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Artículos originales

The Cohen Kappa of the Liverpool and the Naranjo Adverse Drug Reaction Causality Assessment Tool on Nervous System Drugs

La Kappa de Cohen de la Herramienta de Evaluación de la Causalidad de Reacciones Adversas a Medicamentos de Liverpool y Naranjo en medicamentos para el sistema nervioso

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Conflict of interests

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Resumen

Objetivo: Un método para identificar la causalidad de los efectos secundarios es el algoritmo de Naranjo. Actualmente, existe un algoritmo de Liverpool, que es un refinamiento del algoritmo Naranjo. Este estudio pretende comparar de Naranjo y de Liverpool en la identificación de la causalidad de los efectos secundarios de los fármacos que actúan sobre el sistema nervioso.

Métodos: Esta investigación es un estudio observacional con un método longitudinal. La recogida de datos se realizó de forma prospectiva en pacientes a los que se les prescribieron anticonvulsivantes, antidepresivos o antipsicóticos. Cuatro investigadores observaron a los pacientes durante tres meses. Los eventos adversos se reportaron y evaluaron utilizando de Naranjo por dos investigadores y de Liverpool por otros dos. Los resultados de las mediciones de los dos algoritmos se comprobaron con la fiabilidad entre evaluadores (IRR) mediante el valor del coeficiente de concordancia Kappa (K) de Cohen.

Resultados: En el estudio participaron 133 pacientes, 74 (55,64 %) experimentaron efectos secundarios con probabilidad de causalidad probable y posible. El valor kappa para Naranjo es de 0,465 («moderado» IRR). Para Liverpool, el valor K es de 0,352 (TIR «regular»), lo que indica que el acuerdo de los investigadores fue mejor en el algoritmo de Naranjo que en el de Liverpool.

Conclusiones: Este estudio concluye que de Naranjo ofrece un valor kappa más alto que de Liverpool. Es necesario que otros investigadores de Indonesia lleven a cabo investigaciones con de Liverpool para determinar su viabilidad en la práctica clínica.

Palabras clave: Algoritmo de Naranjo; algoritmo de Liverpool; efecto secundario; Kappa de Cohen; inter-fiabilidad; fármacos del sistema nervioso.

Abstract

Objective: Monitoring of side effects is essential to prevent and overcome the occurrence of drug side effects. Drugs that act on the nervous system have many similar side effects. One method of identifying side effect causality is using the Naranjo algorithm. Currently, there is a Liverpool algorithm, a refinement of Naranjo. This study aims to compare the Naranjo algorithm and the Liverpool algorithm in identifying the causality of side effects of drugs that act on the nervous system.

Methods: This research is an observational study with a longitudinal method. Data collection was carried out prospectively in patients who were prescribed anticonvulsants, antidepressants, or antipsychotics. Four researchers will observe patients for three months. Adverse events were reported and tested using the Naranjo algorithm by two researchers and the Liverpool algorithm by two researchers. The measurement results of the two algorithms were tested with the Inter-Rater Reliability (IRR) by looking at the Cohen Kappa (K) agreement coefficient value.

Result: The study involved 133 patients. Of the 133 patients, 74 (55.64%) experienced side effects with probable and possible causality. The kappa value for Naranjo is 0.465 (“moderate” IRR). It is 0.352 (“fair” IRR) for Liverpool, indicating that the researchers’ agreement was better on the Naranjo algorithm than the Liverpool algorithm.

Conclusion: This study concludes that the Naranjo algorithm gives a higher kappa value than the Liverpool algorithm. Research using the Liverpool algorithm needs to be carried out by other researchers in Indonesia to find out the possibility of its use in clinical practice.

Keywords: Naranjo algorithm; Liverpool algorithm; side-effect; Cohen Kappa; inter-reliability; nervous system drugs

Introduction

Drug side effects often result in therapy failure and increased morbidity and mortality. Side effects increase with long-term drug therapy, especially for drugs that act on the nervous system. Drugs that act on the nervous system affect neurotransmitters, leading to many side effects. In a study in New Delhi of 224 psychotic patients, 38 side effects occurred. The most significant cause of side effects is risperidone, followed by olanzapine. The causality relationship using Naranjo obtained the results of 34 “probable” events[1]. In a study conducted by Marasine et al., it was reported that 174 patients received antidepressants, 74.13 % experiencing side effects. The most common side effects experienced were insomnia and anxiety (using the Naranjo algorithm). These side effects affect patient adherence, where 52.29 % of patients were found to be non-adherent (using Morisky Green Levine Adherence)[2].

Another study in Ethiopia obtained results: out of 300 patients using first-generation antipsychotics, 97.7 % experienced side effects. These side effects are cardiovascular 56.3 %; sedation and effects on CNS 49.6 %; and extrapyramidal 38.0 %[3].

