Drug Safety 2005; 28 (12): 1159-1161
0114-5916/05/0012-1159/$34.95/0

A New Algorithm to Identify the Causality of Adverse Drug Reactions

Adverse drug reactions (ADRs) are recognised as a major contributor in iatrogenic illness. They are known to complicate existing disease, affect quality of life and may delay cure of the original disease.[1] The clinical, legal and financial consequences of ADRs have made reporting a major initiative for healthcare organisations,[2] and pharmacovigilance has become an integral part of governmental drug regulation.[3] However, for the regulatory authorities, assessing causality of a reported ADR unambiguously remains a major challenge. To assess causality, differential diagnosis of ADRs can usually be achieved with the use of clinical judgements and/or algorithms.[4] Algorithms are either flowcharts or questionnaires that attempt to determine drug causation in the occurrence of an ADR. They are preferred over clinical judgment for assigning ADR causalities because of their systematic approach to information acquisition, which helps to improve the reliability of assessments, as well as intra- and inter-rater agreement.[5,6] However, the problem of uncertainties pertaining to the causal involvement of the suspected drugs still remains because of the structure or data requirement of several commonly used algorithms. Therefore, a new or improved algorithm that can provide more consistent risk probability and differential diagnosis assessment of a plausible adverse drug event, but without the disadvantages of the existing algorithms, would be beneficial.

In developing the new algorithm, we used the information commonly gathered in ADR reporting forms as a platform to formulate the necessary questions. This was to ensure that the questions for our algorithm could be answered from routinely collected information. With this approach we hoped that the resulting algorithm would be of practical use and impose minimal extra burden on information collection. The preliminary questions derived were matched and modified against the 56 questions in Kramer's algorithm,[7] which was used as the 'gold' standard for comparison in the evaluation because of its comprehensive nature. Those questions from Kramer's algorithm that cannot be answered using information available on the ADR reporting form were eliminated. The remaining questions in Kramer's algorithm were then summarised to form main questions and reconciled with the preliminary questions we developed to arrive at the final questions for the new algorithm.

The scores for the final questions were developed based on their importance in determining the ADR causality of the suspected drug. The cut-off points for the various causality categories were determined by analysing the total number of theoretical 'unlikely', 'possible', 'probable' and 'definite' cases in Naranjo's and Kramer's algorithms. The new algorithm was then tested together with seven other algorithms (Kramer,[7] Naranjo,[6] Karch,[8] Jones,[9] Begaud,[10] Adverse Drug Reactions Advisory Committee [ADRAC] guidelines[11] and WHO Uppsala Monitoring Centre [WHO-UMC] causality assessment[12]) using ADR reports consolidated from hospitals and clinics in Singapore over an 8-month period. The results obtained from the various algorithms were translated into four categories of causality (unlikely, possible, probable and definite) and compared to Kramer's algorithm in terms of percentage congruency.

Our final proposed algorithm consists of eight questions with a scoring scale (table I). A total of 450 ADR reports were used for the congruency study. Results from this comparison are shown in table II (for absolute number of cases in the different causality categories) and table III (for percentage of congruency with Kramer's algorithm).

In this study, we used percentage of congruency, i.e. the percentage of cases that have exactly the

Table I. List of questions for a proposed adverse drug reaction algorithm[a]

Questions	Yes	No	Do not know	Not applicable
1. Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?[b]	2	−4	0	–
2. Has the adverse reaction been associated with the suspected drug before?	2	−2	0	–
3. Could this adverse reaction be due to an existing clinical condition?	0	4	0	–
4. Is there any overdose of the suspected drug?	2	0	0	–
5. If the drug was discontinued, did the adverse reaction improve? (if the drug brought about irreversible changes, please classify as 'do not know')	1	−2	0	0
6. If the drug was NOT discontinued, did the reaction resolved on its own?	−2	0	0	0
7. Did the reaction improve when a specific antagonist/antidote was administered?	4	0	1	0
9. Did the adverse reaction recur when the suspected drug was discontinued and readministered again?	4	−2	0	0
Total score				

a Scores: ≥12 = definite, 8–11 = probable, 0–7 = possible, <0 = unlikely.

b Within 24–48 hours.

same causality assignments, to evaluate the comparative performance of all the algorithms against Kramer's algorithm. From the results obtained among the other six established algorithms, Naranjo's algorithm showed the best agreement with Kramer's, followed by the algorithms from ADRAC, Jones, Begaud, Karch and the WHO-UMC. On the other hand, our new algorithm managed to reach 98.44% congruency with Kramer's algorithm.

The relatively poor performance of several established algorithms such as those of Jones, Karch and the WHO-UMC was due to the presence of substantial unclassifiable cases, which ranged from 16.7% (WHO-UMC) to 40.2% (Jones). Hence, these three algorithms are not particularly suited for our use based on the type of information from our ADR reports.

In pharmacovigilance, the ability to identify 'definite' ADR cases is of paramount importance. These comparative results showed that our algorithm has a lower threshold than the other algorithms tested in triggering warning signals, i.e. in the assigning of 'definite' cases. The lower threshold represents a more conservative approach that would be acceptable in the context of public safety. Hence, with this short algorithm, we feel that it provides ease of use and requires less time to get a causality assignment for the suspected drug than Kramer's algorithm. Although patient-unrelated factors such as the quality-of-data documentation and the medical knowledge of the assessors are likely to influence the assessment outcomes, the presence of such an

Table II. A comparison of the different causality categories for the 450 adverse drug reaction reports

Algorithm	Definite	Probable	Possible	Unlikely	Unclassifiable
Kramer	12	370	64	4	0
Proposed algorithm	13	367	70	0	0
ADRAC	4	436	10	0	0
Jones	0	248	21	0	181
Karch	4	236	1	35	174
Naranjo	4	391	54	1	0
WHO-UMC	3	196	175	1	75
Begaud	4	226	165	55	0

ADRAC = Adverse Drug Reactions Advisory Committee; **WHO-UMC** = WHO Uppsala Monitoring Centre.

Table III. Results from a comparative study of the various algorithms against Kramer's algorithm

Algorithm	Congruency (%)	95% CI
Our new algorithm	98.44	96.82, 99.37
Naranjo	94.67	92.17, 96.55
ADRAC	84.44	80.76, 87.67
Jones	56.44	51.72, 61.08
Begaud	55.33	50.61, 59.99
Karch	52.22	47.49, 56.92
WHO-UMC	45.11	40.45, 49.84

ADRAC = Adverse Drug Reactions Advisory Committee; **WHO-UMC** = WHO Uppsala Monitoring Centre.

algorithm is nevertheless still valuable for improving the ADR reports by focusing on pertinent information, particularly the dates concerning drugs and events.

In conclusion, by evaluating the advantages and disadvantages of several established algorithms for assigning ADR causality, we have developed a simple algorithm that requires no extra data collection than those routinely collected in most ADR reporting forms. The algorithm also adopts an additional safety feature of using a lower threshold in assigning 'definite' ADR cases than most established algorithms, a feature that may be desirable in the context of public safety. However, the trade off for such a feature will be a possible increase in the number of false positive 'definite' ADR cases.

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Acknowledgements

The authors would like to thank Ms Cheng Leng Chan, Miss Bee Him Tan and Miss Pei San Ang from the Pharmacovigilance Unit in the Centre for Drug Administration (CDA), Health Sciences Authority, Singapore, for their valuable comments and their help in providing the data required for this study.

No funding was received for the conduct of this study. The authors have no conflicts of interest that are directly relevant to the contents of this study.

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