Comparison of the Liverpool Causality Assessment Tool versus the Naranjo Scale for Predicting the Likelihood of an Adverse Drug Reaction

Sung Um[1], Awatif Abuzgaia[2], and Michael (Guest Editor) Rieder[1]

[1]University of Western Ontario
[2]Western University

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Abstract

Abstract Objective To compare the Liverpool Causality Assessment Tool versus Naranjo Scale for screening suspected adverse drug reaction (ADR) cases. Methods We retrospectively reviewed patient charts with a history of suspected ADR, scored using both instruments and determined how each correlates with laboratory and other investigations. 924 charts from the Clinical Pharmacology Clinic at the London Health Sciences Centre were reviewed and 529 charts contained objective findings to support or against the diagnosis of ADR. The participant age ranged from 1 month old to 93 years. We determined the sensitivity and specificity of Liverpool and Naranjo tools for predicting ADRs with scores ranging from "Possible" to "Definite" were considered positive and "Unlikely/Doubtful" as negative for ADR. These results were confirmed by laboratory or clinical (re-challenge) testing in 529 cases. Results Liverpool causality tool had sensitivity (SN) of 97.2% ± 2.4% and specificity (SP) of 2.3% ± 1.57%. The positive (PPV) and negative predictive values (NPV) were 34.1% and 61.5%, respectively. The Naranjo scale had SN of 81.2% ± 5.69% and SP of 13.2% ± 3.56%. PPV and NPV were 32.7% and 57.5%, respectively. Conclusions The Liverpool Causality Assessment Tool is a more sensitive tool than the Naranjo Scale in the assessment of possible ADRs but both tools have poor specificity. The Liverpool Tool can be a useful screening tool in settings where other tests may not be readily available. However the low PPV and NPV of both instruments suggests pursue further testing is needed to confirm or deny an ADR.

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Sung Ho Um MD[1], Awatif Abuzgaia MD M.Sc[1], Michael Rieder MD Ph.D FRCPC FBPhS FRCP(Edinburgh) [1]

Departments of Paediatrics, Physiology & Pharmacology and Medicine, Schulich School of Medicine & Dentistry, University of Western Ontario

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Data Sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Results

Liverpool causality tool had sensitivity (SN) of 97.2% ± 2.4% and specificity (SP) of 2.3% ± 1.57%. The positive (PPV) and negative predictive values (NPV) were 34.1% and 61.5%, respectively. The Naranjo scale had SN of 81.2% ± 5.69% and SP of 13.2% ± 3.56%. PPV and NPV were 32.7% and 57.5%, respectively.

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The Liverpool Causality Assessment Tool is a more sensitive tool than the Naranjo Scale in the assessment of possible ADRs but both tools have poor specificity. The Liverpool Tool can be a useful screening tool in settings where other tests may not be readily available. However the low PPV and NPV of both instruments suggests pursue further testing is needed to confirm or deny an ADR.

What is already known about this subject?

Adverse Drug Reactions (ADRs) are an important and common problem in healthcare.

It is difficult to determine if an adverse event during therapy is an ADR.

The most widely used tool for ADR causality – the Naranjo Scale – can be problematic given current approaches to health care.

What this study adds.

This study compared the Naranjo Scale to a new tool, the Liverpool Causality Assessment.

The Liverpool Causality Assessment has significant better sensitivity in assessment of possible ADRs than the Naranjo Scale.

Both instruments has relatively poor positive and negative predictive value suggesting further research in this area is necessary.

Introduction

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a drug administered at doses normally used for desired effect [1]. They are encountered in all disciplines of medicine. Unfortunately patients with disorders such as cancer or requiring intensive care have higher rates of ADRs, and this is often accepted as an undesired but necessary part of life-saving therapies[2, 3]. Of note, ADRs do not include adverse drug events such as errors in drug administration or dosing.

There are significant consequences for ADRs as they produce significant morbidity, mortality and economic burdens to healthcare worldwide. The overall incidence of serious ADRs in hospitals requiring prolonged hospitalization, permanent damage or death is more than 5%, and up to 6.5% of all hospital admissions are related to ADRs[4, 5]. ADRs rank between 4^{th} and 6^{th} most common causes of death in the United States, ranking only behind heart diseases, cancer, and stroke[4]. ADRs are a considerable burden to the healthcare system costing billions of dollars annually for screening and treatment [6]. These financial figures are comparable to system wide high-cost diseases such as diabetes and obesity[7]. Despite identifying ADRs as a socioeconomic concern they continues to be underreported and challenges are faced in establishing causality between a drug and ADR[8].