Based on the explanation above, side-effect monitoring is needed to prevent, overcome, and minimize side effects. Monitoring is necessary so that the patient can achieve therapeutic goals. The side effect reporting system that has been widely used in Indonesia is using the Naranjo algorithm. The Indonesian Food and Drug Authority currently has an MESO form in the form of an e-form (https://e-meso.pom.go.id). This MESO form uses the Naranjo algorithm as the Naranjo algorithm already exists in Indonesian.

The Liverpool algorithm is a simplified form of the Naranjo algorithm. One of Naranjo's weaknesses is that there are several "don't know" answers as it is difficult or impossible to do, affecting the sensitivity of the assessment. Gallagher et al. modified the Naranjo algorithm to produce the Liverpool algorithm[4]. The Liverpool algorithm has yet to be widely used in Indonesia. Several hospitals in Indonesia are currently using Liverpool's algorithm to identify side effect causality. Theoretically, the Liverpool algorithm is more straightforward than the Naranjo algorithm, so it is expected to be easier to use. This study compares the Naranjo and Liverpool algorithms in Indonesia.

Methods

This research is an observational study with a longitudinal method. Researchers collected data prospectively. The population in this study were outpatients who received a prescription for anticonvulsants, antidepressants, or antipsychotics for three months. Inclusion criteria were outpatients who received prescriptions for anticonvulsants, antidepressants, or antipsychotics. The patient experienced side effects and was willing to become a respondent. Samples were taken using purposive sampling; then, patients were followed for three months to determine any side effects that occurred. The exclusion criteria in this study were patients whose data was incomplete and could not be analyzed using Naranjo or Liverpool. Demographic data, patient clinics, and side effects were obtained from medical records. Side effect data were also obtained from interviews with patients and their families. The samples obtained were 138 patients. Adverse events were reported and tested with the Naranjo algorithm by two different researchers (researcher A and researcher B). Two other investigators (researchers C and D) reported and tested adverse events in the same patient using the Liverpool algorithm. The evaluator is a pharmacist who works in a hospital where the patient is an outpatient. These pharmacists have undergone training in using the Naranjo and the Liverpool algorithms because they have a license to practice pharmacy. These pharmacists are also accustomed to identifying side effects using the Naranjo algorithm in daily practice. The researcher tested the measurement results of the two algorithms with the Inter-Rater Reliability (IRR) by looking at the Cohen Kappa (K) agreement coefficient value.

Results and Discussion

Patient characteristics

Table 1. Patient characteristics

characteristics		n	%
Gender	Male	36	48.65
	Female	38	51.35
Age (y)	17-25	18	24.32
	26-35	7	9.46
	36-45	15	20.27

characteristics		n	%
	46-55	12	16.22
	56-65	10	13.51
	66-74	8	10.81
	75-90	4	5.41
Diagnosis			
	Residual Schizophrenia	15	20.27
	Anxiety disorder	5	6.76
	Episodes of Major Depression without psychological symptoms	4	5.41
	Mixed Anxiety and Depressive Disorder	4	5.41
	Lir-Schizophrenia organic delusional disorder	4	5.41
	Delusional disorder	3	4.05
	Depressive-type schizoaffective disorder	3	4.05
	Somatic symptom depression	2	2.70
	Moderate Recurrent Depressive Disorder Current Episode without Somatic Symptoms	2	2.70
	Mental and behavioral disorders due to multiple substance use SEP	2	2.70
	Moderate depressive episode with somatic symptoms	2	2.70
	myalgia	2	2.70
	Major Depressive Disorder	1	1.35
	Hypochondriasis	1	1.35
	Bipolar Affective Disorder Current Episode Western Depression without Psychotic Symptoms	1	1.35
	Bipolar Affective Disorder Current Episode Major Depression with psychotic symptoms	1	1.35
	Recurrent Depressive Disorder Severe Current Episode without Psychotic Symptoms	1	1.35
	Bipolar current episode of depression	1	1.35
	Manic-type schizoaffective disorder	1	1.35
	Generalized Anxiety Disorder	1	1.35
	Adjustment disorder with depressive reactions	1	1.35
	Insomnia	1	1.35
	Stroke Parkinsonism	1	1.35
	Trigeminal neuralgia post extraction of molar teeth dyspepsia	1	1.35
	Acute transmural myocardial infarction of the anterior wall	1	1.35
	lbp ec hnp vl 4-5 post ckb dyspepsia	1	1.35
	epilepsy	1	1.35
	Ischalgia Neuropathy Vertigo	1	1.35
	Chronic Cephalgia Myofascial Pain	1	1.35
	Stroke ICHTT Sinister Hemiparese Aphasia	1	1.35
	Parkinsonism. Stroke Infraction Hypertension Polyarthralgia	1	1.35
	Post Stroke Neuropathy Epilepsy	1	1.35

characteristics		n	%
	LBP infarct stroke with cephalalgia hypertensive neuropathy	1	1.35
	Parkinson's Dementia Cervical Syndrome ec HNP VC 5-6-7 DM Neuropathy	1	1.35
	Psychological and behavioral factors	1	1.35
	Psychosomatic	1	1.35
	Low back pain Radiculopathy	1	1.35
	Hypertension Dyslipidemia Myalgia	1	1.35
Total		74	100

