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RESEARCH ARTICLE

Antimicrobial-associated adverse drug reaction profiling and assessing the agreement between the WHO-UMC scale and the Naranjo algorithm for causality assessment at a tertiary care teaching hospital in India

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ABSTRACT

Background: Adverse drug reactions (ADRs) are not uncommon due to medications, especially antimicrobials (AMs), given to the patients during their stay in the hospital. **Aim and Objective:** The present study aims to assess the ADRs related to AMs, causality assessment using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment scale and the Naranjo scale and to evaluate their agreement. **Materials and Methods:** A prospective, observational study conducted over a period of one year in general medicine and pulmonary medicine wards, including 206 patients. WHO-UMC scale and the Naranjo algorithm were used to assess the causality followed by evaluating the agreement between these two scales. **Results:** The most common antibiotic accounted for ADRs was Piperacillin+ Tazobactam (36.10%). The most common organ system involved was gastrointestinal (83.30%), followed by skin and soft tissue (11.10%) and immunological (5.60%). While 58.30% of the ADRs were latent in onset, 30.60% and 11.10% were sub-acute and acute, respectively. The majority of the ADRs were mild (66.70%), followed by moderate (22.20%) and severe (11.10%) in nature. As per the WHO-UMC scale, 19.4% ADRs were certain, 47.2% were probable, 27.8% were possible, and 5.6% were found to be unlikely. As per Naranjo algorithm, 75% of the ADRs were probable and 25% were of possible. Overall agreement analysis showed "Poor" agreement between the WHO-UMC scale and the Naranjo algorithm (kappa statistics with 95% confidence interval = 0.2195 [0.0065, 0.4325]). **Conclusion:** Using both the WHO-UMC scale and the Naranjo algorithm is advisable for better evaluation of ADRs related to AMs.

KEY WORDS: Antimicrobials; Agreement; World Health Organization-UMC Scale; Naranjo Scale; Causality Assessment

INTRODUCTION

Medication-related adverse drug reactions (ADRs) are the most commonly encountered events in the health-care settings, which are unwanted and harmful depending on the severity of the reaction. Antimicrobials (AMs) are part and parcel of patient care, which account for ADRs in a considerable amount. ADR monitoring studies will help us to keep watch over the unwanted effects related to the misuse of the AMs. According to the World Health Organization (WHO) definition an ADR is the one which is noxious and unintended and occurs in doses normally used in human for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological functions.[1] ADRs are responsible for a significant amount of burden on the health-care settings in terms of finances, disease burden, and quality of patient care. AMs are among the most commonly used medications inpatient care to treat various infections globally and proportionately, accounting for a greater amount of ADRs

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related to their use.[2] Data show that AMs account for 19% of hospital consultations in the United states,[3] eight percent of the consultations in Greece,[4] six percent of the admissions in Spain,[5] five percent in Netherlands,[6] and eleven percent in India[7] and also accountable for a greater amount of hospital generated ADRs all over the world.[2,8] There is an increase in the AM utilization by the developing nations accounting to more than 75% leading to increase in the AM associated ADRs proportionately.[9] Causality assessment is the process of evaluating whether a particular intervention is attributable to the reported ADR or not. WHO-Uppsala Monitoring Centre (UMC) causality assessment scale and the Naranjo algorithm are the most commonly used causality assessment scales. While the WHO-UMC system considers the clinical pharmacological perspectives of the case that has been reported, the Naranjo algorithm considers the temporal association between the suspected medication and the ADR reported, other possible explanations for the reported ADR. But these two scales are not considered as the gold standard options in ADR monitoring.[10] Therefore, in this study, we focused on assessing the agreement between these two tools along with the ADR analysis.