Adults and children alike are all at risk for ADRs. Children can be considered to be at higher risk due to limited clinical trial data on safety of drugs in children[9, 10] and also as drugs are often prescribed off-label. It is estimated up to one third of medications prescribed for children are off-label in the community and up to 60% on hospital wards[11]. It is reported that ADR incidence is approximately 1.5% for outpatient children and up to 10% for hospitalized children[12]. The majority of children only require one or less prescription per year but those that do require regular therapy often receive multiple prescriptions, placing them at higher risk for ADRs given increased complexity in their care[13]. With this increased complexity in clinical presentation and the lack of clinical trials specifically in children, it is more challenging for clinicians to establish causality of ADRs in children.

There are multiple scales and tools to establish causality between a drug and suspected ADR. The most commonly used assessment tool is the Naranjo Scale[14] but its poor consistency with confounders was recognized by Macedo *et al* . when comparing a large panel of existing ADR algorithms[15]. Other investigators also questioned its reliability in multiple clinical settings including the paediatric population[16, 17, 18]. Investigators at the University of Liverpool and Alder Hey Children's Hospital pursued the question of causality analysis and developed the Liverpool Causality Assessment Tool after analyzing questions from the Naranjo Scale[19]. This tool is a flow chart rather than a scoring system as a more user-friendly appraohc. The investigators considered possible confounders in suspected ADRs such as sequela even after discontinuing the drug and objective evidence supporting ADR mechanism. This instrumenbt had improved inter-rater reliability when it was evaluated over 80 case reports and 37 published ADR cases[19]. This instrument was developed based on an in-patient population. We investigated the use of the Liverpool Causality Assessment Tool compared to the Naranjo scale in a larger number of suspected ADR cases which were assessed in an ambulatory setting.

Methods

Study Population

Patient charts from the Clinical Pharmacology clinic at London Health Sciences Centre (LHSC) were retrospectively reviewed for ADR cases. The London Health Sciences Centre is a regional tertiary care centre in London, Ontario which includes two adult hospitals and a Children's Hospital, serving as the sole tertiary care referral centre for a region containing 2.5 million people.

Over the period of study between 2008 and 2015 there were 924 patients seen at the clinic for suspected ADRs. Of these, 529 charts were included in the study which contained all results from investigations such as allergy skin test, lymphocyte toxicity assay (LTA), *in vitro* platelet toxicity assay (iPTA) and radioallergosorbent test (RAST) and oral challenge.

The patients studied ranged in age from 1 month to 93 years of age. There were 227 males and 302 females in this study. The most common culprit drug in these suspected ADR cases were antibiotics such as penicillin class and sulfonamide. Other medications included various vaccines and chemotherapy drugs such as methotrexate and mercaptopurine.

Ethical Approval

This study was reviewed and approved by the Human Subjects Research Ethics Board, University of Western Ontario.

Data collection and statistical analysis

Each patient chart was scored using the Naranjo scale (Fig 1) and the Liverpool causality assessment tool (Fig 2). For the questions addressing whether there has been any objective evidence for the adverse event, a score of 0 was assigned to all charts since this study aims to retrospectively assess the tools based only on history and clinical impression prior to any investigations as a screening method. Charts scoring "Doubtful" on Naranjo scale and "Unlikely" on Liverpool tool were considered negative for ADR, and any higher scores were considered positive for ADR screening. The results of the investigations were considered as true positive and true negatives. All data was organized in Microsoft Excel and calculations were done using its algorithm functions. Positive and negative predictive values as well as the sensitivity and specificity for Naranjo and Liverpool tools were calculated using appropriate formulas [20, 21]. The confidence intervals were determined using McCallum Layton confidence interval calculator for proportions with confidence level at 95%.

Results

There were 181 patients who were diagnosed with ADR and 348 ADR negative. The vast majority of the patients scored "Possible" on both Liverpool assessment tool (480/529) (Table 2.) and Naranjo scale (415/529) (Table 1.). No patient scored "Definite" on the Naranjo Scale whereas 31 patients scored "Definite" on the Liverpool tool.

When both Naranjo scale and Liverpool assessment tool were correlated with investigations used to diagnose ADR, both tools showed high sensitivity but low specificity. The Liverpool tool had the higher sensitivity at 97.2% ± 2.4% compared to Naranjo scale's 81.2% ± 5.69%. The specificities for both tests were low at 2.3% ± 1.57% and 13.2% ± 3.56% for Liverpool and Naranjo, respectively.

Positive predictive values for Liverpool and Naranjo were similar at 34.1% and 32.7%, respectively. The negative predictive values were also similar but higher for assessment tools at 61.5% for Liverpool and 57.5% for Naranjo.