In this study 138 patients met the inclusion criteria. and 74 experienced side effects. The number of female patients was more than that of male patients. although not significantly different. According to Patton and Borshoff, women are at a 2x more significant risk of experiencing side effects than men influenced by differences in pharmacokinetic profiles related to body mass. hormones and hepatic clearance[5]. Patient characteristic data can be seen in Table 1.

Patients involved in this study were dominated by productive age, 17-25 years (25.56 %). The results of this study differed from the theory that children and older people were the age group at risk for side effects. Age is sometimes a risk factor for side effects[5,6]. In this study, the productive age affected more side effects related to the most common diagnosis, namely schizophrenia. Schizophrenia is currently suspected to appear at an earlier age, as in Chan's review[7].

The incidence of side effect

Table 2. The incidence of side effects

No	Side-effects	number (n)	Percentage (%)
1	Somnolence	22	16.54
2	Nauseous	11	8.27
3	Insomnia	8	6.01
4	Dizziness	6	4.51
5	Weight gain	6	4.51
6	Increased appetite	6	4.51
7	Appetite Down	4	3.00
8	Heartbeat	4	3.00
9	Hypersomnia	4	3.00
10	Hypotension	3	2.25
11	Weight loss	3	2.25
12	Hypertension	3	2.25
13	Disturbed menstrual cycle	3	2.25
14	Aches	2	1.50
15	Frequency	2	1.50
16	Nervous	2	1.50
17	Confused	2	1.50
18	Numb	1	0.75
19	Lactation non puerperal	1	0.75
20	Shiver	1	0.75
21	Hard to breathe	1	0.75
22	Weak	1	0.75

No	Side-effects	number (n)	Percentage (%)
23	Abdominal pain when taking medicine	1	0.75
24	Dry mouth	1	0.75
25	Seizures	1	0.75
26	Constipation	1	0.75
27	Rigidity	1	0.75
28	Allergic reaction	1	0.75
29	Cough	1	0.75
30	Easily tired	1	0.75
31	Stomach acid	1	0.75
32	Easy to forget	1	0.75
33	Swollen foot	1	0.75
Total		107	100

Of the 74 respondents who experienced side effects, the number of side effect events was 107, as seen in Table 2.

One patient may experience more than one side effect. The side effects are drowsiness, nausea. and insomnia. Many of these side effects occur due to drugs that act on the nervous system. Some of the drugs in this study with drowsy side effects included clozapine, risperidone, trihexyphenidyl, chlorpromazine, alprazolam, carbamazepine, haloperidol clobazam and others. One drug can also cause multiple side effects, such as clobazam causing drowsiness and dizziness.[2,8]medication adherence (MA). Meanwhile, a patient involved in the study may be prescribed drugs that act on the nervous system more than one drug. This condition is the reason for the importance of looking for the causality of side effects to ensure that the drug is suspected of causing the side effects. In this study, the researcher only carried out inter-rater reliability on probable and possible causality as it is the most causal relationship and is closer to the certainty of the cause of side effects. The result of Naranjo is in line with Harichandran et al. research. where out of 53 ADR events, almost all were in the probable category and only one was possible when analyzed using Naranjo[9]. Meanwhile. according to Gupta and Kumar, causality analysis using Naranjo and Liverpool to obtain the most probable results[10].

Table 3. Kappa values from side effect causality analysis using Naranjo

Naranjo Researcher A	Naranjo Researcher B				Kappa	P
	Probable		Possible			
	N	%	N	%		
Probable	86	80.4	21	19.6	0.465	0.000
Possible	3	15.8	16	84.2		

Table 4. Kappa value from side effect causality analysis using Liverpool

Liverpool ResearcherC	Liverpool Researcher D				Kappa	P
	Probable		Possible			
	N	%	N	%		
Probable	78	72.9	29	27.1	0.352	0.000
Possible	0	0.0	12	100.0		

The results of Naranjo's analysis from researchers A and B and the Liverpool algorithm analysis results from researchers C and D sought agreement through inter-rater reliability analysis. The results of the kappa values are presented in Tables 3 and 4.

