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Can Decisional Algorithms Replace Global Introspection in the Individual Causality Assessment of Spontaneously Reported ADRs?

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Abstract

Aim: The usefulness of algorithms for assessing the causality of suspected adverse drug reactions (ADRs) has yet to be established and, since the validation of causality algorithms depends upon their sensitivity and specificity, our study was carried out to evaluate these measures.

Method: In this study, an expert panel assessed causality of adverse reports by using the WHO global introspection (GI) method. The same reports were independently assessed using 15 published algorithms. The causality assessment level 'possible' was considered the lower limit for a report to be considered to be drug related. For a given algorithm, sensitivity was determined by the proportion of reports simultaneously classified as drug related by the algorithm and the GI method. Specificity was measured as the proportion of reports simultaneously considered non-drug related. The analysis was performed for the total sample and within serious or unexpected events.

Results: Five hundred adverse reports were studied. Algorithms presented high rates of sensitivity (average of 93%, positive predictive value of 89%) and low rates of specificity (average of 7%, negative predictive value of 31%).

Conclusion: Decisional algorithms are sensitive methods for the detection of ADRs, but they present poor specificity. A reference method was not identified. Algorithms do not replace GI and are not definite alternatives in the individual causality assessment of suspected ADRs.

Introduction

Adverse drug reactions (ADRs) are one of the leading causes of morbidity and mortality in healthcare[1-5] that could, for the most part, be prevented.[4,6-9]

Causality assessment of identified adverse events is crucial in pharmacovigilance activities because of its implications on the benefit-risk ratio evaluations of medicines. Causality assessments of reported ADRs are important as they are included in periodic safety update reports of the involved drugs. The safety profile of approved products is continuously monitored through signal detection, issue evaluation, the updating of product labelling and liaison with regulatory authorities.

The 'Núcleo de Farmacovigilância do Centro' (NFC) or the central Portugal regional pharmacovigilance unit started receiving ADR reports from family physicians and community pharmacists in January 2001. According to regulatory responsibilities, spontaneous reporting of suspected ADRs is mandatory and it is supported by a national reporting form developed according to CIOMS standards. As a component of the adopted standard operating procedures the global introspection (GI) method, based on the WHO scale of imputability, is currently used for causality assessment of reported events and WHO-ART (WHO Adverse Reaction Terminology) is employed as the coding classification.

Several methods have been proposed for imputation of observed untoward clinical events. The GI method, despite its usefulness, has been subject to criticisms of subjectivity and imprecision since it is mainly based on expert clinical judgements.[10,11] Concurrently, but not alternatively, several decisional algorithms have been published, which, by combining and scoring different criteria as an explicit approach, have claimed the advantage of avoiding subjective bias.[10-13] However, none of the algorithms published since 1976 have been universally accepted as a gold standard. Several studies have revealed discrepancies between the results obtained from the use of the different algorithms in assessing causality for the same adverse events[14-20] and there is a lack of comparative analysis of all decisional strategies under similar conditions.[16,18,20-22]

Much work is being done on data-mining methodologies for signal detection[23-26] but the usefulness of algorithms in combination with these tools remains to be studied and the usefulness of decisional algorithms for causality assessment of suspected ADRs has not yet been established.

In recent published studies, the causality of 200 adverse drug reports was evaluated using both a GI expert panel (the established gold standard) and 15 selected decisional algorithms.[27,28] The extent of agreement between decisional algorithms and GI was analysed for each level of imputation using the kappa statistic. Overall, observed agreement was found to be moderate (average 47%), although the extent of reproducibility beyond what would be expected by chance was low (average kappa = 0.26), confounding variables being a shortcoming of this concordance. Despite these findings of moderate agreement, the validation of causality algorithms depends upon their sensitivity and specificity. The current study was therefore carried out to evaluate the proportion of reports simultaneously classified as drug related by the algorithm and the GI method and the proportion of reports simultaneously considered non-drug related in order to analyse if decisional algorithms can replace GI in the individual causality assessment of spontaneously reported ADRs.

Method

Adverse drug reports continuously received by the NFC were studied.

