A Study of Agreement between WHO-UMC Causality Assessment System and the Naranjo Algorithm for Causality Assessment of Adverse Drug Reactions Observed in Medical ICU of a Tertiary Care Teaching Hospital

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Causality assessment is crucial step involved during assessment of Adverse Drug Reactions (ADRs). WHO-UMC causality assessment system and Naranjo algorithm are widely used methods for analysis of ADRs. Study was carried out to evaluate agreement between WHO-UMC causality assessment system and the Naranjo algorithm for causality assessment of ADRs observed in medical ICU of a tertiary care teaching hospital. Causality assessment of all ADRs was done by both WHO-UMC causality assessment system as well as the Naranjo algorithm and classified accordingly. Total 59 ADRs were analyzed. According to WHO-UMC system causal relationship between drug and ADR was certain in 16 ((27.12%), probable in 22 (37.29%), possible in 17 (28.81%), unclassified in 01 (01.69%) and unclassifiable in 03 (05.09%). As per Naranjo algorithm causality was definite in 10 (16.95%), probable in 26 (44.07%) and possible in 23 (38.98%) cases. The agreement between two scales was highest for probable (84.2%) category followed by possible (73.92%) and certain/definite (62.5%) category. on comparing overall agreement between WHO-UMC causality assessment system and Naranjo algorithm using weighted Kappa (?) test "Moderate" agreement was established (Kappa statistics with 95% confidence interval = 0.60 [0.441,0.758]). For Better evaluation it is recommended to use both the criteria while assessment of causality of ADRs.

Keywords: Causality Assessment; Naranjo Algorithm; WHO-UMC System.

Adverse Drug Reaction (ADR) can be defined as a response 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 modification of physiological function.[1] There are wide ranges of factors which can influence ADR development like patient related factors, social factors, drug related factors and disease related factors.[2] Detection and reporting of ADR is very important in current scenario of clinical practice and this can be fairly achieved by Pharmacovigilance. Pharmacovigilance is the science of the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problem.[3] The crucial step involved in Pharmacovigilance process after detection is assessment, which can be achieved by causality assessment.

Causality assessment of ADRs is a method used for estimating the strength of relationship

between drug exposure and occurrence of ADR.[4] There are many methods and algorithms available for causality assessment which includes the Jones' algorithm, the Naranjo algorithm, the Yale algorithm, the Karch algorithm, the Begaud algorithm, the ADRAC, WHO-UMC and a newer quantitative approach algorithm.[5] The basic concept involved behind all these methods or algorithms is to establish proper relationship between ADR and drug. The causality assessment system proposed by World Health Organization Collaborating Centre for International Drug Monitoring, The Uppsala Monitoring Centre (WHO-UMC) and the Naranjo algorithm are most widely used and accepted methods for causality assessment of ADR due to their simplicity of analysis.[6] Both of them have their own way of establishing causality in distinct manner with their own advantages and disadvantages. The WHO-UMC system takes into account the clinical-pharmacological aspects of case history, with a less prominent role of previous knowledge and statistical chance.[7] The Pharmacovigilance Programme of India (PvPI) recommends WHO-UMC system while many clinicians prefer Naranjo algorithm for its

simplicity.[8] There are evidence of studies[9,10,11] conducted to compare both these tools of causality assessment, but there is no set gold standard for causality assessment of ADR. So, this study was designed to evaluate agreement between WHO-UMC system and the Naranjo algorithm.

MATERIALS AND METHODS

The study was an analytical study based on analysis of causality of ADR forms which were filled during a Pharmacovigilance study conducted in Medical ICU after obtaining permission from Institutional Ethics Committee (IEC). Total 59 CDSCO ADR reporting forms complete with all the required information were included in analysis. Causality assessment was done by WHO-UMC causality assessment system[12] classifying ADR in to certain, probable, possible, unlikely, unclassified and unclassifiable. ADRs were also assessed according to Naranjo algorithm[13] for causality, which categories ADR in to definite, probable, possible and doubtful. As the assessment of causality may get influenced by rater's characteristics, the same author who assess

Table 1. Category wise distribution of ADR using WHO-UMC causality assessment system and Naranjo algorithm

WHO-UMC System	No. of ADRS (%)	Naranjo Algorithm	No. of ADRS (%)
Certain	16 (27.12)	Definite	10 (16.95)
Probable	22 (37.29)	Probable	26 (44.07)
Possible	17 (28.81)	Possible	23 (38.98)
Unlikely	00 (00.00)	Doubtful	00 (00.00)
Unclassified	01 (01.69)		
Unclassifiable	03 (05.09)		

