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ORIGINAL REPORT

The value of time-to-onset in statistical signal detection of adverse drug reactions: a comparison with disproportionality analysis in spontaneous reports from the Netherlands

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ABSTRACT

Purpose In pharmacovigilance, the commonly used disproportionality analysis (DPA) in statistical signal detection is known to have its limitations. The aim of this study was to investigate the value of the time to onset (TTO) of ADRs in addition to DPA.
Methods We performed a pilot study using individual case safety reports (ICSRs) for three drugs (Cervarix®, nitrofurantoin and simvastatin) from the Lareb spontaneous reporting database. TTO distributions for drug – ADR associations were compared to other ADRs for the same drug and to other drugs for the same ADR using two-sample Anderson–Darling testing. Statistically significant associations were considered true positive (TP) signals if the association was present in the official product information of the drug. Sensitivity and specificity for the TTO method were compared with the DPA method. As a measure of disproportionality, the reporting odds ratio (ROR) was used.
Results In general, sensitivity was lower, and specificity was higher for the TTO method compared to DPA. The TTO method showed similar sensitivity for all three drugs, whereas specificity was lower for Cervarix®. Eight additional TP signals were found using the TTO method compared to DPA.
Conclusions Our study shows that statistical signal detection based on the TTO alone resulted in a limited number of additional signals compared to DPA. We therefore conclude that the TTO method is of limited value for full database statistical screening in our setting. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—signal detection; time to onset; latency; pharmacovigilance; ADR; pharmacoepidemiology

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INTRODUCTION

Disproportionality analysis (DPA) is a common method for statistical signal detection (SSD) in spontaneous reporting systems (SRS) of adverse drug reactions (ADRs). Several methods of DPA exist, and their common goal is to detect statistically significant differences in observed-versus-expected ratios for different drug-ADR combinations.[1] Although DPA has demonstrated its value as a screening tool in recent years, it also has its limitations. One major issue is that it does not take the quality of individual case safety reports (ICSRs) into account, because it is solely based on the (relative) number of ICSRs for a certain association. SSD is subject to several types of bias, including selective reporting, notoriety bias,[1] masking[2] and the Weber effect.[3]

One of the trivial elements present in ICSRs is the time to onset (TTO) which can be defined as the duration from the start of the suspect drug until the start of the ADR. Although this information is usually applied in a qualitative manner in the analysis of ICSRs, it is quantitative in nature. For different drug–ADR combinations, the TTO distributions can vary considerably because of several factors, including the underlying mechanism of toxicity. This aspect can be used in both clinical causality assessment and SSD, as shown in previous studies.[4–11] In particular, several studies by Van Holle *et al.* have shown the additional value of

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TTO in SSD for events following immunization, using non-parametric Kolmogorov–Smirnov (KS) testing.[7,8,12] However, these studies were limited to vaccines and therefore concern a rather selective population of mainly healthy individuals. Additionally, TTO distributions for ADRs related to vaccines may differ from those related to non-vaccines because of several factors. Most importantly, vaccines are generally administered once whereas many non-vaccines are administered on a daily basis, both temporary and chronically. Therefore, ADRs with longer TTOs may be less likely to be reported for vaccines. Furthermore, the spectrum of ADRs related to vaccines, and therefore their TTO distributions, differs from that of non-vaccines. For instance, a large proportion of vaccine-related ADRs concern injection site disorders with a typical TTO whereas most ADRs related to non-vaccines in our database are reported for drugs that are taken orally. Taking these differences in TTO distributions into account, the Anderson–Darling (AD) test seems more appropriate for databases containing both vaccines and none vaccine ICSRs, because it has more power than the KS test.[13]

In this study, we used two-sample AD testing to investigate how TTO-based signal detection performs compared to DPA in a spontaneous reporting database containing ICSRs of both vaccines and non-vaccines. In order to capture the diversity of the database, we analyzed three different types of drugs used in patient populations with different demographical and clinical features. The objective is to determine if TTO-based signal detection can be a useful addition to standard DPA in a database containing reports related to both vaccines and non-vaccines.

METHODS

In this proof of concept study, differences in TTO distributions for selected drug–ADR combinations were tested using two-sample AD testing. The performance, in terms of sensitivity and specificity, was compared with DPA based on the reporting odds ratio (ROR).[14]

Data source

The data for this study were derived from the database of the Netherlands Pharmacovigilance Centre Lareb. This database consists of spontaneous reports of suspected ADRs reported by both healthcare professionals and consumers from all parts of the Netherlands. All reports (both serious and non-serious) since the start of reporting (1986) until the cut-off date (31 July 2015) were eligible.