From a literature search, the following 15 published decisional algorithms were selected, all supported by the combination of five common major criteria for causality assessment: challenge, dechallenge, rechallenge, previous bibliographic description and aetiological alternatives: Australian;[29] Blanc;[11] Cornelli;[30] Dangoumau;[31,32] Emanueli;[33] Hsu Stoll;[34] Irey;[35] Jones;[36] Karch and Lasagna;[10] Kitaguchi;[37] Kramer;[38-40] Naranjo;[41] Stephens;[42] Venulet;[43] and Weber.[44]

A pharmacist investigator assessed the causality of the adverse drug reports using the decisional algorithms. Causality assessment was carried out based on spontaneously reported data. Information concerned mainly the five major imputation criteria. Additional information requested by the algorithms (for example, information about the drug being detected in any body fluid in toxic concentrations required by Naranjo's algorithm[41]) was taken into account when available. For purposes of causality assessment, Naranjo's criterion "previous well documented reports"[41] was considered to equate to 'previous bibliographic description'.

Reports were simultaneously and independently assessed by an expert panel comprising two clinical pharmacologists, two pharmacists, an internal

medicine specialist and a general practitioner, using the GI method based on the WHO scale of imputability.[45] For each causality assessment, the panel identified and dialogued the reasons for disagreement until a consensus was reached.

Causality assessments produced from both modalities were finally compared and analysed. Software Epi Info 3.2 was used for the analysis.

The causality assessment level 'possible' was considered the lower limit for a report to be considered to be drug related (i.e. an ADR). We evaluated the agreement between a given algorithm and the GI method for any of the terms above the level 'possible' (established to assume a report as drug related) or below the level 'possible' (established to assume a report as non-drug related) [figure 1]. The following measures were determined:

- Sensitivity: the proportion of reports simultaneously considered as drug related by a given algorithm and the GI method, in the total ADRs identified by the GI, i.e. A/(A + C).
- Positive predictive value (PPV): the proportion of reports simultaneously considered as drug related by the algorithm and the GI method, in the total ADRs identified by a given algorithm, i.e. A/(A + B).
- Specificity: the proportion of reports simultaneously considered as non-drug related by a given algorithm and the GI method, in the total ADRs excluded by the GI, i.e. D/(D + B).
- Negative predictive value (NPV): the proportion of reports simultaneously considered as non-drug related by the algorithm and the GI method, in the total ADRs excluded by a given algorithm, i.e. D/(C + D).

		Global introspection (gold standard)		
		ADR	**Non-ADR**	**Total**
Algorithm	**ADR**	A	B	A + B
	Non-ADR	C	D	C + D
	Total	A + C	B + D	A + B + C + D

Fig. 1. Parameters used to assess sensitivity specificity and predictive values of the various algorithms compared with the global introspection method. **ADR** = adverse drug reaction.

The analysis was performed for the total sample and within serious or unexpected events, as these reports are the most concerning.

Results

Five hundred adverse drug reports were included in this study. The sample included a large spectrum of clinical events. On average, two clinical manifestations were described for each report, mainly gastrointestinal system disorders (26.8%) and skin and appendage disorders (18.5%).

Five hundred and seven different, suspected branded drugs were reported as responsible for the suspected ADRs. In 74% of the reports concurrent medications were present (maximum 11; average 2.5). A total of 27.4% of the reported ADRs were considered serious according to the WHO criteria.[46] Sixteen percent of the reported ADRs were considered as unexpected according to the information in the drug's summary of product characteristics or in Martindale.[47]

The total sample, the group of serious and the group of unexpected reports presented similar characteristics for the five major causality-assessment criteria.

According to the expert panel, 112 reports were classified as 'definitive', 175 as 'probable', 142 as 'possible' and 71 as 'unlikely', 'conditional' (reports under follow-up evaluation) or 'unclassifiable' cases (reports with insufficient or contradictory information). Therefore, a total of 429 reports were considered drug related and 71 reports were considered non-drug related by the GI method.

Sensitivities and specificities of different decisional algorithms are presented in table I. Algorithms presented high rates of sensitivity (average of 93%, PPV of 89%) and low rates of specificity (average of 7%, NPV of 31%).

The Cornelli,[30] Emanueli,[33] Hsu Stoll,[34] Jones,[36] Kramer[38-40] and Naranjo[41] algorithms imputed all the adverse events as ADRs therefore presenting 0% specificity and 0% NPV.

