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LETTERS TO THE EDITOR

Studying the causes of adverse drug reactions: circumvent the warning-interfered bias using the case–case comparison approach

To the Editor:

The case–control approach is often used in the spontaneous reporting system (SRS) to examine whether a drug may cause an adverse drug reaction (ADR). Evans et al. [1] proposed to take all ADRs other than the ADR of interest in the SRS database as the controls. But the controls such defined may include some events that are also related to the drug under study; hence, the study will underestimate the true effect. Rothman et al. [2] proposed to select only those events known a priori not to be associated with the drug under study to be controls. However, such ''clean'' control events may not be easy to find if the drug under study is notorious for many ADRs or if that prior knowledge is lacking.

Here, we introduce a new form of bias that can not be solved simply by dealing with the controls. We note that once the regulatory or other medical authorities warn that a certain drug might be responsible for a certain ADR, the medical staffs may be driven to report those drug–event pairs to the SRS even if the drug is actually not associated with the event, creating what we call a ''warning-interfered bias.''

To circumvent the problem, one can divide the case itself into two or more case subgroups, and make a comparison among the case subgroups themselves [3]. For example, supposed that following a warning that erythropoietin (EPO) might be responsible for anemia [4], a researcher sets out to examine whether such an association is real. He decides to divide all reported anemia cases in the SRS into two case subgroups of pure red-cell aplasia (PRCA) and non-PRCA (by reviewing the medical charts and the laboratory data). The grouping into PRCA and non-PRCA is based on his or her knowledge that the EPO antibody, if formed, can only destroy the red cell line in the bone marrow [5], causing the PRCA but not the non-PRCA. The researcher then compares the EPO-using proportions between these two case subgroups. If the proportion is statistically higher in the PRCA than in the non-PRCA, he concludes that the EPO–PRCA association is real, otherwise it is not. The researcher can be confident about his or her claim is because of this: although the odds of EPO exposure proportion in both PRCA and non-PRCA are increased by the warning-interfered bias, the degree of such bias should be the same in these two case subgroups and thereby can reasonably be canceled out using an association measure such as the odds ratio.

The ''case–case comparison approach'' described herein will be useful for studying the causes of ADRs in SRS, when the ADR of interest consists of two or more case subgroups that each has disease mechanism distinct from one another and the drug under study is only responsible for certain subgroup(s). Examples other than the above EPO–PRCA association could be the association between vancomycin and immune-type thrombocytopenia [6], and the association between isoniazid and hepatocellular-type hepatoxicity [7], etc. In these circumstances, the elusive warning-interfered bias can be circumvented using the case–case comparison approach.

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