Malaysian Journal of Pharmaceutical Sciences,
Vol. 5, No. 1, 7–17 (2007)

ADVERSE DRUG REACTION REPORTS IN MALAYSIA: COMPARISON OF CAUSALITY ASSESSMENTS

HOE SEE LEI[1*], AB FATAH AB RAHMAN[1] AND ABIDA HAQ SYED M. HAQ[2]
[1]School of Pharmaceutical Sciences, Universiti Sains Malaysia,
11800 USM Pulau Pinang, Malaysia
[2] National Pharmaceutical Control Bureau, Jalan Universiti, P.O. Box 319
46730 Petaling Jaya, Selangor, Malaysia

Causality assessment of reported adverse drug reactions (ADR) is an important component of pharmacovigilance as they contribute to better evaluation of the risk-benefit profile of drugs. The main objective of the present study was to evaluate the agreement of causality assessments of ADR between the spontaneous ADR reporters, the expert panel and the Naranjo algorithm. We retrospectively reviewed ADR reports received by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) between January to June 2003. Causality assessments were categorized as Certain, Probable, Possible, Unlikely and Unclassifiable. A total of 384 reports were included. Spontaneous reporters assessed 30.4% as Certain, 46.1% as Probable, 21.9% as Possible and 1.6% as Unlikely. MADRAC panel assessed 21.9%, 13.0%, 64.6% and 0.5% as Certain, Probable, Possible and Unlikely, respectively. Using the algorithm, 16.4%, 83.1% and 0.5% were categorized as Probable, Possible and Unlikely, respectively. No reports achieved the Certain/Definite category using the algorithm. The total percentage of agreement between spontaneous reporters, MADRAC and Naranjo's algorithm in causality assessment was 15.1%. Among the three groups, no agreement was found in the Certain and Unlikely categories. Spontaneous reporters attributed a higher level of causality compared to MADRAC and Naranjo's algorithm. The difference in aims and methods in causality assessment among the three methods of assessment could be the main reason of disagreement.

Keywords: *Adverse drug reactions, Causality assessment, Spontaneous reporters, Expert panel, Algorithm*

INTRODUCTION

Causality assessment of ADR is an important component of pharmacovigilance as they contribute to better evaluation of the risk-benefit profile of drugs. Assessment methods based on clinical judgments may be subjective and imprecise (Karch *et al*. 1976; Blanc *et al*. 1979). As a result, several algorithms have been developed to identify the important aspects of an ADR and to integrate them into an objective rating. Comparisons between these algorithms have been made (Busto, Naranjo

* Corresponding author: Hoe See Lei, e-mail: seelei@yahoo.co.uk

and Sellers 1982; Michel and Knodel 1986). Although they were found to be comparatively reliable, Naranjo's algorithm is less complex and less time consuming. The advantages of decisional algorithm scale over clinical judgment are its consistency and objectivity. With the use of published algorithms, the agreement between observers improved considerably compared to when the same observers used their unaided judgment or global introspection (Hutchinson and Lane 1986).

In Malaysia, ADR reports are submitted by the reporter (e.g. doctor, pharmacist) using a standardized report form to the MADRAC. MADRAC is established under the Drug Control Authority (DCA) of Malaysia to monitor the safety profiles of drugs registered in Malaysia. The committee comprises of 12 members including physicians, clinical pharmacologists and pharmacists. The number of reports received by MADRAC has been increasing steadily over the last few years. In fact, MADRAC received more than 2000 ADR reports in 2005 (Ministry of Health Malaysia 2005).

Information available from each report includes a brief description of the ADR, the extent and outcome of the reaction, and causality classification. Classification of causality or drug reaction relationship is also provided by the reporter based on his/her own assessment. This is classified as *Certain*, *Probable*, *Possible*, *Unlikely* and *Unclassifiable*.

For each ADR report submitted to MADRAC, a causality assessment is made based on consensus agreement by the committee members during their bimonthly meetings. The method used is based on the WHO-Uppsala Monitoring Centre (WHO-UMC) guidelines on causality assessment (WHO-UMC 2005). This is classified as *Certain, Probable, Possible, Unlikely and Unclassifiable*. This final causality classification is available in MADRAC's database.

The present study is carried out to compare the results of causality assessment of ADRs made by spontaneous reporters, an expert panel (MADRAC) and using a published decisional algorithm.

METHODS

All ADR report forms received by MADRAC from January to June 2003 were retrospectively reviewed. Reports were excluded if important information like the name of the suspected agent or causality assessment was missing. They were also excluded if the causality assessment was categorised as *Unclassifiabl*e. Only reports available at the time of study were analysed.

