The case-crossover method to analyse registry data on rare Severe Cutaneous Adverse Reactions (SCAR)

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Introduction
Severe cutaneous adverse reactions (SCAR) like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) – the more severe form of SJS – are rare reactions induced by various drugs. The estimated incidence of SJS or TEN is about 1-2 cases per 1 million persons per year. As both reactions are marked by substantial morbidity and high mortality (the overall death rate is about 20%), the goal of the Dokumentationszentrum schwerer Hautreaktionen (dZh) in Freiburg is to systematically collect data of all patients with SJS and TEN and also patients with other forms of SCAR in Germany. To reach this goal the dZh actively contacts hospitals and departments likely to treat such patients in periodical intervals.
One of the methodological challenges in this setting is to detect drugs causing SJS and TEN and to estimate their risk. Since the registry contains only cases, standard methods like multivariate logistic regression used in case-control studies cannot be used. As an alternative, the case-crossover method for analyzing case series (Maclure, 1991) could be applied. The aim of our presentation is to evaluate this method for this setting. Using the data of a case-control study (EuroSCAR study), conducted by the dZh in cooperation with partners from five other countries, will allow us to compare the case-crossover method with the standard method for case-control studies. Furthermore, differences between the estimators of the corresponding odds-ratios are investigated in general.

Study Design
The EuroSCAR study is an international case-control study, conducted in six countries from 1997 until 2001. Cases were actively detected patients, admitted to an hospital with a diagnosis of SJS or TEN. For each case three controls matched on age, gender, region and date of interview were enrolled among patients hospitalized for an acute condition which was not suspected to be drug induced. For cases and controls detailed data including drug exposure in the four weeks before hospitalization was documented using a standardized questionnaire. A group of experts reviewed all cases and controls for validation of the reaction or eligibility, respectively, and determined an indexday as the day of onset of the reaction for cases or of the acute condition for controls.

Statistical Methods
For analysing the case-control study multivariate logistic regression analysis was used as the standard method to estimate the risk of drugs causing SJS or TEN. As exposure of specific drugs is sometimes very low among cases and controls, exact methods are used.
The case-crossover method proposed by Maclure for analysing case series assumes that each case can serve as its own matched control. Since this design was originally developed to examine transient effects of brief exposure on an acute event, it is stringent that for each patient an effect period just before the event and an earlier control period must be defined. The risk can then be estimated using the Mantel-Haenszel estimator for matched pair analysis where only discordant pairs will be considered.

Results
During the EuroSCAR study 513 potential cases and 1763 potential controls were enrolled. After review by an expert group 379 cases of SJS or TEN and 1505 controls could be included in the analysis. Multivariate logistic regression for the case-control analysis and the case-crossover method were applied to the data. It is shown that the choice of effect and control period regarding position and length is highly influential on the results.

Discussion
The case-crossover method seems to be a valuable alternative to estimate the risk of drugs which have a relatively short half-life. As each case is used as its own control, confounding by constant characteristics is eliminated. This is one of the problems in case-control studies regarding control selection. On the other hand, careful definition of effect and control period must be considered as crucially important.

References

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