MATERIALS AND METHODS

It was a prospective observational study conducted for one year including the patients from the departments of general medicine and pulmonary medicine after the institutional Ethics Committee approval. ADRs reported among the patients who are on at least one antibiotic agent were included in the present study. Patients on anti-tubercular drugs and anti-retroviral drugs were excluded since they receive multiple medications for a prolonged period of time, making the causality assessment difficult. Data regarding the confirmed ADRs were collected using the case report forms, ADR checklist, and the ADR collecting forms. The resident doctor from pharmacology department trained in pharmacovigilance collected the reports. ADR analysis and causality assessment were done and discussed with other researchers to arrive at a conclusion. ADRs were reported to ADR Monitoring Centre (AMC) of the institute under the Pharmacovigilance Program of India (PVPI). Patient demographic data and information regarding patient diagnosis, comorbidities, antibiotics administered, concomitant medication was collected. Patients with suspected ADRs were followed up till the day of discharge. The WHO-UMC causality assessment scale and the Naranjo algorithm were used to establish the causality. According to Common Terminology Criteria for Adverse Events version 4.0, ADRs are classified as mild (manifestations are minimal in severity and do not require any intervention); moderate (severe enough to limit daily activities and requires non-invasive intervention); and severe (clinically important, limits the daily activities and requires hospitalization or increasing the duration of hospital stay and sometimes resulting in disability).[11] Moreover, the ADR is considered "severe" if it leads to hospitalization or increasing the duration of stay in the hospital or causing death or leading to persistent, clinically considerable disability/incapacitation, or causing malignancy, teratogenicity or if not reverted by acute management.[12] Regarding the time of onset, ADRs are called acute (manifesting within 1 h); sub-acute (manifesting within 60 min to 1 day); and latent (manifesting after 48 h).[13]

RESULTS

During the study period, a total of 36 confirmed ADRs were noted and analyzed from both the departments. The mean age of patients in the study was 48.3 (28–68) years. Baseline characteristics of the study population are described in Table 1. Male patients experienced relatively high number of ADRs (55.6%) compared to females (44.4%). Intravenous (I.V) route of administration accounted for maximum ADRs (83.30%) compared to oral (16.70%). The most common antibiotic accounted for ADRs was Piperacillin+ Tazobactam (36.10%), followed by Amoxicillin+ Clavulanic acid (25%) and Vancomycin (11.10%). Gastritis was most commonly reported (66.70%), followed by loose stools (16.60%) and skin rash (8.33%). The most common organ system involved was gastrointestinal (83.30%), followed by skin and soft tissue (11.10%) and immunological reactions (5.60%). While 58.30% of the ADRs were latent in onset, 30.60% and 11.10% of them were sub-acute and acute, respectively. The majority of the ADRs were mild (24; 66.70%), followed by moderate (8; 22.20%) and severe (4; 11.10%) in nature. Moreover, 34 (94.4%) ADRs were non-serious and 2 (5.60%) were serious in nature [Figure 1]. Intervention was required in 30 cases (83.33%) to treat the ADRs, while 6 cases (16.7%) resolved spontaneously after stopping the offending drug. As per the WHO-UMC scale, 7(19.4%) ADRs were certain, 17 (47.2%) were probable, 10 (27.8%) were possible, and 2 (5.6%) were found to be unlikely. As per Naranjo algorithm, 27 (75%) ADRs were probable and 9 (25%) were found to

Table 1: Baseline characters of the patients

Characteristics	Category	Number (%)
Gender distribution	Male	20 (55.6)
	Female	16 (44.4)
Underlying Pathology	CNS disorder	2 (5.5)
	GIT disorder	4 (11)
	Hematological disorder	2 (5.5)
	Metabolic disorders	2 (5.5)
	Respiratory disorder	24 (66.66)
	Renal disorder	1 (2.7)
	Systemic infection	1(2.7)
Comorbidities	Diabetes	5 (13.9)
	Hypertension	2 (5.5)