Drug and ADR selection

In order to cover the diversity of ICSRs in our database, three drugs with different indications and different patient populations were selected: bivalent human papillomavirus vaccine (Cervarix®), used for prophylaxis in a young and relatively healthy female population; nitrofurantoin, used for uncomplicated urinary tract infections in a diverse population in terms of age and co-morbidities; and simvastatin, used in a generally older population with multiple co-morbidities. Drugs were classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system, using the level of chemical substance (fifth level).[15] ICSRs with suspected drugs containing more than one active substance (e.g. simvastatin/ezetimibe), and those with drugs reported as interacting were excluded. Additionally, duplicate reports were excluded, based on the duplicate detection procedure used at Lareb during assessment of individual ICSRs.

All ADRs with an exact TTO were selected and coded using the preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0). The TTO was considered to be exact if both the start date of the suspect drug and ADR were full dates (i.e. yyyy-mm-dd). This was done because the majority of associations in the database has a TTO of several days to weeks, and using partial dates would introduce too much statistical imprecision.

Statistical testing

Statistical testing for differences in TTO distributions was performed using the two-sample AD test. The test statistic of this non-parametric test belongs to the quadratic class of empirical distribution function (EDF) statistics and determines if two samples come from the same continuous distribution. Compared to the KS test, it has in general more power and is more sensitive to differences in the tails of the distributions, shift, scale or symmetry.[13,16] For each drug – ADR combination, the TTO distribution was compared with two comparator distributions:

- The TTO distribution of all other ADRs for the same drug
- The TTO distribution of all other drugs for the same ADR

Each ICSR was used only once per statistical test. In other words, if an ICSR was used for the drug – ADR

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combination to be tested, it was not used for "all other ADR for same drug" or "all other drugs for same ADR".

The null hypothesis for each test was that both EDFs came from the same distribution and the alternative hypothesis was that both EDFs did not come from the same distribution (two-sided testing). The significance level was set at $\alpha = 0.05$.

DPA was performed using the ROR, which is similar to the odds ratio in a case–control study[17] and can be calculated from a standard 2×2 table using the formula ROR = ad/bc (see Table 1). Additionally, a 95% confidence interval (95% CI) is calculated and the ROR is considered statistically significant if the lower limit of the 95% CI exceeds 1.

Sensitivity and specificity analyses

The performance of the TTO method in terms of sensitivity and specificity was compared with the ROR, which is the standard method for SSD at Lareb. Sensitivity and specificity were defined as described in Equations (1) and (2).

$$Sensitivity = \frac{TP}{TP + FN} \quad (1)$$

$$Specificity = \frac{TN}{TN + FP} \quad (2)$$

where TP is the number of true positive, TN is the number of true negative, FP is the number of false positive and FN is the number of false negative signals. The summary of product characteristics (SPC) was used as a reference for signal classification (see Table 2). For each ADR described in the SPC, the applicable MedDRA PTs were matched. Cases of reported symptoms not listed in the SPC that were considered highly indicative of a diagnosis mentioned in the SPC were discussed with a clinically qualified assessor. Based on the outcome of the discussion, it was decided whether the association was considered to be present in the SPC or not. Although there are issues and limitations regarding its use as a gold standard, the SPC has been used in several studies aimed at SSD.[7,18] For each of the drugs investigated, one SPC was used as the gold standard. In case of multiple Marketing Authorization Holders (MAHs) for one drug the SPC of the innovator was used.

Because the AD test is sensitive to both dispersion and skewness, outliers may influence the results and performance. Therefore, sensitivity and specificity were determined for the full dataset without restrictions and for the dataset restricted to ICSRs with a TTO of 0 – 30 days. Because the TTO has no effect on disproportionality, separate sensitivity analysis for the 0 – 30 day time window for the DPA method was not applicable.

Statistical analyses were performed with R statistics version 3.2.3.

Table 1. Two-by-two contingency table for calculation of the reporting odds ratio (ROR)

	ICSRs with event	ICSRs with other events
ICSRs with the suspect drug	a	b
ICSRs with other drugs	c	d

ICSR = Individual Case Safety Report; ROR = ad/bc.

