Original Research Article

An assessment of reported adverse drug reactions in a Tertiary Care Hospital in South India: A retrospective cross-sectional study

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Abstract

Objective: The primary objective of this study was to assess the causality of ADRs using World Health Organization-Uppsala Monitoring Centre (WHO–UMC), Naranjo and Liverpool ADR Causality Assessment Tool (LCAT). Other primary objective was to assess the agreement between the WHO-UMC criterion, Naranjo algorithm and LCAT. The secondary objective was to assess the reported adverse drug reactions in a tertiary care hospital in South India.

Materials and Methods: This was a cross-sectional retrospective study. All the ADRs which were reported by the Pharmacovigilance Unit between July 2016 and March 2017 were assessed. Causality assessment was performed by two well-trained independent pharmacologists by applying the three methods–WHO, Naranjo and LCAT. Concurrence between the two algorithms was compared using the Cohen's weighted kappa statistic.

Results: Causality assessment of adverse reactions according to Naranjo criteria shows that 81% cases were of probable type, 9.5% cases were possible and 9.5% cases were unlikely. Causality assessment of adverse reactions according to WHO-UMC criteria shows that 85.7% cases were of probable type, 4.8% cases were possible, 4.8% cases were unlikely and 4.8% cases were definite. Causality assessment of adverse reactions according to Liverpool criteria shows that 61.9% cases were of probable type, 4.8% cases were possible and 33.3% cases were definite. Cohen's kappa test shows that negative and poor concurrence was seen between WHO and Naranjo causality comparison ($\kappa = -0.161$). Positive but poor concurrence based on kappa values was seen between Liverpool and Naranjo's causality comparison ($\kappa = 0.133$). Negative and poor concurrence based on kappa values was seen between WHO and Liverpool causality comparison ($\kappa = -0.161$).

Conclusion: The most frequent causality category observed by the WHO-UMC criteria, Naranjo as well as the Liverpool algorithm was "Probable." Full concurrence was not found between any of two scales of causality assessment.

Keywords: Adverse drug reaction, causality assessment, kappa, Naranjo's adverse drug reaction probability scale, pharmacovigilance, World Health Organization-Uppsala Monitoring Centre causality assessment system

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INTRODUCTION

Adverse drug reactions (ADRs) are deemed as one of the major reasons of morbidity and mortality.[1] The causality appraisal is assessment of the probability that the detected adverse event is produced by a specific medication. The causality appraisal is recognized as an important tool of pharmacovigilance. Nonformally health-care providers discretely evaluate causality while dealing with ADRs. Causality assessment can help regulatory authorities in evaluating signal detection and risk-benefit decisions about medicines.[2,3] Algorithms for causality assessment, being organized frameworks, help in objective decision making on causality.[4]

The most commonly used causality assessment scales, i.e., Naranjo Probability Scale and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality scales have similarities and differences. The WHO-UMC causality system consider the clinico-pharmacological details of the case and the quality of corroboration of surveillance, while previous knowledge of the ADR plays a less important role.,[5,6] In the Naranjo algorithm, probability is determined via a grading termed definite, probable, possible or doubtful.[7] A new algorithm, the Liverpool ADR Causality Assessment Tool (LCAT) was developed by researchers involved in the Adverse Drug Reactions in Children project.[8,9] The LCAT arranges ten revamped questions with their dichotomous responses into a sequential diagram to arrive at one of four outcome categories: "definite," "probable," "possible," or "unlikely."[10] These causality assessment methods have not been validated so far. Therefore, it becomes very essential to investigate the degree to which various methods concur with each other. None of the causality assessment tools have been universally accepted as the gold standard.[3] Hence, the primary objective of present study was to assess the causality (possible/probable/definite) of ADRs using three different algorithms (WHO-UMC, Naranjo and LCAT). Other primary objective was to assess the concurrence between the WHO-UMC criterion and Naranjo algorithm-the two widely accepted tools in pharmacovigilance.