Table 2. Distribution of disagreement between WHO-UMC system and Naranjo algorithm

Total disagreements	16 (27.12%)
Cases where probability was lower by Naranjo algorithm	10
Certain (WHO-UMC) to Probable (Naranjo)	07
Probable (WHO-UMC) to Possible (Naranjo)	03
Cases where probability was higher by Naranjo algorithm	06
Probable (WHO-UMC) to Definite (Naranjo)	01
Possible (WHO-UMC) to Probable (Naranjo)	01
Unclassified (WHO-UMC) to Possible (Naranjo)	01
Unclassifiable (WHO-UMC) to Possible (Naranjo)	03

for WHO-UMC causality of an ADR was subjected to assess for Naranjo algorithm for that particular ADR.

Statistical analysis

Statistical analysis was done using SPSS 24 software. The agreement between WHO-UMC causality assessment system and Naranjo algorithm was done by weighted Kappa (?) test. The Kappa value ranges from -1 (perfect disagreement) to +1 (perfect agreement).

RESULTS

ADR forms were assessed using WHO-UMC causality assessment system and Naranjo algorithm. According to WHO-UMC system causal relationship between drug and ADR was certain in 16 ((27.12%), probable in 22 (37.29%), possible in 17 (28.81%), unclassified in 01 (01.69%) and unclassifiable in 03 (05.09%). As per Naranjo algorithm causality was definite in 10 (16.95%), probable in 26 (44.07%) and possible in 23 (38.98%) cases. Under the category unlikely and doubtful for WHO-UMC and Naranjo algorithm respectively, no causality was found. (Table 1)

The agreement between two scales was highest for probable (84.2%) category followed by possible (73.92%) and certain/definite (62.5%) category. Overall disagreement in causality assessment was seen in 16 (27.12%) cases. (Table 2)

However, on comparing overall agreement between WHO-UMC causality assessment system and Naranjo algorithm using Kappa test "Moderate" agreement was established. (Kappa statistics with 95% confidence interval = 0.60 [0.441,0.758])

DISCUSSION

This study was carried out with an aim of analyzing agreement between WHO-UMC causality assessment system and Naranjo algorithm. Total 59 CDSCO ADR forms were evaluated. Routine causality assessment is part of first step in case assessment and it categorizes it in semi quantitative way.[14]

The overall level of agreement between WHO-UMC system and Naranjo algorithm found in present study was moderate with 27.12% and

kappa value of 0.60. This is higher when compared to studies done by Rehan *et al.* (31%; ?=0.214)[10], Belheker *et al.* (4.9%; ?=0.145)[9] and Rana *et al.* (33.33%; ?=0.014)[15]. Higher value of kappa in spite of lower percentage agreement as compared to other studies may be due to smaller sample size of our study. However, it is lower as compared to similar study done by Mittal (?=0.701)[7]. The observed difference may be due to limitation of assessment scales arising out of subjectivity while assessing the causality of ADR. However, various studies[16,17,18] have been observed indicating disagreement or poor agreement between various algorithms. Apart from this both the criteria has its own limitations and issues like how much mandatory rechallange is for certainty in WHO-UMC and subjectivity in questions like question no. 1 in Naranjo algorithm.[7]

Relation of ADR with the drug is very important not only due to safety of patient but as a vital issue for prescriber, which can guide future treatment of patient. After considering above results it is evident that due to high subjectivity, algorithm alone cannot decide the outcome. It should be combined with clinical knowledge and experience for accurate analysis. It is also important to update assessment criteria to minimize confounding factors associated with causal imputation process.[19]

In our study, in both WHO-UMC system and Naranjo algorithm highest numbers of ADR fall under probable category. These results are in consonance with the study conducted by Rehan *et al*.[10], which showed 70% ADR by WHO-UMC system and 75% ADR by Naranjo algorithm were under probable category. The most frequently assigned causality category with Naranjo algorithm and WHO-UMC criteria was possible (99.2% and 93.9%, respectively).[9] Using the algorithm, 16.4%, 83.1% and 0.5% were categorized as probable, possible and unlikely respectively.[15] Results of these two studies are in contrast showing high numbers of ADR falling under possible category. Such variation in assessment may be attributed either due to difference in the types of ADR observed or due to subjective difference in case of WHO-UMC system.

Major limitation of this study is that we have used only two assessment criteria for ADR analysis and agreement. Number of ADRs used for analysis was also comparatively smaller, which

could be a drawback of this study. Further studies are warranted to establish agreement between WHO-UMC causality assessment system and Naranjo algorithm.