RESULTS

Descriptive statistics

A total of 3313 ICSRs, containing 6660 drug – ADR associations, were included into the analysis. The total number of unique drug–ADR associations was 252. For the analysis of the 0 – 30 days time window, the numbers are similar, with the exception of the relatively high percentage of drug – ADR associations with a TTO of more than 30 days for simvastatin (see also Table 3). This was mainly because of the high number of reports of simvastatin-associated musculotendinous complaints. The percentage of reports containing an exact TTO was 79.1% for Cervarix®, 85.2% for nitrofurantoin and 73.6% for simvastatin.

Table 2. Definitions of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) signals

	TTO	ROR
True positive	Both AD tests $p < 0.05$ and ADR present in SPC	LL95%CI > 1 and ADR present in SPC
True negative	At least one AD test $p \geq 0.05$ and ADR not present in SPC	LL95%CI ≤ 1 and ADR not present in SPC
False positive	Both AD tests $p < 0.05$ and ADR not present in SPC	LL95%CI > 1 and ADR not present in SPC
False negative	At least one AD test $p \geq 0.05$ and ADR present in SPC	LL95%CI ≤ 1 and ADR present in SPC

AD = Anderson–Darling; LL95%CI = lower limit of 95% confidence interval; ROR = reporting odds ratio; SPC = summary of product characteristics; TTO = time to onset.

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Table 3. Overview of number of reports included in the study

	Number of ICSRs	Total number of ADRs*	Number of unique ADRs*
Cervarix®			
All	966	2757	55
0–30 days	929	2664	54
Nitrofurantoin			
All	893	1592	76
0–30	848	1561	76
Simvastatin			
All	1454	2311	121
0–30	811	1319	78

*coded as MedDRA preferred term.
ICSR = individual case safety report; ADR = adverse drug reaction.

Performance

From the 252 unique associations, 42 TP signals (17%) were identified by the TTO method compared to 94 by DPA (37%). For the full dataset, sensitivity ranged from 0.27 to 0.32 for TTO and from 0.57 to 0.77 for DPA, where sensitivity was highest for Cervarix® in both methods. Sensitivity for TTO decreases when the time window is restricted to 0 – 30 days, particularly for simvastatin. The TTO method showed a higher specificity (TTO, 0.75 – 0.98; DPA, 0.42 – 0.79) (see Table 4 for more details). Eight associations were identified by the TTO method that were not identified by DPA. Conversely, 59 associations were identified by DPA and not by TTO.

Because sensitivity was in general low for the TTO method, empirical cumulative distribution (ECD) plots were made for the TTO of several drug – ADR associations to provide a visual insight into the TTO distributions. For illustrative purposes, one TP signal (nitrofurantoin – interstitial lung disease) and one false negative signal (simvastatin – myopathy) were selected based on the well-known causal relationship of both associations.[19,20]

DISCUSSION

In this study, we investigated the performance in terms of sensitivity and specificity of TTO-based signal detection versus DPA, to see if the TTO method would be a valuable addition to DPA. The quality of the TTO data in our database was satisfactory with an exact TTO reported in approximately 75% – 85% of the analyzed associations. For simvastatin, the relatively high percentage of drug – ADR associations with a TTO of more than 30 days may be explained by the fact that it was the only drug in our study that is used chronically. The major difference between the current study and the initial study by Van Holle *et al.*[7] is the use of the AD test instead of the KS test. Because of its higher power in case of, among others, differences in the tails of the distributions, we consider the AD test to be more appropriate in databases containing both vaccines and non-vaccines, because of the (theoretical) diversity of TTO distributions in these databases. In our study, we used three types of drugs with different indications and user populations as a proxy for the diversity of our database. It should be noted, however, that this selection was somewhat arbitrary, and a different set of drugs could have been used for our study. On the other hand, our results regarding sensitivity were similar for all three drugs and clearly show that the added value of the TTO method is limited and in our opinion a different set of drugs would not have made a substantial difference.

One could debate whether pharmacokinetics (PK) should have been incorporated in the analyses, because there are several parameters that may influence the TTO, such as the half-life ($t_{1/2}$) of the drug or its time to maximum plasma concentrations (t_{max}). We did not consider this appropriate for several reasons: First, PK is not fully informative about the presence of the drug in the body. Rather, it is a measure of the drug concentrations

Table 4. True positive signals, sensitivity and specificity for TTO and DPA signal detection for the total dataset and the 0 – 30 days time window

	Cervarix®		Nitrofurantoin		Simvastatin	
	DPA	TTO	DPA	TTO	DPA	TTO
True positive signals (%*)						
All	24 (44)	10 (18)	34 (45)	15 (20)	36 (30)	17 (14)
0–30 days		9 (17)		6 (8)		6 (8)
Sensitivity						
All	0.77	0.32	0.63	0.29	0.57	0.27
0–30 days		0.29		0.12		0.15
Specificity						
All	0.42	0.75	0.79	0.88	0.79	0.98
0–30 days		0.87		1.00		0.97

*Percentage of the total number of association per drug.
DPA = disproportionality analysis; TTO = time to onset.

