The principal concern of pharmacovigilance is the timely discovery of adverse events that are novel in terms of their clinical nature, severity and/or frequency as early as possible after marketing with minimum patient exposure. We are currently studying computational signal detection algorithms, also known as data mining algorithms (DMAs), in large post-marketing safety databases in order to determine whether these automated methods might usefully supplement our traditional pharmacovigilance strategies. The reporting of clinical observations by the alert practitioner is the crucial first step in pharmacovigilance surveillance. Since feedback to reporters is an important component of public health surveillance, we would like to share findings from our retrospective data mining exercise with dobutamine-induced myoclonia to illustrate how evolving technologies and quantitative methods are being evaluated in the hope of fully utilizing clinical observations contained in drug safety databases.

Most DMAs under investigation are based on some form of disproportionality analysis. While the precise operational details of each DMA may differ, they all use the internal association structure of the database to derive the number of reports that might be expected if drug and event were distributed independently in the database. If the number of a given drug–event combination (DEC) significantly exceeds the number that is expected based on the model, then the particular DEC may be considered to be disproportionally represented in the database and may be a potential signal in certain clinical contexts [2].

There are two basic categories of these techniques: ‘simple’ or ‘classical’ disproportionality analysis such as proportional reporting ratios (PRRs) and methods that use additional statistical adjustments and Bayesian modelling, such as the multi-item gamma poisson shrinker (MGPS) and the Bayesian confidence propagation neural network. Both approaches provide metrics related to the background probability of drug (across all events) and event (across all/most drugs) to derive the aforementioned internal control or model of expected reporting frequency in the absence of data on the level of drug exposure.

We retrospectively applied the technique of PRR and MGPS for dobutamine and the event terms myoclonus and myoclonic epilepsy using commonly cited protocols [3,4] to screen data retrospectively from the US Food and Drug Administration Adverse Event Reporting System (AERS). No other relevant event terms were identified. AERS data are generally composed of post-marketing published and unpublished reports submitted by consumers, health professionals and drug manufacturers.

A signal of disproportionate reporting with dobutamine was generated with PRR for myoclonic epilepsy in 1999 (1993 was the first year a report for this event was in the database) based on five cases. There was no signal obtained with MGPS using the cited protocol and there were no reports for the event term myoclonus. It should be noted that a ‘signal’ of disproportionate reporting with a DMA does not establish or even suggest causality and does not provide information on the possible contribution of co-morbid illnesses (e.g. renal failure), only that there is a possible DEC worthy of further investigation in certain clinical contexts. A significant limitation of our analysis is that retrospective data mining exercises may not accurately reflect prospective data mining practices in ‘real-life’ pharmacovigilance settings. An additional limitation of this exercise was our inability to access individual comprehensive patient data.

Our analysis illustrates the potential of DMAs to usefully direct the attention of drug safety reviewers faced with the...
challenge of screening very large safety databases. It also illustrates the potential for simple forms of disproportionality analysis (PRR) to identify potentially meaningful DECs that fail to be identified by certain Bayesian methods such as MGPS, when commonly cited thresholds are used [5,6]. The cost of such enhanced sensitivity could be an over-abundance of ‘signals’ including ‘false-positive’ signals not reflective of causality that would be likely to require additional triage criteria for practical implementation. The Bayesian methods were developed in the hope of improving the signal to noise ratio by down weighing signals associated with DECs for which there are small numbers of reports with corresponding statistical instability. However, they may also ‘filter out’ real ‘signals’ either absolutely or relatively in terms of timing, when compared with simple disproportionality analysis. However, since these methods currently are unvalidated and the choice of thresholds somewhat arbitrary and adjustable, performance differentials between DMAs using commonly cited thresholds are of uncertain clinical significance.

We and other drug safety specialists are continuing to study the proper positioning of these newer pharmacovigilance techniques within the universe of methods that have been used historically for routine signal detection. Our preliminary conclusion is that DMAs are promising tools but should only be considered as potential supplements to, not substitutes for, standard signalling strategies. Finally, we would like to re-emphasize the crucial role of clinicians as the first line of post-marketing safety surveillance by their publishing and/or reporting of unanticipated, possibly drug-related events to the manufacturer, not substitutes for, standard signalling strategies. DMAs using commonly cited thresholds are of uncertain clinical significance.

DC cardioversion during continuous veno-venous haemofiltration

Sir,

Recently, we delayed starting continuous veno-venous haemofiltration (CVVH) treatment because we were reluctant to perform direct current (DC) cardioversion during CVVH. In the end, it proved to be no problem.

Case. A 15-year-old, previously healthy, girl was admitted with acute fulminate liver failure of unknown origin. She received an orthotopic liver transplantation without any subsequent problems. One day post-operatively, she was hypotensive in spite of noradrenaline, and became anuric with normal blood electrolytes, but rising BUN and creatinine. Furthermore, she developed an atrial flutter with a heart rate of 180 b.p.m. for which medical treatment was started.

It was decided to start renal replacement therapy. Because of her circulatory problems, we opted for CVVH treatment. However, as there was nearly no reaction to the d-sotalol given for the atrial flutter, there was a possible need for DC cardioversion.

We were all reluctant to try cardioversion during CVVH because it was not clear whether the system was adequately protected against electric cardioversion.

In the literature, we could not find any publications in which it was stated if this would give any problems. Therefore, we delayed the start of the CVVH treatment.

After several hours, when the heart rhythm seemed to normalize, we started CVVH. Unfortunately, after another few hours, she deteriorated again and DC cardioversion was needed. We phoned Hospal, the makers of the CVVH machine. They said there should be no problem although, according to them, it had never been tried before. It was stated in the machine description that there would be no interaction. Indeed there was no problem at all. Our patient was cardioverted (20 J, 50 J, 50 J) without any change in blood flow or on the CVVH machine, and 3 h later had to be cardioverted again (50 J, 70 J).

After each cardioversion, the atrial flutter reinitiated after a short period. Finally, normal sinus rhythm was obtained with amiodarone. The patient recovered completely.

Comment. DC cardioversion during CVVH treatment led to no interference in our setting. After all, we delayed the CVVH treatment unnecessarily.

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