions of Monoclonal Antibodies Used to Treat Colorectal Cancer—Identification, Prevention, and Management. J Support Oncology 2007;5:451-7
2. San Diego Patient Safety Consortium, How-to Guide: Standardization of High-Risk IV Medications. 2006
3. Christin.H.C, et.al, Managing Premedication's and the Risk for Reactions to Infusion Monoclonal Antibody Therapy. The Oncologist 2008; 13:725–32.
4. Bhat S, Pauline D. et al. Are Accelerated Infliximab Infusions Safe in Patients with Inflammatory Bowel Disease? Inflamm Bowel Dis. 2010;16(1922):11.
5. National Cancer Institute. Guidelines: Adverse Event

Reporting Requirements. Washington, DC: U.S. Department of Health and Human Services. 2011.

6. Olsson S. Adverse drug reaction. In: G. Parthasarathi G. A text book of clinical pharmacy practice. Orient Longman Pvt Ltd. Hyderabad, India 2004:92-3.

7. Naranjo CA, Busto.U. et al. A method for estimating the probability of Adverse drug reaction. Clin Pharmacol Ther 1981;30:239-45.

8. The use of WHO-UMC system for standardized case causality assessment. Available from URL: http://www.who. umc.org/ graphics/4409.{last accessed on 2011 Feb 12}

9. Salvatore. S, Robert glynne, et al. Reduced Incidence of Infusion-Related Reactions in Metastatic Colorectal Cancer during Treatment with Cetuximab plus Irinotecan with Combined Corticosteroid and Antihistamine Premedication. Cancer 2010;116:1827–37

10. Bert. H. O, David R, et al. High Incidence of Cetuximab-Related Infusion Reactions in Tennessee and North Carolina and the Association with Atopic History. J Clin Oncol 2007;25:3644-8.

11. Pramod SJT. et al. Cephalosporin allergy, N Engl J Med 2001;345(11)

12. Blas. Y.B, Maria A Marrero, et al. Pharmacovigilance program to monitor adverse reactions of recombinant streptokinase in acute myocardial infarction. BMC Clinical Pharmacology 2005;5:5.

13. Pilar C, Lopez Ana, et al. Trends of adverse drug reactions related hospitalizations in Spain (2001-2006), Biomed central Health Services Research 2010;10:287