INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

COMPARISON OF THREE METHODS OF CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS TO ANTIHYPERTENSIVE DRUGS

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Article Received on: 26/12/18 Approved for publication: 23/01/19

DOI: 10.7897/2230-8407.1003104

ABSTRACT

Background: Causality assessment is crucial to assess the role of the drug in event causation. Various methods of causality assessment have been developed so far but all the methods have limitations including weak reproducibility; being too complex and time consuming; and non-inclusion of Drug-Drug interaction (DDI) parameter. There is need for a method which can overcome these limitations; and give valid and reproducible results. Objectives: The present analysis is aimed to evaluate the agreement among three methods of causality assessment of adverse drug reactions [two widely accepted method and one recently developed Versatile Causality Assessment Tool (VCAT) method for which reliability and validity has been established]. Methods: A total of 1339 previously reported literature cases of suspected adverse drug reactions with antihypertensive drugs from year 1990 to 25th February 2016 were assessed using World Health Organization-Uppsala Monitoring Centre (WHO-UMC) method, Naranjo's Algorithm and VCAT method. Kappa (k) was used as a measure of the agreement among these methods. Results: The most common causality category in all three methods was Possible (ranging from 48.3% to 62.4%). Excellent agreement was observed between VCAT method and WHO-UMC method (k = 0.943, p <0.001); followed by good agreement between VCAT method and Naranjo's Algorithm (k = 0.678, p <0.001); and WHO-UMC method and Naranjo's Algorithm (k = 0.669, p <0.001). Conclusions: This study showed excellent agreement between VCAT method and WHO-UMC method, indicating that VCAT method is a better standardised tool of causal assessment which could give results equivalent to the expert's judgement method.

Keywords: Adverse drug reaction, Algorithm, Antihypertensive, Causality assessment, Raters

INTRODUCTION

Causality assessment could be defined as the evaluation of the likeliness of a drug to cause an adverse event.[1,2] It is crucial for the pharmacovigilance activity, as it will directly impact the signal to be validated or refuted. Broadly, the methods assessment of the causal association has been categorised in three main categories: 1) expert judgment or global introspection;[3,4,5,6] 2) probabilistic or Bayesian approaches;[3,7,8] 3) algorithms or standardised assessment methods.[3,9,10]

The study aimed to assess the agreement between WHO-UMC method, Naranjo's Algorithm, and VCAT method. First two methods are widely in practice and the third is a newly developed method that has been proved to be valid and reliable.[11]

MATERIALS AND METHODS

Data collection

A literature search was performed in Embase and Medline databases (via Embase.com) from year 1990 to 25th February 2016 (inclusive) to identify all literature case reports, reporting adverse drug reactions to antihypertensive drugs. Preclinical/non-human reports/studies were excluded. The search ('antihypertensive agent'/exp/mj) was limited to major focus to retrieve the most related publications. This search retrieved a total of 7845 citations and from these a total of 1339 cases were identified to be relevant.[11] Of these 1339 cases, 110 cases were identified with DDI leading to ADRs and the remaining 1229 cases were identified with suspected Adverse drug reactions (ADRs) without Drug-drug Interaction (DDI). The 1229 cases of suspected ADRs to antihypertensive drugs without DDIs were assessed for measurement of agreement among the three methods (WHO method, Naranjo's Algorithm and VCAT method). Cases with DDI were assessed and presented separately to study the impact of the DDI parameter on the causal association.

The assessment of ADR depends on four parameters: 1) rater, 2) characteristics of ADR, 3) quality of the information, and 4) type of the method used for causal association. Hence, to compare the agreement among the three methods we kept the first three variables constant. Same rater assessed all the 1339 cases with all the three scales, at three months' gap after assessment with each scale to allow enough time to forget the case information.

WHO-UMC method has six categories for a case to be rated into viz. Certain, Probable, Possible, Unlikely, Unclassified, and Unclassifiable; Naranjo's Algorithm has four categories: Definite, Probable, Possible, and Doubtful; and VCAT method has five categories: Certain, Probable, Possible, Unclassified, and Unlikely.

As the literature reports were medically confirmed, there were no cases identified with lack of information; hence, Unclassified and Unclassifiable categories as per WHO-UMC method; and Unclassified category as per VCAT method, were not applicable to any of the cases. Thus, all the three methods had four categories

each for a case to be rated and placed into. Certain category of WHO-UMC and VCAT method was aligned with Definite category of the Naranjo's Algorithm due to similar characteristics of these categories. Similarly, Unlikely category of WHO-UMC and VCAT method was aligned with Doubtful category of the Naranjo's Algorithm for ease of the statistical assessment.

