## Clinical causality assessment for adverse drug reactions

Sir,

I have read with interest the articles of Chowdhry *et al*., and Tripathy *et al*., on adverse reactions to various drugs published in IJA.[1,2] I would like to address certain issues related to reporting of adverse drug reactions (ADR).

ADRs caused by immune and non-immune mechanisms are a major cause of morbidity and mortality worldwide. Hence, it is important to identify ADRs and to demonstrate a causal relationship between the drug and the untoward clinical event. Causality assessment is used to determine the likelihood that a drug caused a suspected ADR. There are a number of methods used to judge causation. Each has pros and cons associated with its use and most require some level of expert judgement to apply. The causality assessment systems put forth by the World Health Organisation Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC), the Naranjo Probability Scale and the Venulet algorithm are the generally accepted and most widely used methods for causality assessment in clinical practice as they are simple to apply.[3-5] The WHO-UMC Causality Assessment System and the Naranjo Probability Scale offer objective, reliable and valid causality assessment of ADRs along with the convenience of being easy to apply methods. Table 1 depicts the "Naranjo Probability Scale," which may be helpful for assessing unexpected ADRs and useful for evaluators with little experience.[4] The WHO-UMC causality system is basically a combined assessment, taking into account the clinical-pharmacological aspects of the case history and the quality of documentation of observation, while prior knowledge of the ADR plays a less significant part. Table 2 shows the WHO-UMC Causality Assessment System.[3]

For each of these methods, the quality of data and documentation influence the reliability of the method. Moreover, individual systems of causality assessment have, in some instances, found to be non-comparable.[6] In fact, Agbabiaka *et al*.,[7] conclude that there is still no method universally accepted for causality assessment of ADRs. Thus, validating an ADR report needs to take into consideration which causality assessment technique was employed.

Anaesthesiologists can be encouraged to use assessment based on either of the above two scales while reviewing articles related to ADRs.

***Satyen Parida***

**Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India**

**Address for correspondence:**
Dr. Satyen Parida,
Qr. No. D (II) 18, Jawaharlal Institute of Postgraduate Medical Education and Research Campus, Dhanvantari Nagar, Puducherry - 605 006, India.
E-mail: jipmersatyen@gmail.com

**Table 1: The Naranjo adverse drug reaction probability scale[4]**

**To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score**

| | Yes | No | Do not know | Score |
|---|---|---|---|---|
| Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | |
| Did the adverse event occur after the suspected drug was administered? | +2 | −1 | 0 | |
| Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | |
| Did the adverse reaction reappear when the drug was re-administered? | +2 | −1 | 0 | |
| Are there alternative causes (other than the drug) that could have on their own caused the reaction? | −1 | +2 | 0 | |
| Did the reaction reappear when a placebo was given? | −1 | +1 | 0 | |
| Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | |
| Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | |
| Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | |
| Total | | | | |

The ADR is assigned to a probability category from the total score as follows: 'Definite' if the overall score is 9 or greater, 'probable' for a score of 5-8, 'possible' for 1-4 and 'doubtful' if the score is 0, The Naranjo criteria do not take into account drug-drug interactions, Drugs are evaluated individually for causality, and points deducted if another factor may have resulted in the adverse event, thereby, weakening the causal association

**Table 2: WHO-UMC causality categories[3]**

| Causality term | Assessment criteria* |
|---|---|
| Certain | *Event or laboratory test abnormality, with plausible time relationship to drug intake |
| | *Cannot be explained by disease or other drugs |
| | *Response to withdrawal plausible (pharmacologically, pathologically) |
| | *Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) |
| | *Rechallenge satisfactory, if necessary |
| Probable/Likely | *Event or laboratory test abnormality, with reasonable time relationship to drug intake |
| | *Unlikely to be attributed to disease or other drugs |
| | *Response to withdrawal clinically reasonable |
| | *Rechallenge not required |
| Possible | *Event or laboratory test abnormality, with reasonable time relationship to drug intake |
| | *Could also be explained by disease or other drugs |
| | *Information on drug withdrawal may be lacking or unclear |
| Unlikely | *Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) |
| | *Disease or other drugs provide plausible explanations |
| Conditional/ Unclassified | *Event or laboratory test abnormality |
| | *More data for proper assessment needed, or |
| | *Additional data under examination |
| Unassessable/ Unclassifiable | *Report suggesting an adverse reaction |
| | *Cannot be judged because information is insufficient or contradictory |
| | *Data cannot be supplemented or verified |

*All points should be reasonably complied with

## REFERENCES


1. Chowdhry V, Debasish G, Dharmajivan S. Anaphylaxis to vecuronium: A rare event. Indian J Anaesth 2012; 56:314-5.
2. Tripathy S, Nair PV. Adverse drug reaction, patent blue V dye and anaesthesia. Indian J Anaesth 2012; 56:563-6.
3. The use of the WHO-UMC system for standardised case causality assessment. Available from: http://www.WHO-UMC.org/graphics/4409.pdf [Last accessed on 2012 Dec 16].
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239-45.
5. Venulet J, Ciucci AG, Berneker GC. Updating of a method for causality assessment of adverse drug reactions. Int J Clin Pharmacol Ther Toxicol 1986:24:559-68.
6. Tiberio López G, Hueto Pérez de Heredia J, Moreno Baquedano M, García de Lucas L, Sánchez Alvarez J, Nagore Indurain C, *et al*. Adverse drug reactions: Naranjo's and Venulet's algorithms. Rev Clin Esp 1992; 191:270-3.
7. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: A systematic review. Drug Saf 2008;31:21-37.



| Access this article online | |
|---|---|
| Quick response code | Website: www.ijaweb.org |
| | DOI: 10.4103/0019-5049.115608 |