One of the authors (HSL), determined causality assessment using the Naranjo's algorithm (Naranjo *et al.* 1981) based on information provided in the ADR report form. Criteria used in the Naranjo's algorithm are shown in Table 1. This algorithm was chosen because its four levels of causality assessment coincide with the causality categories in the ADR report form. This algorithm has been widely used (Dalton-Bunnow and Halvachs 1993; Dormann *et al.* 2000) and is the recommended algorithm for reporting ADR in the *Annals of Pharmacotherapy*.

Reporter's assessment was obtained from each ADR report form whereas MADRAC's causality assessment was obtained from MADRAC's database. MADRAC committee members formulate their assessment based on the information in the report forms and their clinical judgement. Criteria used to guide them in making the final causality assessment are shown in Table 1. Causality assessments obtained from the ADR forms (reporters), MADRAC database and the algorithm were categorized into *Certain* or *Definite*, *Probable*, *Possible*, *Unlikely,* and *Unclassifiable*.

All data were entered and analysed using Statistical Package for Social Sciences (SPSS) version 10.0.1. The agreements between the algorithm, expert panel (MADRAC) and spontaneous reporters were evaluated using kappa (κ) statistical test. The κ value ranged from –1 (perfect disagreement) to +1 (perfect agreement).

Table 1: Guide to causality assessment used in Naranjo's algorithm and MADRAC.

Method	Criteria	Probability scale
Naranjo's algorithm	Previous report of the same reaction Temporal relationship Dechallenge (i.e., drug withdrawal or use of antagonist) Rechallenge Alternative etiologies Placebo rechallenge Blood concentration of the drug Dose-severity relationship Previous exposure (similar reaction or similar drug) Event confirmed by objective evidence	A score ranging from +2 to –1 is given for each criteria. The probability scale is based on the total score; ≤ 0 *Doubtful*, 1 to 4 *Possible*, 5 to 8 *Probable*, ≥ 9 *Definite*
MADRAC		
	Plausible time, not related to underlying condition/concurrent disease or other drugs or chemicals, related pharmacologically, positive challenge, positive rechallenge	C1 *Certain*
	Reasonable time, unlikely to be related to concurrent disease, other drugs, positive dechallenge, no rechallenge	C2 *Probable*
	Reasonable time, may be due to concurrent disease, other drugs, no information on dechallenge	C3 *Possible*
	Improbable temporal relationship. Other confounding factors such as drugs, chemical, underlying disease	C4 *Unlikely*
	Insufficient information	C5 *Unclassifiable*

RESULTS AND DISCUSSION

A total sample size of 495 ADR reports was reviewed. Reports were excluded from the study for various reasons like no drug name (n = 6), reporters did not report his/her causality assessment (n = 63), causality assessment reported as *Unclassifiable* (n = 16), reports about drug abuse or overdose (n = 5), and one report about therapeutic failure. We also excluded reports where MADRAC did not specify the causality

assessment (n = 9) or classified them as *Unclassifiable* (n = 4). Five reports were found to be duplicates of previous reports and two reports which, were registered in the MADRAC database were not available at the time of review. The total number excluded was 111 and the final sample size was 384. The majority of those reports came from doctors (n = 308; 80.2%). There were 48 (12.5%) pharmacists who contributed to the ADR reports.

The reported ADRs included a large spectrum of clinical manifestations, which are summarized based on WHO Adverse Reaction Terminology (WHOART) system-organ class (Fig. 1). The total number of manifestations was 494; 87 cases affected more than one organ system. The most common organ-system affected was the skin (47.4%). This was followed by central and peripheral nervous system (10.3%), gastro-intestinal system (9.3%), vision and ocular system (7.5%), and cardiovascular system (7.3%).