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in the blood. For several drugs, however, concentration in different tissues can be substantially different from those in plasma. As a result, the tissue concentrations for each drug should be taken into account depending on the type of ADR (e.g. concentrations in skin tissue for dermatological ADRs, concentrations in cerebral spinal fluid for central nervous system ADRs etc.). In addition, it is not clear when an ADR may occur. This may be the case when the maximum concentration has been reached, but possibly also sooner or later. Second, the TTO of an ADR cannot be predicted by the PK of the drug alone. This typically applies to type B ADRs, but even type A ADRs can have a longer TTO than would be expected based on their PK. For instance metformin-induced diarrhea can still occur several months or even years after initiation.[21] Third, several drugs have active metabolites with their own PK characteristics, and it would not be feasible to incorporate this into our study.

In general, the sensitivity for the TTO method was low compared to DPA, but showed similar results for the three drugs. The low sensitivity may be because of several causes. First, reporters tend to report the TTO in different units as its duration increases. Therefore, it is likely that actual TTOs of, for example, 8 or 10 days, respectively, will both be reported as one week. This phenomenon leads to TTO clustering, possibly resulting in decreased statistical precision. Second, most associations in our study have a relatively short TTO, which makes it more difficult to achieve statistical significance. It would be of interest to investigate the current method in a specific dataset containing drug – ADR associations with a longer TTO to see how this will affect performance. Third, our definition of a TP signal required both AD tests to be statistically significant for each association. This may have been an overly conservative approach, but enables us to make a proper comparison with the results from Van Holle *et al.*[7] Fourth, the use of the SPC as the gold standard has its limitations because not all ADRs listed in this document have a proven causality. Vice versa, if an ADR is not listed in the SPC, it does not necessarily mean that a causal relationship is absent. The appropriateness of use of the SPC as gold standard depends on the goal of signal detection. Because SRS are initially intended to detect hitherto unknown associations, the SPC is less suitable for validation purposes, because, ADRs are listed in this document with a more or less proven causal relationship. However, we expect reporters to submit ADRs with an established causal relationship more frequently. It should be noted that the above also affects the performance of DPA, and can therefore not be the only explanation for the difference in performance between these two methods.

Although specificity was in favor of the TTO method compared to DPA, we considered the added value of introducing TTO into the analysis of our full dataset to be limited. In SSD with spontaneous data, it is important not to miss a true signal, and as a result, a high sensitivity (albeit at the cost of a higher amount of false positives) is considered more important than a high specificity.

In order to analyze the effect of outliers on performance, we decided to perform an additional analysis with a restricted TTO time window of 0 – 30 days. This analysis resulted in a decreased sensitivity, most likely because of the lower number of cases compared to the full data set, resulting in decreased statistical precision.

The time-to-onset ECD plots did not reveal clues that might explain the low sensitivity for this method. As can be seen from Figure 1b, ECD curves that seem similar at visual inspection can still result in a statistically significant difference for the AD test ($p < 0.001$). Conversely, two visually distinct curves (Figure 1d) showed no statistically significant difference ($p = 0.352$). Although sensitivity was low for the TTO method, this method could still have been a valuable addition as a screening tool if the identified TP signals were different from those identified by DPA. However, because this was the case for only eight associations (where 59 associations identified by DPA were not identified by TTO), this strengthens our conclusion of the limited value of the TTO method for full database screening. Because the Lareb database has a limited number of reports compared to, for example, the EudraVigilance database, it would be of interest to investigate the performance of our method in a larger database. This was, however, beyond the scope of our study because the intention was to develop an additional SSD method specifically for the Lareb database. Additionally, using a larger dataset would have led to results that cannot automatically be extrapolated to our local database because different databases show different results for SSD methods.[22] However, the method we used can be tested in other databases as well, but in our opinion, the results acquired would only apply to that particular database.

