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ORIGINAL ARTICLE

Parametric time-to-onset models were developed to improve causality assessment of adverse drug reactions from antidiabetic drugs

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Abstract

Objectives: The aim of this study was to investigate whether the time to onset (TTO) of common adverse drug reactions (ADRs) of antidiabetic drugs could be modeled using parametric distributions and whether these TTO distributions were dependent on patient characteristics. Furthermore, information relevant for daily clinical practice was to be obtained.

Study Design and Setting: We performed an exploratory TTO modeling study, using a cohort of diabetes mellitus patients. Four parametric distributions (exponential, lognormal, gamma, and Weibull) were compared in terms of their goodness of fit. Covariates that could influence the TTO were investigated. In addition, TTO mean and median values were summarized for use in clinical practice.

Results: Overall, the gamma distribution provided the best goodness of fit, although differences with the Weibull distribution were negligible in some instances. No differences in TTO distributions between different antidiabetic drugs for a given ADR were found. The TTO was influenced by suspected concomitant medication for metformin-associated diarrhea. Mean and median TTO values were similar for different drug−ADR combinations.

Conclusion: Our study shows that the TTO of common ADRs associated with antidiabetic drugs can be modeled using the gamma or Weibull distribution. Furthermore, clinically relevant information about these ADRs can be obtained.

Keywords: Parametric modeling; Time to onset; Latency; Pharmacovigilance; ADR; Causality assessment

1. Introduction

Every patient using a drug is at risk of developing adverse drug reactions (ADRs). These ADRs are a heterogeneous group of medical conditions with different pathophysiological mechanisms, which can be mild and transient in nature, but also life threatening or even fatal. The HARM (Hospital Admissions Related to Medication) study showed that, in the Netherlands, approximately 5.6% of unplanned hospital admissions were drug related. In addition, the results showed that 46.5% of these drug-related admissions were possibly preventable [1].

Before registration of a drug, it has been tested in clinical trials for both efficacy and safety, resulting in, among others, a spectrum of ADRs that can be expected when using the drug. The information regarding ADRs is present in the summary of product characteristics (SPC), a regulatory document approved by the health authorities, containing the main characteristics of a drug, including ADRs that have been identified in research. Unfortunately, most of the information regarding ADRs that is present in the SPC of approved drugs is limited to the frequency of occurrence of the ADRs that can be expected. Although this provides the medical community with valuable information regarding the risk of experiencing a certain ADR on a population basis, it is less informative for causality assessment in an individual patient. In other words, when a physician sees a patient with a possible ADR, the frequency of occurrence in the population using the drug is of limited use to determine the actual causality in his/her patient, and additional information is required for causality assessment. As mentioned in Hill's criteria for causation, temporality is

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What is new?

- Although the time to onset (TTO) is an important parameter in the causality assessment of adverse drug reactions (ADRs), limited information about it available to physicians and their patients.
- Parametric modeling of the TTO can provide useful information in clinical decision making in individual patients.
- The gamma and Weibull distribution can be used to model the TTO of common adverse events in patients using antidiabetic drugs.
- New information regarding known ADRs can be found through TTO modeling.
- Although a long TTO may not seem indicative of a causal relationship with a drug, it should not be dismissed in advance.

one of the aspects that should be taken into account [2]. When this is applied to causality assessment of possible ADRs in individual patients, an important variable is the time to onset (TTO) of the event [3−7], which can be defined as the time from the start of the suspected drug(s) till the start of the patient's complaints. Intuitively, a long TTO may not always seem indicative of a causal relationship. However, depending on the drug, the type of ADR and the underlying mechanism of toxicity, the TTO can vary considerably in length. For instance, visual field defects due to vigabatrin use can manifest years after the start of the treatment [8], whereas varenicline-induced nausea usually occurs within several days [9]. During the period of drug use, the risk of developing the ADR is not necessarily a constant but can be seen as a function that changes over time. Previous studies seem to indicate that parametric TTO modeling can be used as a signal detection tool in cohorts of patients starting treatment [10,11] and using registry data of spontaneous reports of adverse events [12]. The parametric methods either statistically test for a nonconstant hazard (rate of occurrence of the adverse event) [10,11] or allow for visual inspection of the hazard over time for the parametric model providing the best fit to the data [12]. In addition, nonparametric methods have been considered for comparing the TTO distributions of adverse events and different vaccines in both spontaneous reports and cohort data [13,14] and for assessing temporal associations between adverse events and medication use using electronic patient record data [15]. In pharmacovigilance, a signal detection tool can be used to pick up signals of ADRs previously not recognized, whereas a prediction tool could help to determine causality in individual cases. The aforementioned studies used the exponential, normal, lognormal, and Weibull distributions for modeling, but not the gamma distribution, which is commonly used in failure time models of continuous variables [16]. In addition, they did not investigate the possible effect of covariates that might influence the TTO of ADRs. This could, however, be relevant when assessing causality and determining optimal treatment in individual patients.

In this exploratory study, we investigated whether the TTO distribution of common ADRs in a cohort of type 2 diabetes mellitus (T2DM) patients using antidiabetic drugs could be modeled into a cumulative survival function using different parametric distribution models. We investigated whether the TTO distribution depended on age, sex, and suspected concomitant medication. In addition, possible differences in TTO between different groups of antidiabetic drugs, given a certain common ADR, were investigated. Finally, descriptive information that could be relevant for prescribers and their patients regarding TTO of drug−ADR combinations was obtained.

This study provides insight into the distribution of TTO of some common ADRs in patients using antidiabetic drugs and will assist physicians and their patients to determine whether complaints experienced by patients are drug related or not.

2. Methods

2.1. Patient selection

For this exploratory study, we used an existing cohort of patients with T2DM from the Lareb intensive monitoring (LIM) system. This is an observational Web-based intensive monitoring system developed to capture more detailed information on the time course of ADRs compared with spontaneous reporting. Patients were eligible if they had T2DM and started using an antidiabetic drug less than 2 weeks before inclusion. A period of 2 weeks was chosen to minimize the risk of recall bias. Data regarding the start of the drug and the start of the complaints were obtained through questionnaires that were sent 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 1 year after the patient started using the antidiabetic drug. More details regarding the LIM methodology have been described previously [17,18]. For our study, patients who started treatment with an antidiabetic drug that was a combination of more than one active substance were excluded from the analysis.

2.2. ADR selection

For each patient, all reported ADRs were screened. If a patient experienced more than one different type of ADR, the first occurrence of each type of ADR was included for analysis. Consequently, if a patient experienced the same type of ADR more than once, only the first occurrence after the start of the antidiabetic drug was included. ADRs were selected for analysis based on five criteria.