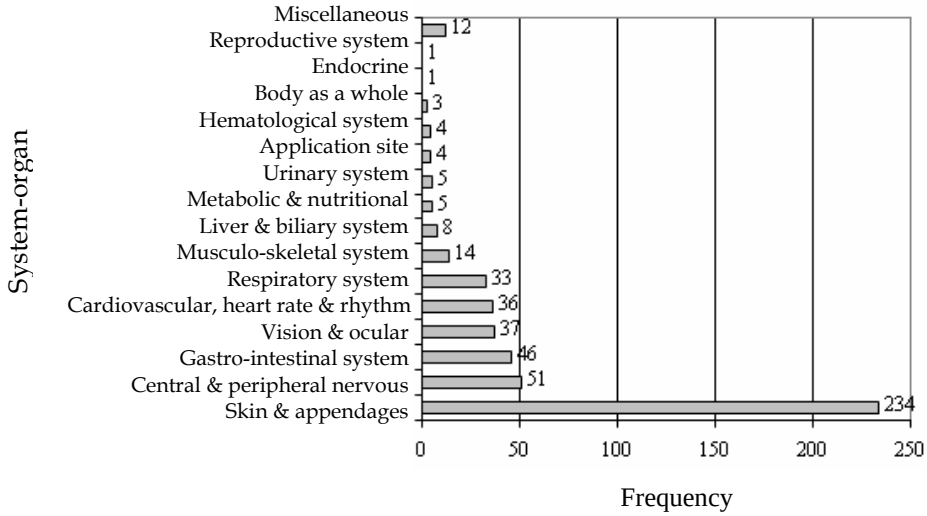

Fig. 1: Distribution of ADR based on system-organ classification.

ADR causalities of C*ertain* and *Probable* were most frequently reported by spontaneous reporters compared to the other two methods. Out of 384 reports, spontaneous reporters assessed the causal relationship of drugs and ADRs as 30.4% *Certain*, 46.1% *Probable*, 21.9% *Possible* and 1.6% *Unlikely* (Fig. 2). Although they used the same category scale like the MADRAC expert panel, spontaneous reporters were not provided with any guideline to assess causality. Instead, we assumed that they rely on their clinical judgments and experiences to make their assessments. Dukes (1984) listed three factors that may influence a physician's assessment of an ADR. They are (i) physician's lack of experience in causality assessment and thus, may overlook other causal factors, (ii) physician's clinical knowledge of the patient and (iii) physician's knowledge of previous similar cases. Our finding is consistent with Miremont *et al*. (1994), who also found that physicians tend to assess ADRs with very high level of causality. They argued that in clinical practice, physicians need to have definite judgment because they have to decide whether or not to discontinue the suspected drug causing the ADRs. As a result, spontaneous reporters often assess a very high or very low level of causality between the drugs and suspected ADRs. In general, our findings showed that spontaneous reporters tend to report ADRs with higher level of causality. It may seem that ADRs with a higher causality assessment favor spontaneous reporting compared to those with lower causality categories.

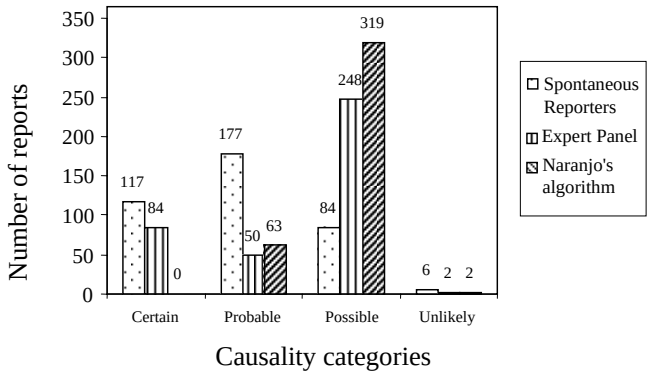

Fig. 2: Causality assessments of ADR.

The most frequent causality assessment by the MADRAC panel was *Possible* (64.6%). MADRAC expert panel categorized 21.9% as *Certain*, 13.0% as *Probable*, 64.6% as *Possible* and 0.5% as *Unlikely*. Macedo *et al.* (2003) has shown that *Probable* and *Possible* were the most common (68%) causality assessment of ADR by global introspection, which is the same method as the WHO-UMC system. Similarly, the most frequent causality categories in ADRs cases reported by WHO-UMC were also *Possible* and *Probable* (WHO-UMC 2005). Using the WHO-UMC approach, positive rechallenge is one of the criteria for *Certain* but it does not always need to be present in order for the event to be assessed as *Certain*. Therefore, the causality assessment for *Certain* was less strict and ADRs reports assessed as *Certain* were more common in MADRAC results compared to using the Naranjo's algorithm.