GIT: Gastrointestinal tract, CNS: Central nervous system

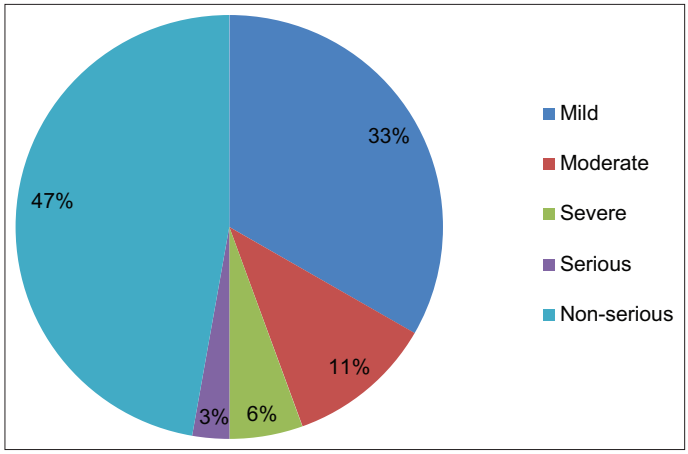

Figure 1: Nature of the reported adverse drug reactions

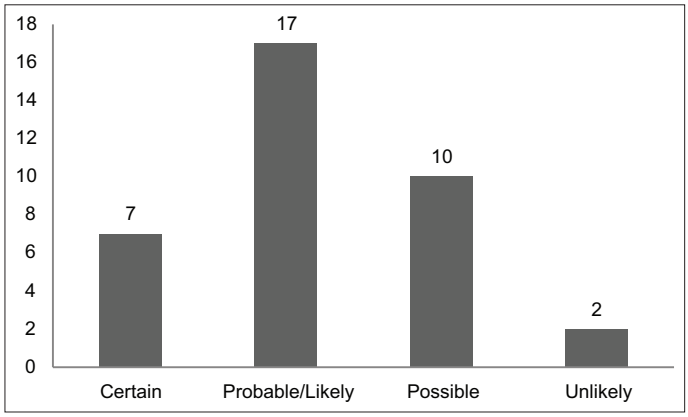

Figure 2: Classification of adverse drug reactions according to the World Health Organization-Uppsala Monitoring Centre scale

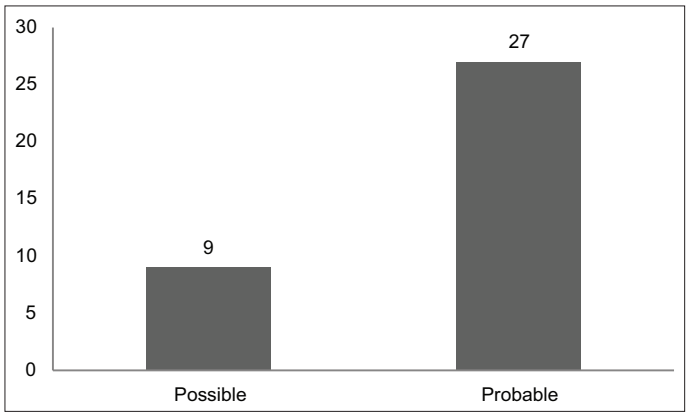

Figure 3: Classification of adverse drug reactions according to the Naranjo algorithm

be possible [Figures 2 and 3]. When compared the overall agreement between the W.H.O-UMC scale and the Naranjo algorithm, highest agreement was found for "Probable" (41.7%), followed by "Possible" (13.9%). Overall contradiction between the two scales was found to be 44.4% [Table 2]. While quantitative measurement of the agreement between the two scales using the Kappa statistics had shown "poor" agreement (kappa statistics with 95% confidence interval = 0.2195 [0.0065, 0.4325]).