Materials required

Medical Dictionary for Regulatory Activities (MedDRA) (latest version) was used to categorise ADRs into appropriate System Organ Classes (SOCs). Textbooks (Meyler's, Martindale, and Micromedex) and UK database (emc[+]) were used to identify drugs acting as confounders. Class effect and past experiences were identified from existing literature and textbooks. Common Terminology Criteria for Adverse Events (CTCAE) was used to characterise abnormal lab values. Physician/existing literature was referred to identify important medical history, concurrent conditions, and risk factors.

Statistics

Descriptive analysis was used to present the data. Kappa (k) statistics was used for measurement of percentage agreement among three methods (ranging from -1 to +1) and $\alpha = 0.05$ was considered statistically significant. IBM SPSS (Statistical Package for Social Sciences) statistical version 20.0 was used to perform the statistical analysis. All statistical tests were seen at two-tailed level of significance ($p \leq 0.01$ and $p \leq 0.05$). Value of k was characterised as almost perfect (0.81-1.00); substantial (0.61-0.80); moderate (0.41-0.60); fair (0.21-0.40); and slight (0-0.20) by Landis et al. [12]

Based on the formula by Cantor et al. [13] i.e.$= \left\{\frac{Z_\alpha\sqrt{Q_0} + Z_\beta\sqrt{Q_1}}{k1-k0}\right\}$, the minimum sample size required was 830 case reports for assessment of agreement between two methods.

RESULTS

Of these 1339 cases, 711 ADRs (53.1%) were in male patients and 621 ADRs (46.4%) were in female patients and the remaining seven ADRs (0.5%) were in unknown gender group. These 1339 cases included 35 neonates (2.6%), 30 infants (2.2%), 48 children (3.6%), 16 adolescents (1.2%), 762 adults (56.9%), 436 elderlies (32.6%) and age group was unknown in 12 cases (0.9%). Death was reported in 53 (4%) of the 1339 cases.

Event outcome was "recovered" in 707 cases (52.8%), "recovering" in 449 cases (33.5%), "not recovered" in 27 cases (2%), "worsened" in one case (0.07%), "unknown" in 131 cases (9.8%), "fatal" (death due to event of interest) in 20 cases (1.5%) and "not applicable" in four cases (0.3%).

Maximum adverse events were related to the following SOCs: Skin and subcutaneous tissue disorders: 373 cases (27.9%); Gastrointestinal disorders: 155 cases (11.6%); and Cardiac disorders: 148 cases (11.1%). Most frequently reported events by preferred terms (PTs) are presented in Table 1.

Among these 1339 cases, the most cases belonged to Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), and Calcium Channel Blockers (CCBs). The most commonly implicated drugs included lisinopril, sildenafil, enalapril, amlodipine, and losartan.

For the 1229 cases without DDIs, the most common causality category in WHO-UMC, Naranjo's Algorithm and VCAT was Possible (62.1%, 48.3% and 62.4%, respectively) followed by Probable (27.9%, 44.8% and 27.3%, respectively) as presented in Table 2. Agreement among three methods for Possible category was 75.4% (Table 3).

Highest percentage agreement among all the methods was in "Unlikely/Doubtful" category and lowest was in Probable category as presented in Table 3. Maximum percentage agreement (>90%) was overserved between WHO-UMC method and VCAT method among all the causality assessment categories (Table 3).

WHO-UMC method and Naranjo's Algorithm had good agreement (k = 0.669); WHO-UMC method and VCAT method had high agreement (k = 0.943); and Naranjo's Algorithm and VCAT method had good agreement (k = 0.678), with a p-value = 0.001, in all the three comparisons (Table 4).

For the 110 cases with DDIs, there was 100% agreement between WHO-UMC method and VCAT method as all cases were classified into Possible category. There was 96.4 % agreement between Naranjo's Algorithm and WHO-UMC method; and same for Naranjo's Algorithm and VCAT method, as only four cases were classified into Probable category in Naranjo's Algorithm (Table 5).

Mean time engaged for causality assessment was 12 ± 1 min, 14 ± 0.5 min., and 15 ± 1.25 min. with WHO-UMC method, Naranjo's Algorithm, and VCAT method, respectively.