Causality assessment using Naranjo's algorithm have shown that the most common category is *Possible* (83.1%). Our results showed (Fig. 2) that 16.4% of ADRs was *Probable*, 83.1% was *Possible*, and 0.5% was *Unlikely*. None of the ADRs reports was assessed as *Certain* using this method. The results are consistent with other studies using Naranjo's algorithm, which reported about 50% were classified as *Possible* and less than 10% as *Definite* (Dalton-Bunnow and Halvachs 1993; Dormann *et al*. 2000). Using the same algorithm, Michel and Knodel (1986) also reports that the majority (n = 27; 96%) of ADR assessments were categorized as *Probable* and *Possible* and only (n = 1; 3.6%) as *Certain*. Another study showed that out of 98 cases, only 13.3% were able to achieve a score of 4 or greater on the Naranjo's scale (Berry *et al*. 1988). However, when the use of this algorithm is applied at bedside, 62% of ADRs detected were categorized as *Definite* and less than 1% as *Possible* (Classen *et al.* 1991). This increase in *Definite* category has been attributed to more complete information that is available at the time of assessment.

The agreement of causality assessment by Naranjo's algorithm, expert panel and spontaneous reporters using the same ADRs reports was compared. Total agreement of ADRs causality was achieved in 15.1% (58 of 384 reports). The agreement on causality assessment was 14.8% in *Possible* cases and 0.3% in *Probable* cases. No agreement was found among the three assessors in causality categories of *Certain* and *Unlikely*. Kappa value could only be analyzed for comparison between the MADRAC

panel and spontaneous reporters for which values for all categories were available. A positive but poor agreement was obtained (Table 2).

Table 2: The percentage agreement of causality assessment between Naranjo's algorithm, MADRAC expert panel and spontaneous reporters.

Between assessors	Percentage Agreement (%)					
	Certain	*Probable*	*Possible*	*Unlikely*	Total	κ
N & EP & SR	0	0.3	14.8	0	15.1	-
N & EP	0	1.6	59.1	0	60.7	-
N & SR	0	4.4	19.0	0.3	23.6	-
EP & SR	9.9	5.5	15.6	0	31.0	0.057

N denotes Naranjo's algorithm; EP denotes expert panel; SR denotes spontaneous reporter

A study on comparison of causality assessment of ADRs from published decisional algorithms and expert panel using global introspection shows that full agreement was not found in any level of causality assessment. However, the highest concordance was on *Probable,* which is about 61% (Macedo *et al.* 2003). Miremont *et al.* (1994) has shown that complete agreement between a French algorithm and physicians' opinion occurred only in 6% of cases.

The percentage agreement of causality assessment was highest between Naranjo's algorithm and MADRAC panel. Unlike spontaneous reporters who assess the causality during the clinical practice or with more complete information, the causality assessment of Naranjo's algorithm and MADRAC panel use similar source of information i.e. the reporting forms. In addition, MADRAC panel also use their clinical judgment (eg. previous experience) to make their assessments. The aims of causality assessment and the components for causality assessment are similar between MADRAC panel and Naranjo's algorithm. Causality assessment of MADRAC panel and Naranjo's algorithm aims to classify ADR reports according to the strength of the association between a drug and ADR. On the other hand, the aim of spontaneous reporters in assessing the ADRs is to make a definite decision whether or not to discontinue the suspected drugs. Therefore, it is reasonable that the percentage of agreement between Naranjo's algorithm and MADRAC panel is relatively higher compared to the agreement between Naranjo's

algorithm and spontaneous reporters, or between the MADRAC panel and spontaneous reporters.

Spontaneous reporters, particularly the physicians were able to access directly to the whole range of information and clinical evidence of patients who suffered from the ADRs. There is probably some loss of information because all relevant information and clinical evidence needed for causality assessment may not be transmitted in the ADR report forms. Therefore, loss and lack of data that are needed for causality assessment by the MADRAC panel and Naranjo's algorithm could contribute to the low percentage of agreements between the assessors in the present study, with higher level of causality in spontaneous reporters but lower level of causality in MADRAC panel and Naranjo's algorithm.

The results of causality assessment of ADRs depend on the quality and state of information used for evaluation. Incomplete information in reporting forms was a limiting factor in causality assessment using established guidelines (i.e. MADRAC panel and Naranjo's algorithm). Therefore, the familiarity and understanding of health professional with the components in ADR reporting forms could directly affect the quality of data used for causality assessment in the present study.

CONCLUSION

ADR voluntary reporting to MADRAC may favor reporters, who will usually attribute a higher level causality to an adverse drug event. The difference in aims and methods in causality assessment among the three groups of assessors could be the reasons of disagreements. Variability among spontaneous reporters in making causality assessment may also contribute to such disagreement.

ACKNOWLEDGEMENTS

We thank the Director, National Pharmaceutical Control Bureau for allowing us to conduct and publish the findings of this work.

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