The ADRs data generated during the drug development phase is not comprehensive. Additionally, there are dissimilarities in the ADR manifestation between countries due to which locally inferred information are of greater importance. Most ADRs are avoidable and alertness is required to avoid dubious drugs and observe drugs with foreseeable adverse effects. So surveillance of ADRs becomes a vital mechanism to recognize unexpected and serious ADRs.[11,12] Hence the secondary objective of this study was to assess the reported adverse drug reactions in a tertiary care hospital in South India.

Objective

The primary objective of present study was to assess the causality of ADRs using WHO-UMC, Naranjo and LCAT. Other primary objective was to assess the concurrence between the WHO-UMC criterion, Naranjo algorithm and LCAT. The secondary objective was to assess the reported adverse drug reactions in a tertiary care hospital in South India.

MATERIALS AND METHODS

Study design

A retrospective cross-sectional study.

Setting

The study was conducted at the Dhanalakshmi Srinivasan Medical College and Hospital (DSMCH), Perambalur, India. The institution Ethics Committee had approved the study. All the ADRs which were reported by the Pharmacovigilance Unit between July 2016 to March 2017 were assessed.

Data sources

The data was obtained from the suspected adverse drug reaction reporting form used in the hospital for reporting ADRs to the ADR monitoring center as a part of the Pharmacovigilance program of India.

Variables

Causality assessment was performed by two well-trained independent pharmacologists by applying the three methods–WHO, Naranjo and Liverpool– on each ADR proforma, after which they discussed the causality with each other and discrepancies, if any, were resolved by consensus. Concurrence between the two algorithms was compared using the Cohen's weighted kappa statistic. The causality is categorized as Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified and Un-assessable/Unclassifiable by The WHO-UMC causality assessment. The Naranjo's ADR probability scale also evaluates the causality of the ADRs but categorizes them as Definite, Probable, Possible and Doubtful.[7] LCAT is a flow diagram designed by a multidisciplinary team to be quick and easy to use.[12] The Hartwig and Siegel ADR severity assessment scale was used to assess the severity of the ADR and classify them from Level 1 to Level 7.

Statistical methods

The data was analyzed using SPSS (Statistical Package for the Social Sciences), IBM Corporation, version 16

and summarized using frequencies and percentages. The measure of concurrence between the WHO-UMC causality assessment system and Naranjo's ADR probability scale was done using Cohen's weighted kappa (κ) test.

RESULTS

In this study, 21 patients were reported to experience ADR during study period. Out of 21 patients, 13 (61.9%) patients were male while 8 (38.1%) patients were female. The mean age of the patient was 37.42 ± 15.85 years. The youngest patient was of 8 years and oldest being 63 years. Maximum patients belonged to the age group of 21–30 year [Table 1]. The reported ADRs included a large spectrum of clinical manifestations, which are summarized based on common terminology criteria for adverse events [Table 2]. The total number of manifestations was 49. The most common organ-system affected was the Skin and subcutaneous tissue (61.2%). This was followed by nervous system (10.2%), General disorders and administrative site conditions (6.1%), Cardiac disorders (6.1%), and cardiovascular system (6.1%) [Table 2]. Antimicrobials were the major drug class involved followed by nonsteroidal anti-inflammatory drugs (NSAIDs)/anti-pyretics-analgesics. Table 3 Shows the major drug group's involved and detailed list of various drugs that were implicated in adverse drug reaction during study period. The Hartwig and Siegel ADR severity assessment scale classified 14 ADRs as level 4 severity, 4 ADRs as level 3, 1 ADR as level 5, 1 ADR as level 1 and 1 ADR as level 7. Causality assessment of adverse reactions according to Naranjo criteria shows that 81% cases were of probable type, 9.5% cases were possible and 9.5% cases were unlikely. Causality assessment of adverse reactions according to WHO-UMC criteria shows that 85.7% cases were of probable type, 4.8% cases were possible, 4.8% cases were unlikely and 4.8% cases were definite. Causality assessment of adverse reactions according to Liverpool criteria shows that 61.9% cases were of probable type, 4.8% cases were possible and 33.3% cases were definite. Please refer Table 4 for data on causality assessment by Naranjo, WHO-UMC and Liverpool algorithm. Table 5 shows the kappa value for comparison of strength of concurrence between different scales of causality assessment using Cohen's kappa test. İt shows that negative and poor concurrence was seen between WHO and Naranjo causality comparison (κ = −0.161). Positive but poor concurrence based on kappa values was seen between Liverpool and Naranjo's causality comparison (κ = 0.133). Negative and poor concurrence based on kappa values was seen between WHO and Liverpool causality comparison (κ = −0.161).