Discussion

Assessment of adverse events that occur during therapy to determine whether they represent an ADR versus the underlying disease of interest is problematic. The development of tools to provide a more objective approach rather than relying solely on clinical intuition would permit a more evidence-based approach to care, notably for patients for whom the nihilistic approach of simply avoiding the drug may place them at risk or compromise their care. The Naranjo Scale was developing at the University of Toronto in the late 1970's to help address this issue [14]. This scale was developed and validated in a cohort of patients undergoing psychotherapy and the various domains on the scale reflect this and the practice of psychopharmacology in the 1970s. As the practice of medicine has evolved this has made practical implementation of the scale more problematic; as an example, while the use of a placebo (item 6 on the Naranjo Scale) was considered at the time the scale was developed this would be unlikely to be a realistic option currently [Fig 1]. This and other elements of the scale have made made the Naranjo Scale less helpful in a clinical context, and consequently groups have developed alternate approaches. One such approach, developed by investigators at the University of Liverpool and Alder Hey Children's Hospital, was the Liverpool Causality Assessment, created based on data from in-patients at Alder Hey [19].

This study was conducted to examine the value of screening suspected ADR cases prior to any investigations using history and clinical presentation alone in a ambulatory care setting and to compare the Naranjo Scale to the Liverpool Causality Assessment. The two published assessment tools: the older Naranjo Scale and newly developed tool by the Liverpool group were correlated with well studied diagnostic tests such as the allergy skin test, LTA, iPTA, RAST and oral challenge [22-25].

Both assessment tools have a high sensitivity in predicting ADR cases but poor specificity. Liverpool causality

assessment tool (97.2% ± 2.4%) proved to be the more sensitive tool compared to its predecessor, Naranjo scale (81.2% ± 5.69%). This is likely related to design; the Naranjo Scale is a summative score of all the questions to determine the likelihood of ADR while the Liverpool instrument has a flowchart format. This significantly impacted the score distribution as all cases lost two points on the Naranjo Scale due to following two reasons. First, a score of 0 was given for the question addressing whether the reaction reappeared when a placebo was given; as noted above placebo challenge was not administered at the LHSC Clinical Pharmacology clinic. Secondly, our study attempted to retrospectively score charts assuming no diagnostic tests were performed for all cases, therefore a score of 0 was given for the last question addressing if there were any objective evidence supporting ADR. This essentially made it impossible for any cases to score "Definite" on Naranjo Scale as the maximum score any case can receive was 8/10, which is equivalent to "Probable". The placebo question was rejected by the Liverpool group when their tool was developed as it was not a common practice currently [19]. Moreover, the Liverpool tool's flowchart format made it possible for the cases to achieve "Definite" without having an objective evidence to support ADR.

The low specificities of the two tools were expected as the authors of both Naranjo and Liverpool assessment tool designed the questions to evaluate the sequence of events and reaction response to drug initiation and/or cessation. The tools were not designed to examine ADR causality directly or mechanistically but to screen suspected ADR cases in the clinic setting in a timely manner prior to ordering more expensive, time consuming diagnostic tests.

Predictive values for both Naranjo and Liverpool tools were similar in comparison but both tools are more accurate with its negative results than predicting true positives. Both tools had negative predictive value of approximately 60% and positive predictive value of just over 30%. This can be related back to the above explanation for low specificities observed. The results from either tool are not diagnostically reliable and should only be used to screen patients in conjunction to clinical picture to aid in decision making to pursue further investigations.

This is the first study to compare the newer Liverpool Causality Assessment Tool with its predecessor, Naranjo Scale, independently from the developers of the two tools and in an ambulatory setting. Our study population was also independently selected from the cases previously identified in the papers describing the two tools[14, 19]. The tools were applied in more than 500 suspected ADR cases and the large sample size allowed this study to determine the sensitivities and specificities with narrow 95% confidence intervals.

As previously described by Gallagher *et al.* , the Liverpool assessment tool demonstrated a moderate inter-rater reliability with a global kappa score of 0.48[19]. However in our study, only one rater scored all charts and the potential for inter-rater difference was not a concern. By having only one rater, all charts were scored with consistent interpretation and application of the data.

It should be noted that only a handful number of cases that scored at the polar ends on both Liverpool and Naranjo scales, either "Unlikely/Doubtful" or "Definite". This may have led to skewing of the negative predictive values as only a limited number of samples were available for statistical analysis. A future study identifying more suspected ADR cases that score at the extreme ends would be a useful addition to our findings, although in the case of the Naranjo Scale given the items used to scoring findings of Definite are quite uncommon.