DISCUSSION

Hypertension has a worldwide prevalence of more than 40% in adults aged more than 25 years.[14] Antihypertensive drugs cause a variety of adverse events which should be assessed to evaluate causal role of the drug or alternative explanations. Causality assessment is a pivotal component of pharmacovigilance, contributing to better evaluation of the risk-benefit profiles of medicines; and is a critical part of evaluating ADR reports in early warning systems and for regulatory purposes.[3,15]

In the present study for the cases without DDIs, agreement between WHO-UMC method and VCAT method was highest (k = 0.943); followed by Naranjo's Algorithm and VCAT method (k = 0.678); and WHO-UMC method and Naranjo's Algorithm (k = 0.669). High degree agreement between WHO-UMC method and VCAT method implies results equivalent to expert judgement method with the advantage of providing reproducible results even when used by non-clinicians. However, high level of agreement could also be attributed to retrospective literature reports, like that explained by Kane-Gill et al.,[9] where retrospective phase of study (k = 0.794) have more agreement than the prospective phase (k = 0.635). This difference could be since the assessor was unable to discuss the findings with the clinician/prescriber.

The agreement between WHO-UMC method and Naranjo's Algorithm (k = 0.669) was higher than in other studies by Belhekar et al.[1] (k = 0.145, 4.9 %), Rehan et al.[16] (k = 0.214, 31%), Son et al.[17] (45%), and Macedo et al.[18] (k = 0.23, 51%). It was lesser than the findings by Lei et al.[19] (84.9%). These differences could be attributed to 1) use of different scales, 2) inter-rater differences, 3) type of the data (prospective or retrospective), and 4) completeness of the information.

In these 1229 cases, the most common causality category in all three methods [WHO-UMC (62.1%), Naranjo's Algorithm (48.3%) and VCAT (62.4%)] was Possible which was suggestive of alternative aetiologies in many cases. Similar findings were

reported in studies conducted by Lei et al.[19], Macedo et al.[18], and Belhekar et al.[1] Rechallenge is not an ethical practice and sometimes not scientifically valid for severe ADRs. However, some accidental rechallenge cases are reported worldwide due to self-medication and polypharmacy. In this study, few cases provided information about positive rechallenge and dose response reactions, like that demonstrated by Arimone et al.,[2] Son et al.,[17] and Belhekar et al.[1] In the present study, majority of the disagreements among methods were in the approach to deal with alternative explanation, dechallenge, and corrective treatment given for the event, whereas in a study by Pere et al.,[20] it was reported that the major criteria were time to onset, alternative aetiologies, and dechallenge.

Hutchinson et al.[21] and Busto et al.[22] have indicated that the common cause of disagreements among assessors was identification of the alternative explanations acting as confounding factors.

For the 110 cases with DDIs, there was 100% agreement between WHO-UMC method and VCAT method; suggesting that the results produced by VCAT method are equivalent to WHO-UMC method, and an expert is not always needed to carry out causal assessments. WHO-UMC method does not quantify the parameters; hence, there is no empirical rationale for the categorisation. VCAT method has the added advantage of quantification of the all the parameters including DDIs, so that the impact of DDI on the causal association can be estimated. There was 96.4 % agreement between Naranjo's Algorithm and VCAT method (Table 5) and only four cases have shown disagreement; and were placed into Probable category by Naranjo's Algorithm and into Possible category by VCAT method. Naranjo's Algorithm does not consider the effect of DDIs on the causal assessment when compared to VCAT method. Although this difference is not significant for this set of 110 cases; yet, it indicates a scope for a more detailed study of the impact of DDIs on causal assessment. Causality assessment categorization can change with the impact of DDIs and this change could be of significance while dealing with fatal/life-threatening events which could affect the drug's position in the market, especially the new medicines. A more detailed study focusing on cases with DDIs could be carried out, to further establish the effect of DDI parameter on causal assessment.

Literature articles have explicit information in comparison to spontaneous reporting; hence, the time taken was more when compared to the causality assessment of spontaneously reported suspected ADRs as described in a study by Belhekar et al.[1]

Time taken using WHO-UMC method was comparatively lesser than Naranjo's Algorithm as also presented in studies by Rehan et al.[16] and Belhekar et al.[1] Aim of this type of causality assessment is to evaluate the role of the drug in causing the event while in spontaneous reporting aim could be to decide further course of the treatment if drug is causing the event. Quality of the data also plays a pivotal role in the assessment and directly impacts the signal validation. Medically confirmed reports provide scientifically valid information to reach a conclusion on the causal assessment.

