Letter to the Editors

A case report of rhabdomyolysis with pentamidine that prompted a retrospective evaluation of a pharmacovigilance tool under investigation

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A report by Delobel and Parinaud [1] describing an association between pentamidine and rhabdomyolysis caught our interest. Rhabdomyolysis is an event of particular concern to public safety because of its medical importance, and high drug-attributable risk. The authors noted that this association is not listed as an adverse effect either by drug manufacturers or in reviews of pentamidine and that only a few cases have been reported in the literature. Recognizing associations between drugs and adverse events can be extremely challenging given increasing volumes of postmarketing safety data that must be screened for potential signals of novel adverse events. In an effort to enhance our capability to detect novel adverse events in a timely manner, we are currently studying computational signal detection algorithms, also known as data mining algorithms (DMAs), in large postmarketing safety databases in order to determine whether these automated methods might usefully supplement our traditional surveillance strategies.

Conceptually, DMAs can be viewed as consisting of two broad categories of techniques: so-called simple disproportionality analysis such as proportional reporting ratios (PRRs) [2], and methods that use additional statistical adjustments and Bayesian modelling such as the multi-item gamma-Poisson shrinker (MGPS) [3]. While Bayesian modelling may improve signal-to-noise ratio, it may be associated with some decreased signalling capacity when commonly cited thresholds are used [4].

Prompted by the aforementioned publication, we set about to compare time to appearance of replicated (i.e. two drug-specific case reports) findings in the published literature of anti-infective-induced rhabdomyolysis with timing of first signal with PRR and/or MGPS.

We manually reviewed 765 citations of chemically induced rhabdomyolysis/muscular diseases in humans generated through a search of MEDLINE (1966 through week 1 of April 2004) to identify relevant drug–event combinations (DECs). We then retrospectively applied the technique of PRRs and MGPS to these drugs using commonly cited protocols [2, 3] to screen data retrospectively from 1968 through the first quarter of 2003 from the United States Food and Drug Administration Adverse Event Reporting System (AERS). AERS data are encoded using the Medical Dictionary for Regulatory Affairs (MedDRA). The following adverse event terms (AEs) were used for retrospective data mining: rhabdomyolysis, muscle necrosis, myopathy, myositis, elevated creatinine phosphokinase (CPK), and muscle injury.

There were at least two published case reports of rhabdomyolysis for four anti-infectives (pentamidine, isoniazid, sulfamethoxazole/trimethoprim, lamivudine). Table 1 shows AEs that generated a signal with either method, year in which the signal was first generated, number of reports that generated the first signal, years of publication of case reports, and whether or not rhabdomyolysis is listed in a standard drug compendium (*Drug Facts and Comparisons Online*).

Citations of rhabdomyolysis for anti-infectives involved only a small number (19) of the MEDLINE search results (765 cases). HMG-CoA reductase inhibitors were most often listed. There were no case reports for macrolides or β lactams or replicated case reports for fluoroquinolones, the most widely used antimicrobials. PRRs would have generated a 'signal' for all four DECs from 1 to 17 years in advance of publication of a second case report. MGPS would have provided a 'signal' for two of the four DECs, 5 and 7 years in advance of a second publication. With respect to pentamidine, a

Table 1

Data mining results and publication dates for relevant drugs and selected muscle injury-related adverse events

Drug (year of publication of 1st and 2nd reports of rhabdomyolysis)	PRR [event: year of first signal (no. of cases)]	MGPS [event: year of first signal (no. of cases)]	Rhabdomyolysis listed in Drug Facts and Comparisons Online?
Pentamidine (1985 and 2002)	Myopathy: 1985 (<i>n</i> = 1)	–	No
Sulfamethoxazole trimethoprim (1988 and 1997)	Rhabdomyolysis: 1996 (<i>n</i> = 11)	–	No
Isoniazid (1989 and 1995)	Myopathy: 1986 (<i>n</i> = 3)	Myopathy: 1989 (<i>n</i> = 8)	No
Lamivudine (1997 and 2002)	CPK increased: 1996 (<i>n</i> = 6)	CPK increased: 1997 (<i>n</i> = 24)	Yes
	Myopathy: 1996 (<i>n</i> = 5)	Myopathy: 1997 (<i>n</i> = 13)	
	Myositis: 1996 (<i>n</i> = 3)		

disproportional PRR for myopathy could have been generated in 1985 based on one case, which in this instance happened to be the first literature report, 17 years in advance of Delobel and Parinaud's case. It should be noted that a signal with a DMA does not establish or even suggest causality, only that there is a possible meaningful DEC worthy of further investigation in the proper clinical context.

This analysis illustrates the potential trade-off in 'sensitivity' and 'specificity' between simple forms of disproportionality analysis such as PRRs and Bayesian methods when commonly cited thresholds are used. The cost of such enhanced sensitivity could be an overabundance of 'signals' including 'false-positive' signals not reflective of causality that would probably require additional triage criteria for practical implementation.

Since commonly cited thresholds are unvalidated, somewhat arbitrary and adjustable, the clinical significance of these performance gradients is unknown. We are continuing to study the proper positioning of these newer pharmacovigilance techniques involving DMAs within the totality of methods that have been historically used for routine signal detection based on various frequency criteria and clinical pharmacological judgement. However, our preliminary conclusion is that DMAs are promising tools but should be considered only as supplements to, not substitutes for, standard signalling strat-

egies. The potential utility and performance gradients of such tools is meaningful only in the context of a comprehensive pharmacovigilance programme that utilizes multiple approaches for signal detection.

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