The Liverpool Causality Assessment tool has superior sensitivity compared to the Naranjo Scale. The Liverpool tool has an observed sensitivity of 97.2% ± 2.4% which suggests that it can be a useful screening tool in the clinic setting. Nonetheless its specificity and predictive values are low and should not be used as the sole method of measuring the likelihood of ADR in suspected cases. This reserves clinicians to consider the overall clinical impression and use the tool as a supplementation when making ADR diagnosis or decisions to pursue further investigations. Other diagnostic tests should be performed for understanding the mechanism of ADR or to prove direct causality between a drug and symptoms. Liverpool Causality Assessment Tool is useful for screening ADR prior to pursuing diagnostic investigations, such as during initial patient encounter.

The utility of ADR screening tools such as the Liverpool causality assessment tool or Naranjo scale has

not been verified prospectively in an ambulatory or primary care setting. As well, the value of these tools perceived by clinicians using them in clinical settings should be evaluated by collecting data after applying the tools when suspecting ADRs in patients suggesting that more research is needed to refine causality instruments for the evaluation of potential ADRs.

References

1. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting.*Ann Intern Med* 2004;140:795–801.
2. Rosoff PM. The two-edged sword of curing childhood cancer. *N Engl J Med* 2006;355:1522–3.
3. Agarwal S, Classen D, Larsen G, et al. Prevalence of adverse events in pediatric ICUs in the United States. *Pediatr Crit Care Med*2010;11:568–78.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.*JAMA* 1998;279:1200–5.
5. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 2004;329: 15-19.
6. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. *Pharmacoeconomics* 1999;15:445–58.
7. Carleton BC, Smith MA. Drug safety: Side effects and mistakes or adverse reactions and deadly errors? *BCMJ* 2006;48:329-33.
8. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions.*Drug Safety* 2006;29: 385-96.
9. Hoppu K. Paediatric clinical pharmacology: at the beginning of a new era. *Eur J Clin Pharmacol* 2008;64:201–5.
10. Bonati M, Choonara I, Hoppu K, et al. Closing the gap in drug therapy.*Lancet* 1999;353:1625.
11. Pandolfini C, Bonati M. A literature review on off-label drug use in children. *Eur J Pediatr* 2005;164:552–8.
12. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systemic review and meta-analysis of prospective studies. *Br J Clin Pharmacol*2001;52: 77-83.
13. Khaled LA, Ahmad F, Brogan T, et al. Prescription drug use by one million Canadian children. *Paediatr Child Health* 2003;8(Suppl A):6A–56A.
14. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*1981;30:239–45.
15. Macedo AF, Marques FB, Ribeiro CF, et al. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel. *Pharmacoepidemiol Drug Saf* 2005;14:885–90.
16. Avner M, Finkelstein Y, Hackam D, Koren G. Establishing causality in pediatric adverse drug reactions: use of the Naranjo probability scale. *Paediatr Drugs* 2007;9:267–70.
17. Kane-Gill SL.Are the Naranjo criteria reliable and valid for determination of adverse drug reactions in the intensive care unit?*Annals Of Pharmacotherapy* 2005;39:1823–7.
18. Garcia-Cortes M, Lucena MI, Pachkoria K, et al. Evaluation of Naranjo Adverse Drug Reactions Probability Scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther*2008;27:780–9.
19. Gallagher RM, Kirkham JJ, Mason JR, et al. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. *PLoS One* 2011;6:e28096.
20. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity.*BMJ* 1994;308(6943):1552.
21. Altman DG, Bland JM. Diagnostic tests 2: predictive values. *BMJ* 1994;309(6947):102.
22. Wong T, Atkinson A, t'Jong G, Rieder MJ. Beta-lactam in the paediatric population. Paediatr Child Health 2020;25:762-3.
23. Line J, Thomson P, Naisbitt DJ. Pathology of T-cel mediated drug hypersensitivity reactions and impact of tolerance mechanisms on patient susceptibility. Curr Opin Allergy Clin Immunol 2022;22:226-233.
24. Elzagallaai AA, Rieder MJ. Model based evaluation of hypersensitivity adverse drug reactions for

antimicrobial agents in children. Front Pharmacol 2021 30;12:63888..
25. Elzagallaai AA, Koren G, Rieder MJ. The predictive value of the in vitro platelet toxicity assay (iPTA) for the diagnosis of hypersensitivity reactions to sulfonamides. J Clin Pharmacol. 2013;53(6):626-32.

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