Based on the results of causality using Naranjo. it was found that of the 107 adverse events considered probable by rater A, there were 86 adverse effects (80.4 %), also rated as probable by rater B. In contrast. rater B rated the remaining 21 side effects (19.6 %) as possible.

Meanwhile. of the 19 adverse events assessed as Possible by Rater A, three side effects (15.8 %) were considered Probable by Rater B. and 16 adverse events (84.2%) were also assessed as Possible by Rater B. A Kappa value of 0.465 indicated no agreement among raters in assessing using the Naranjo algorithm. This condition was also reinforced by a P value of 0.000, indicating a difference in assessment between rater A and B. The Naranjo algorithm has been widely used in Indonesia; the Indonesian National Agency for Drug and Food Control (NADFC), an official agency owned by the Indonesian government, utilized the Naranjo algorithm to report side effects. The moderate Kappa Cohen value could be influenced by the researcher's subjectivity and the assessment's inaccuracy[11]. Furthermore. low agreement among researchers could also be influenced by the Naranjo algorithm developed for side effect causality assessment in randomized controlled trials[12] that is, the World Health Organization-Uppsala Monitoring Center (WHO-UMC). A study by Théophile et al., in testing the sensitivity and specificity of the tools used for causality analysis, stated that the Naranjo algorithm has heterogeneous sensitivity and specificity. Sensitivity values range from 0.5 to 1, while specificity values range from 0 to 1[13].

The results of the causality analysis using the Liverpool algorithm showed that of the 107 adverse events that were assessed as probable by Rater C, there were 78 adverse events (72.9 %) that were also considered probable by Rater D and 29 adverse events (27.1 %) which were assessed as Possible by Rater D. Meanwhile, of the 12 side effects assessed as Possible by Rater C, 100 % were approved by Rater D. A Kappa value of 0.352 indicated no agreement between raters in assessing Liverpool. A p-value of 0.000 indicated a difference in rating between rater C and rater D. The Liverpool algorithm is a simplified form of the Naranjo algorithm. Some omitted items make it easier for users to report adverse events but also eliminate some of the possibilities of causality. The Liverpool algorithm does not require an assessment from a health professional but can be carried out independently or even by patients. On the one hand, it causes the tool's subjectivity to become large. leading to low reliability[14].

The Liverpool algorithm had never been employed in this study, which was conducted at a private hospital in the Yogyakarta area. Indonesia. This situation could also factor in the low agreement between raters. especially since Liverpool's algorithm is still in English.

Comparison of Naranjo and Liverpool

Several studies have examined the inter-rater reliability of Naranjo and Liverpool, with varying results. Varallo et al. revealed the kappa scores for Naranjo consecutively from the three judges to be 0.29 (0.03–0.55), 0.39 (0.13–0.65), 0.41 (0.16–0.69) (fair-moderate). In terms of the Liverpool algorithm, the kappa value of the same three judges is 0.21 (0.01–0.42), 0.41 (0.21–0.60) and 0.26 (0.04–0.50) (slight-moderate)[14]. The results differed significantly from this study, where Naranjo's kappa scores were generally slightly better than Liverpool's. Meanwhile, Behera et al. compared three tools: Naranjo-WHO UMC (World Health Organization-Uppsala Monitoring Centre) -Logistic method, where the highest kappa value was obtained in the Naranjo agreement and Logistic method[15]. In the study of Théophile et al. comparing Naranjo and Liverpool with the Probabilistic Logistics method as a routine case report on pharmacovigilance using consensual expert judgment as a reference, the results of the probabilistic logistic method were closer to consensual expert judgment[13]. Based on various studies with different methods, assessing causality in hospitals required tools fitting the new pharmacovigilance definition. Meanwhile, Naranjo is still an easy-to-use tool in Indonesia, although some points cannot be answered due to the RCT background. Further research is still needed to identify tools to minimize confounding variables in causality analysis[16]. The Liverpool algorithm can be an alternative. especially when it can be translated into a native language. as it is more appropriate than the English version[17] hospitals need a system to support them in monitoring ADE occurrence routinely, rapidly, and at scale. Natural language processing (NLP). Furthermore, the limitation of this study is precisely the assessment of side

effects, as the recording is only conducted through interviews with patients and medical records. There is no record of side effects when the patient does not complain about anything (even if side effects occur).

Conclusion

The Naranjo algorithm showed a higher kappa value (moderate agreement) than the Liverpool algorithm (sufficient). The Liverpool algorithm has been used for a short time in Indonesia. so, research using the Liverpool algorithm needs to be conducted by other researchers in Indonesia to determine the possibility of its use in clinical practice. The selection of tools to analyze side effect causality depends on clinical needs.

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