In the groups of serious or unexpected events, algorithms also presented high rates of sensitivity (average of 92% and 82%, respectively; PPV of

Table I. Algorithms sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV). Results are for the total sample and for serious and unexpected events (95% CI)

Par	Aust	B	Co	D	Em	HS	I	Jo	KL	Ki	Kr	N	St	V	W	Mean (%)
Total sample (n = 500)																
Se	99.8 (98.4, 100)	80.8 (76.6, 84.4)	100 (98.8, 100)	95.9 (93.3, 97.5)	99.7 (98.4, 100)	100 (98.8, 100)	100 (98.8, 100)	95.1 (92.5, 96.9)	73.1 (68.4, 77.2)	99.8 (98.4, 100)	95.6 (93.1, 97.3)	100 (98.8, 100)	99 (97.4, 99.7)	100 (98.8, 100)	57.3 (52.3, 62.1)	93
PPV	89.2 (85.9, 91.8)	90.2 (86.6, 93.0)	88 (84.7, 90.8)	89.6 (86.2, 92.2)	88 (84.6, 90.7)	88 (84.7, 90.8)	88.6 (85, 91.3)	89.3 (85.9, 92.0)	92.6 (89.1, 95.1)	88.4 (85, 91.1)	89.1 (85.8, 91.8)	88 (84.7, 90.8)	88.3 (84.9, 91)	88.2 (84.9, 90.9)	85.5 (80.7, 89.3)	89
Sp	10.7 (4.4, 22.6)	19.6 (13.7, 29.7)	0 (0, 8.0)	17.9 (9.3, 30.8)	0 (0, 8.0)	0 (0, 8.0)	5.4 (1.4, 15.8)	0 (0, 8.6)	21.4 (17.6, 30.8)	3.6 (0.6, 13.4)	0 (0, 8.7)	0 (0, 8.0)	3.6 (0.6, 13.4)	1.8 (0.1, 10.8)	23.2 (19.6, 32.3)	7
NPV	85.7 (42, 99.2)	15.9 (13.1, 29.7)	0[a]	37 (20.1, 57.5)	0[a]	0[a]	100 (31.0, 100)	0[a]	14.8 (8.4, 30.3)	66.7 (12.5, 98.2)	0[a]	0[a]	33.3 (6, 75.9)	100 (5.5, 100)	7.5 (6.7, 28.5)	31
Serious reports (n = 137)																
Se	100 (96.4, 100)	77.5 (69.2, 84.2)	100 (96.4, 100)	93 (86.8, 96.6)	100 (96.4, 100)	100 (96.4, 100)	100 (96.4, 100)	93 (86.8, 96.6)	71.3 (62.6, 78.8)	100 (96.4, 100)	93 (86.8, 96.6)	100 (96.4, 100)	97.7 (92.8, 99.4)	100 (96.4, 100)	48.1 (39.2, 57)	92
PPV	94.2 (88.4, 97.3)	96.2 (89.9, 98.8)	94.2 (88.4, 97.3)	94.5 (88.6, 97.6)	94.2 (88.4, 97.3)	94.2 (88.4, 97.3)	94.2 (88.4, 97.3)	94.5 (88.6, 97.6)	95.8 (89.1, 98.7)	94.2 (88.4, 97.3)	94.5 (88.6, 97.6)	94.2 (88.4, 97.3)	94.7 (89.1, 97.7)	94.2 (88.4, 97.3)	92.5 (87.7, 97.2)	94
Sp	0 (0, 40.2)	37.5 (17.4, 82.6)	0 (0, 40.2)	12.5 (0.7, 53.3)	0 (0, 40.2)	0 (0.0, 40.2)	0 (0.0, 40.2)	0 (0.7, 53.3)	37.5 (17.4, 82.6)	0 (0, 40.2)	0 (0, 53.3)	0 (0, 40.2)	12.5 (0.7, 53.3)	0 (0, 40.2)	25 (10.2, 74.1)	8
NPV	0[a]	13 (4.0, 29.1)	0[a]	10 (0.5, 45.9)	0[a]	0[a]	0[a]	0 (0.5, 45.9)	11.5 (3.2, 24.1)	0[a]	0 (0.5, 45.9)	0[a]	25 (1.3, 78.1)	0[a]	3.3 (1.1, 12.8)	4
Unexpected reports (n = 80)																
Se	100 (93.3, 100)	11.8 (5.6, 22.4)	100 (93.3, 100)	97.1 (88.8, 99.5)	100 (93.3, 100)	100 (93.3, 100)	100 (93.3, 100)	95.6 (86.8, 98.9)	1.5 (0.1, 9)	100 (93.3, 100)	95.6 (86.8, 98.9)	100 (93.3, 100)	95.6 (86.8, 98.9)	100 (93.3, 100)	32.4 (21.8, 44.9)	82
PPV	86.1 (76, 92.5)	88.9 (50.7, 99.4)	85 (74.9, 91.7)	86.8 (76.7, 93.2)	85 (74.9, 91.7)	85 (74.9, 91.7)	86.1 (76, 92.5)	85.5 (75.2, 92.2)	50 (2.7, 97.3)	86.1 (76, 92.5)	85.5 (75.2, 92.2)	85 (74.9, 91.7)	86.7 (76.4, 93.1)	86.1 (76, 92.5)	84.6 (64.3, 95.0)	83
Sp	8.3 (0.4, 40.2)	83.3 (59.8, 99.6)	0 (0, 30.1)	16.7 (2.9, 49.1)	0 (0, 30.1)	0 (0, 30.1)	8.3 (0.4, 40.2)	0 (0, 40.2)	91.7 (59.8, 99.6)	8.3 (0.4, 40.2)	0 (0.4, 40.2)	0 (0, 30.1)	16.7 (2.9, 49.1)	8.3 (0.4, 40.2)	66.7 (35.4, 88.7)	21
NPV	100 (5.5, 100)	14.7 (8.4, 26.5)	0[a]	50 (9.2, 90.8)	0[a]	0[a]	100 (5.5, 100)	0[a]	14.1 (7.6, 24.3)	100 (5.5, 100)	0[a]	0[a]	40 (7.3, 83.0)	100 (5.5, 100)	14.8 (7.1, 27.7)	36