CONCLUSION

From the result and discussion we conclude that moderate agreement exists between WHO-UMC causality system and Naranjo algorithm. For Better evaluation it is recommended to use both the criteria while assessment of causality of ADRs. However, we found WHO-UMC causality assessment system to be a better tool for causality assessment.

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REFERENCES

1. Gupta SK. Key definitions in pharmacovigilance. Textbook of Pharmacovigilance. 1st New Delhi: Jaypee Brothers; p. 1-12 (2011).

2. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J,* (cited in 2019); **22**:83-94 (2014). Available from: http://dx.doi.org/10.1016/j.jsps.2013.02.003

3. Gunasakaran S. Standard terms and definitions in Pharmacovigilance. A practicle guide on Pharmacovigilance for beginners. 1st Chennai: Taramani Magalir Co-operative press; 2010. p. 03-20.

4. Smyth RL, Peak M, Turner MA, *et al.* ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods. Southampton (UK): NIHR Journals Library; 2014 Jun. (Programme Grants for Applied Research, No. 2.3.) Chapter 5, Causality assessment of adverse drug reactions.

5. Srinivasan R, Ramya G. Adverse drug reaction-causality assessment. *International journal of research in pharmacy and chemistry*(cited in 2019);**1**(3):606-612 (2011). Available from: http://www.ijrpc.com/archives3.html

6. Zaki SA. Adverse drug reaction and causality assessment scales. Lung India/ : *Official Organ of Indian Chest Society.;* **28**(2):152-153 (2011). doi:10.4103/0970-2113.80343.

7. Mittal N, Gupta MC. Comparison of agreement and rational uses of the WHO and Naranjo adverse event causality assessment tools. *J Pharmacol Pharmacother*; **6**(2):91-93 (2015). doi: 4103/0976-500X.155486.

8. Sharma S, Gupta AK, Reddy GJ. Inter-rater and intra-rater agreement in causality assessment of adverse drug reactions: a comparative study of WHO-UMC versus Naranjo scale. *Int J Res Med Sci*; **5**: 4389-4394 (2017). doi: http://dx.doi.org/10.18203/2320-6012.ijrms20174564.

9. Belhekar MN, Taur SR, Munshi RP. A study of agreement between the Naranjo algorithm and WHO-UMC criteria for causality assessment of adverse drug reactions. *Indian J Pharmacol;* **46**:117-120 (2014). doi: 4103/0253-7613.125192.

10. Rehan HS, Chopra D, Kakkar AK. Causality assessment of spontaneously reported adverse drug events: Comparison of WHO-UMC criteria and Naranjo probability scale. *Int J Risk Saf Med;* **19**:223-227 (2007).

11. Son MK, Lee YW, Jung HY, Yi SW, Lee KH, Kim SU*, et al.* Comparison of the naranjo and WHO-uppsala monitoring centre criteria for causality assessment of adverse drug reactions. *Korean J Med;* **74**:181-187 (2008).

12. The Uppsala monitoring centre. The use of WHO-UMC system for standardised case causality assessment. [Cited in 2019] Available from http://www.who-umc.org/

13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther*; **30**: 239-245 (1981).

14. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf;* **17**(6):374-389 (1997).

15. Rana DA, Bhadiyadara SN, Shah HJ, Malhotra SD, Patel VJ. Consistency between causality assessments obtained with various scales and their agreement for adverse drug events reported in pediatric population. *Journal of young pharmacists;* **7**(2):89-95 (2015). doi: 10.5530/jyp.2015.2.6.

16. Arimone Y, Salame GM, Haramburu F, Molimard M, Moore N, Reglat AF *et al.* Inter-expert agreement of seven criteria in causality assessment of adverse drug reactions. *Br J Clin Pharmacol;* **64**(4):482-488 (2007). doi: 1111/j.1365-2125.2007.02937.x.

17. Kane-Gill SL, Forsberg EA, Verrico MM, Handler SM. Comparison of three pharmacovigilance

algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. *Drug Saf;* **35**(8):645-653 (2012). doi: 10.2165/11599730-000000000-00000.

18. Pere JC, Begaud B, Haramburu F, Albin H. Computerized comparison of six adverse drug reaction assessment procedures. *Clin Pharmacol Ther;* **40**(4):451-461 (1986).

19. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni Pdc. Imputation of adverse drug reactions: Causality aseessment in hospitals. *PloS ONE,* **12**(2):e0171470 (2017). doi:10.1371/journal.pone.0171470.