Clinicians and pharmacologists need to understand the functioning of different scales and the parameters used to reach a conclusion about the drug's role in causing the event. This will directly impact the decision to continue or discontinue the suspect drug which might affect the quality of life of the patient negatively or positively, respectively. These standardised tools aim to strengthen the conclusion on assessment of suspected ADRs, but expert judgement is always advised to confirm the diagnosis. These standardised tools, however, cannot solve all the problems but increase the precision for certain specific situations.

TABLE 1: MOST FREQUENTLY REPORTED ADRS

PTs	Number (%)
Angioedema	179 (13.4%)
Hepatitis/Hepatotoxicity/Hepatomegaly/Jaundice	50 (3.7%)
Gingival hyperplasia/hypertrophy	30 (2.2%)
Intestinal/Small bowel/Visceral angioedema	28 (2.1%)
Pancreatitis	26 (1.9%)
PT: Preferred Term	

TABLE 2: CAUSALITY CATEGORISATION OF ADRS IN ALL THE THREE METHODS FOR CASES WITHOUT DDI

WHO-UMC method		Naranjo's Algorithm		VCAT method	
Category	Number of ADRs (%)	Category	Number of ADRs (%)	Category	Number of ADRs (%)
Certain	109 (8.9%)	Definite	70 (5.7%)	Certain	113 (9.2%)
Probable	343 (27.9%)	Probable	550 (44.8%)	Probable	335 (27.3%)
Possible	763 (62.1%)	Possible	594 (48.3%)	Possible	767 (62.4%)
Unlikely	14 (1.1%)	Doubtful	15 (1.2%)	Unlikely	14 (1.1%)
ADR: Adverse Drug Reaction					

TABLE 3: PERCENTAGE AGREEMENT AMONG THREE METHODS FOR CASES WITHOUT DDI

Percentage agreement (%)				
Methods compared	**Causality categories**			
	Certain/Definite	**Probable**	**Possible**	**Unlikely/Doubtful**
W and N	63.3%	62.3%	77.9%	93.3%
W and V	96.5%	93.9%	97.4%	100%
V and N	61.9%	60%	76.8%	93.3%
W and N and V	61.1%	58.5%	75.4%	93.3%
W: WHO-UMC method, N: Naranjo's Algorithm, V: VCAT method				

TABLE 4: KAPPA AGREEMENT AMONG THREE METHODS FOR CASES WITHOUT DDI

Methods compared	Kappa (k)	Asymptotic standard error	p-value
W and N	0.669	0.019	0.001
W and V	0.943	0.009	0.001
V and N	0.678	0.019	0.001
W: WHO-UMC method, N: Naranjo's Algorithm, V: VCAT method			

TABLE 5: CAUSALITY CATEGORISATION OF ADRS IN ALL THE THREE METHODS FOR CASES WITH DDI

WHO-UMC method		Naranjo's Algorithm		VCAT method	
Category	Number of ADRs (%)	Category	Number of ADRs (%)	Category	Number of ADRs (%)
Probable	0 (0%)	Probable	4 (3.6%)	Probable	0 (0%)
Possible	110 (100%)	Possible	106 (96.4%)	Possible	110 (100%)
ADR: Adverse Drug Reaction					

CONCLUSION

Agreement between WHO-UMC method and VCAT method was highest compared to Naranjo's Algorithm, implying that the VCAT method is a better standardised tool of causal assessment which can produce results equivalent to that of expert's judgement method. This method should be used for causal assessment of other class of diseases and drugs as well to further establish the versatility of this method.

Of note, use of assessment tools could impact new safety signals especially for new investigational products. Therefore, it is prudent to use more than one method at times.

LIMITATIONS

Only three scales have been used in this study for comparison; however, other scales could also be used to compare the results with the VCAT method.

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Cite this article as:

Ravi Goyal *et al*. Comparison of three methods of causality assessment of adverse drug reactions to antihypertensive drugs. Int. Res. J. Pharm. 2019;10(3):195-199 http://dx.doi.org/10.7897/2230-8407.1003104

Source of support: Nil, Conflict of interest: None Declared