a Confidence intervals were not determined because the algorithm imputed all the adverse events as adverse drug reactions.

Aust = Australian;[29] **B** = Blanc;[11] **Co** = Cornelli;[30] **D** = Dangoumau;[31,32] **Em** = Emanueli;[33] **HS** = Hsu Stoll;[34] **I** = Irey;[35] **Jo** = Jones;[36] **KL** = Karch and Lasagna;[10] **Ki** = Kitaguchi;[37] **Kr** = Kramer;[38-40] **N** = Naranjo;[41] **Par.** = parameter; **St** = Stephens;[42] **V** = Venulet;[43] **W** = Weber.[44]

94% and 83%) and low rates of specificity (average of 8% and 21%, respectively; NPV of 4% and 36%).

Specificity and NPV estimations are less stable (wider 95% CIs) as a result of the small number of cases considered non-drug related by the GI.

The Australian,[29] Cornelli,[30] Emanueli,[33] Hsu Stoll,[34] Irey,[35] Jones,[36] Kitaguchi,[37] Kramer,[38-40] Naranjo[41] and Venulet[43] algorithms imputed all the serious adverse events as ADRs.

The Cornelli,[30] Emanueli,[33] Hsu Stoll,[34] Jones,[36] Kramer[38-40] and Naranjo[41] algorithms imputed all the unexpected adverse events as ADRs.

All the algorithms, except Blanc,[11] Karch and Lasagna[10] and Weber[44] presented sensitivities >90% and specificities <18%, in the total sample and within serious and unexpected reports.

Compared with the total sample, in the group of unexpected cases, the sensitivity of Blanc,[11] Karch and Lasagna[10] and Weber[44] algorithms decreased 55.2% on average and the specificity increased accordingly (59.2% on average). These algorithms presented decreased ability in assessing unexpected events.

Discussion and Conclusions

A major problem hindering the validation of causality algorithms is that there is no well established gold standard. The GI method based on the WHO scale of imputation was selected as the standard for comparisons because it remains the most widely used imputation method. Its reliability lies on the small probability of obtaining different results in analysing similar conditions.

All the algorithms, except Blanc,[11] Karch and Lasagna[10] and Weber,[44] are sensitive methods for identification of ADRs, even serious or unexpected events, but they present poor specificity.

None of the algorithms presented good sensitivity, good specificity and predictive values simultaneously in the total sample and for serious and unexpected events.

A reference method was not identified. Therefore, decisional algorithms cannot replace the GI method and are not definite alternatives in the individual causality assessment of suspected ADR.

Causality assessment of ADRs using decisional algorithms is simple, explicit and can be implemented by means of computational methods. Given an algorithm's high sensitivity, even for serious or unexpected adverse events, they might be useful combined with data-mining methodologies in an automatic sequential two-stage programme of signal detection, such as those already proposed.[48] A serial multiple tests logic, where a simple and sensitive test (such as an algorithm) is generally performed first and only those reports that screen positive (at least imputed as 'possible') are gathered and recalled for further signal testing (using data-mining methodologies) thereby improving final causality-assessment specificity, deserves further investigation.

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