Based on the current results, the TTO method does not provide additional value to DPA and does not seem suitable for general screening purposes. However, this does not imply that the method described may be of additional value for specific drugs or ADRs with a distinctive time of onset. Furthermore, as mentioned above, our approach may have been rather conservative because a TP signal required both AD test results to be statistically significant. For future research, it would be of interest to investigate how different definitions of a TP signal would influence sensitivity and specificity. We

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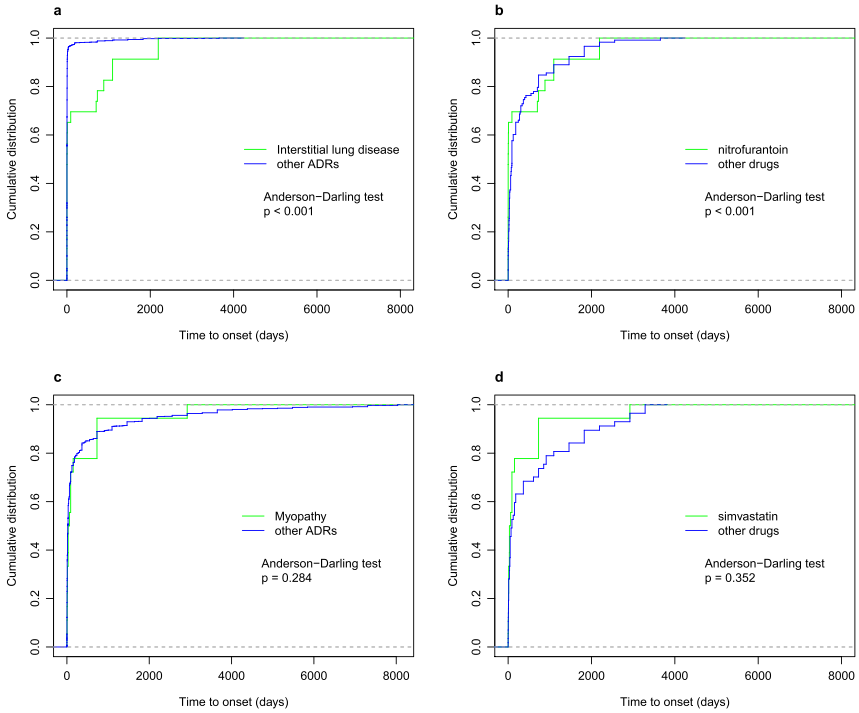

Figure 1. Empirical cumulative distribution plots of the TTO for the true positive signal nitrofurantoin—interstitial lung disease ($n = 23$) and the false negative signal simvastatin—myopathy ($n = 18$). a) nitrofurantoin—interstitial lung disease (green) versus nitrofurantoin with other ADRs (blue). b) nitrofurantoin—interstitial lung disease (green) versus interstitial lung disease for all other drugs (blue). c) simvastatin—myopathy (green) versus simvastatin with other ADRs (blue). d) simvastatin—myopathy (green) versus myopathy for all other drugs (blue). $p = p$-value of the two-sample AD test [Color figure can be viewed at wileyonlinelibrary.com]

hypothesize that comparing the EDF for a drug – ADR association with that for all other ADRs for the same drug will lead to different results than the comparison with the same ADR for all other drugs. Because sensitivity for the TTO method was similar for the three drugs (range 0.27 – 0.32), the method seems robust enough for additional research at first sight.

It should be emphasized that the results of this study should be seen in light of the full pharmacovigilance process. For the process at Lareb, this means that any result from any method of SSD is always followed by case-by-case review if a possible signal is identified. And in addition to SSD, all ICSRs received by healthcare professionals and consumers are assessed in a case-by-case manner, increasing the likelihood of finding new signals. It is the opinion of the authors that using a single method only for signal detection is a suboptimal approach and increases the risk of missing signals.

CONCLUSIONS

Our study shows that TTO-based SSD was less sensitive than the DPA-based method we used for comparison, identifying only a small number of additional associations as possible signals. Therefore, we consider it of no additional value for full database screening purposes in its current form. Whether TTO is the method that can be useful with a different definition of a true positive signal, or in screening subsets of drug – ADR associations, remains to be investigated.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work

KEY POINTS

- Currently, disproportionality analysis is one of the major methods in statistical signal detection in pharmacovigilance, but has its limitations
- We investigated the additional value, in terms of sensitivity and specificity, of the time to onset of an ADR in statistical signal detection
- The small number of true positive signals resulted in a low sensitivity for the TTO method compared to the DPA method
- TTO-based signal detection did not provide additional value for full database screening purposes in its current form

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