Table 2: Disagreement analysis between the WHO-UMC scale and the Naranjo algorithm

Parameter	Frequency (%)
Total disagreements	16 (44.4)
Situation where probability was decreased by Naranjo	"Certain" according to the WHO-UMC to "Probable" according to Naranjo -7 (19.4) "Probable" according to the WHO-UMC to "Possible" according to Naranjo- 2 (5.5)
Situation where probability was increased by Naranjo	"Possible" according to the WHO-UMC to "Probable" according to Naranjo – 5 (13.8) "'Unlikely" according to the WHO-UMC to "Possible" according to Naranjo scale -2 (5.5)

WHO-UMC: World Health Organization-Uppsala Monitoring Centre

DISCUSSION

The appropriate reporting and data management of ADRs are a crucial part of pharmacovigilance and ensure medication safety in patient care, and many studies had reported AM agents being one of the most common causes of ADRs.[14] The present study was conducted in a tertiary care institute in northern India. The institute has their own formulary, according to the National List of Essential Medicines. Drug-related adverse events were regularly reported to the AMC under PVPI at the department of pharmacology by designated personnel after detailed analysis and causality assessment. Richa *et al.*[15] reported I.V antibiotic formulations causing the majority of ADRs compared to the other formulations (52.32%), which is similar to the finding in our study (83.3%). In our study, the most common organ system involving the ADRs was the gastrointestinal tract (GIT) (83.3%), followed by the skin and soft-tissue (11.1%), contrary to the findings by Richa *et al.*[15] and Arulmani *et al.*,[16] where the most commonly involved organ system was skin and soft-tissue (47%), followed by GIT (39%) and skin and soft-tissue (34.1%), followed by central nervous system (18.9%), respectively. Another study reported by Dhar *et al.*[17] had shown that GIT (22%) was the most common organ system, followed by the respiratory system (21%) to involve in the suspected ADRs. The most common antibiotic accounted for ADRs in our study was Piperacillin + Tazobactam (36.10%) (Penicillin group), contrary to the finding by Richa *et al.*[15] which showed Ceftriaxone (36%) (Cephalosporin group). This finding may be due to the fact that the drug is commonly used in the selected departments to treat critically ill patients who have higher propensity to develop ADRs. In our study, the most of the ADRs were mild (66.70%), followed by moderate (22.20%) and severe (11.10%) in nature, which was similar to the findings by[18] that showed the nature of the ADRs as mild (49%), moderate (36%), and severe (15%). Our study found that the majority of the time (83.33%) active intervention was required to alleviate the ADR reported. Causality assessment of our study showed that most of the ADRs were of "probable/likely" (47.2%), according the WHO-UMC system and "probable" (75%) according to the Naranjo algorithm and the results were comparable to the

study reported by Richa *et al*.,[15] which showed the majority of the ADRs being "probable" according to the WHO-UMC scale and "possible" according to the Naranjo algorithm. This finding was relatable to another study reported by Padmavathi *et al*.[19] Various methods are available to assess the causality while reporting the ADRs, which can be classified roughly as global introspection (GI), Bayesian methods, and algorithms, but none of them are considered to be gold standard.[20] Although the WHO-UMC scale (GI method) and the Naranjo algorithm are the most commonly used tools for assessing the causality, they are not validated yet. Therefore, it is necessary to evaluate to what level these two tools agree with each other while using them for causality assessment.[21] In our study, the total disagreement between these two scales was found to be in 16 cases (44.4%), out of which the probability was decreased (24.9%) and increased (19.3%) by the Naranjo scale compared to its counterpart tool. The overall agreement of these two tools with each other was found to be "Poor" with 44.45 and the Kappa value of 0.2195. This value was found to be higher than the study reported by Belhekar *et al*. (0.143)[10] but lesser than the studies reported by Behera *et al*. (0.45)[22] and Acharya *et al*. (0.60).[23]

The major limitation of this study includes that the number of ADRs assessed was relatively less, and we used only two causality assessment tools for ADR analysis and disagreement.

CONCLUSION

As per the results of our study, the WHO-UMC scale and the Naranjo algorithm show "poor" agreement with each other; and it is recommendable to use both the tools for better assessment of ADRs and causality. ADRs are most commonly seen as part of clinical practice. There is very limited reporting of antibiotic-related ADR from Himalayan region of northern India where the study was conducted. Because the currently used tools for ADR assessment are not properly validated it is important to know to what extent they agree or disagree, when used together. Our study has established a poor agreement between ADR monitoring scales when used together.

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