DISCUSSION

In our study, we evaluated the reported ADRs in a tertiary care hospital. The mean age of the patients was

Table 1: Age and gender wise distribution of patients with adverse drug reactions

Age range	Male	Female
≤1-10	1	0
11-20	0	1
21-30	2	4
31-40	4	0
41-50	3	1
51-60	2	2
≥61	1	0
Total patients	13	8

Table 2: Distribution of adverse drug reactions based on based on Common Terminology Criteria for Adverse Events

System organ class	Frequency (%)
Blood and lymphatic system disorders	1 (2.0)
Cardiac disorders	3 (6.1)
Eye disorders	2 (4.1)
Gastrointestinal disorders	1 (2.0)
General disorders and administrative site conditions	3 (6.1)
Immune system disorders	1 (2.0)
Nervous system disorders	5 (10.2)
Respiratory, thoracic and mediastinal disorders	3 (6.1)
Skin and subcutaneous tissue disorders	30 (61.2)
Total	49 (100)

Table 3: Responsible drugs

Drug class	Drug	Frequency of drug
Antimicrobial	Ceftriaxone + sulbactam	2
	Ceftriaxone	1
	Ciprofloxacin	2
	Piperacillin/tazobactam	2
	Cefotaxime	1
	Co-trimoxazole	1
	Cefixime	1
	Cefoperazone	1
	Ofloxacin	1
	Amoxicillin	1
NSAIDs/ anti-pyretics-analgesics	Diclofenac	2
	Paracetamol	3
	Aceclofenac	1
Opioid analgesics	Tramadol	1
Antihistamine	Levocetirizine	2
	Chlorpheniramine	1
Bronchial asthma drugs	Montelukast	1
Corticosteroids	Dexamethasone	1
	Betamethasone	1
Peptic ulcer drugs	Pantoprazole	1
	Ranitidine	1
Anti-emetic/prokinetic drugs	Ondansetron	1
Antipsychotic	Olanzapine	1
	Chlorpromazine	1
Antiepileptic drugs	Phenytoin	1
	Carbamazepine	1
Sedative hypnotics	Lorazepam	1
Others	Iopromide	1
	ORS	1

NSAIDs: Nonsteroidal anti-inflammatory drugs, ORs: Odds ratios

Table 4: Causality assessment by Naranjo, World Health Organization-Uppsala Monitoring Centre and Liverpool algorithm

	Naranjo (%)	WHO-UMC (%)	Liverpool (%)
Unlikely	2 (9.5)	1 (4.8)	0
Possible	2 (9.5)	1 (4.8)	1 (4.8)
Probable/likely	17 (81)	18 (85.7)	13 (61.9)
Definite/certain	0	1 (4.8)	7 (33.3)
Total	21 (100)	21 (100)	21 (100)

WHO-UMC: World Health Organization-Uppsala Monitoring Centre

Table 5: Comparison of strength of agreement between different scales of causality assessment by using Cohen's kappa test

	Naranjo	WHO-UMC	Liverpool
Naranjo	-	−0.122	0.133
WHO-UMC	−0.122	-	−0.161
Liverpool	0.133	−0.161	-

WHO-UMC: World Health Organization-Uppsala Monitoring Centre

37.42 ± 15.85 years. There has been much argument on whether increased age *per* SE is a cause of higher risk of ADRs. A study by Gurwitz and Avorn postulated that patient-specific characteristics are relatively more important in anticipating both adverse and beneficial effects related with drug.[13] Among the ADRs reported, 61.9% patients were male while 38.1% patients were female. These results do not support previous findings that female gender is a risk factor for the development of adverse drug reactions.[14] Most of the ADRs, observed in this study affected the skin and subcutaneous tissue which is similar to the study by Rana *et al.*[15] As per WHO-UMC causality assessment criteria, in our study 85.7% of ADRs was Probable, 4.8% was Possible, and 4.8% was Unlikely and 4.8% was definite [Table 4]. Macedo *et al.* has demonstrated that Probable and Possible were the most common (68%) causality assessment of ADR on WHO causality scale.[16] In a study by Jayanthi *et al.*, 2017, probable category ADRs were 87.6% and possible category ADRs were 12.4% on WHO causality assessment criteria.[17] Assessment of ADRs using WHO-causality scale in a study by Garg *et al.*, 2015 revealed that 80% cases were probable, 27% possible and 3% uncertain in nature.[18] Our results showed [Table 4] that as per Naranjo algorithm, 81% of ADRs was Probable, 9.5% was Possible, and 9.5% was Unlikely. ADRs reports analysed as certain was nil using this method. In the study by Khan *et al.* 2015, Naranjo algorithm was used to assess the causality which revealed that ADRs can be categorized into 55% probable, 42.5% as possible and 2.5% of ADRs as definite.[19] In a study by Harichandran DT 2016, as per Naranjo assessment, all were assessed as probable, except one which was assessed as possible.[20] The result of the study by Manjhi *et al.*, 2017 showed that 88.12% ADRs were probable, 9.37% were classified as possible; 1.25 doubtful and 1.25% were definitely related to the drug as per Naranjo algorithm.[21] The outcomes are consistent with other studies utilizing Naranjo's assessment. Our results showed [Table 4] that as per LCAT, 4.8% possible, 61.9% probable and 33.3% definite. The LCAT was utilized to analyse new suspected ADR case reports from observational study by Gallagher RM, 2011.[8] It showed 85% definite, 12.9% possible, 1.4% probable and 0.7% unlikely.[8] Gallagher *et al.* compared the Naranjo tool with the LCAT. One of their results was that, in the Naranjo scale, most of the cases were classified as either possible or probable. With the Liverpool tool, the scope of classifications was more extensive with a few cases categorized as being definite.[8,22]

Comparison of strength of concurrence between different scales of causality assessment was done by using Cohen's kappa test [Table 5]. It showed that full concurrence was not found between any of two systems of causality assessment. Negative and poor concurrence was seen between WHO and Naranjo causality comparison ($\kappa = -0.161$). Between Liverpool and Naranjo's causality comparison positive but poor concurrence based on kappa values was observed ($\kappa = 0.133$). Negative and poor concurrence based on kappa values was seen between WHO and Liverpool causality comparison ($\kappa = -0.161$). The percentage disagreement (discordance) in causality assessment between the Naranjo algorithm and WHO-UMC criteria was higher in the present study compared with that by Belhekar *et al.*, ($\kappa = 0.145$) Rehan *et al.*, ($\kappa = 0.214$) and Macedo *et al.*, ($\kappa = 0.23$).[2,3,23] However, the observed differences between the present study and earlier studies could be because of intuitive estimation intrinsic to different methods of ADR appraisal. There are studies to prove that causality assessment of ADR is intuitive, inexplicit, and low level of agreement prevails between two observers.[11] The characteristic of data and their corroboration influence the reliability of each of these methods. Besides, discrete systems of causality assessment have, in some instances, found to be noncommensurate.[6] There were some limitations of this study. This investigation endures the primary downside of spontaneous reporting framework i.e., unreported ADRs. Thus, ADR monitoring should be intensified by educating and motivating healthcare providers to report ADRs.

CONCLUSION

The results of our study showed that the most common causality category using the WHO-UMC criteria, Naranjo as well as the Liverpool algorithm was "Probable." This study shows that full agreement was not found between any of two scales of causality assessment. Negative and poor

agreement was seen between WHO and Naranjo causality comparison. Between Liverpool and Naranjo's causality comparison positive but poor concurrence based on kappa values was observed. Negative and poor agreement based on kappa values was seen between WHO and Liverpool causality comparison.

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Conflicts of interest

There are no conflicts of interest.

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