Who’s at risk? Identifying risk groups for adverse drug reactions using VigiBase

Yasunori Aoki, Lovisa Sandberg, Henric Taavola, Rebecca Chandler and G. Niklas Norén, Uppsala Monitoring Centre, Uppsala, Sweden

Background
In recent years, Uppsala Monitoring Centre has initiated a shift toward signal characterisation and risk group identification in support of our vision for wise therapeutic decisions. As a first attempt at broader open-ended risk group detection, we conducted a signal screening focused on identifying risk groups for adverse drug reactions (ADRs).

Objective
To explore the possibility of identifying signals of ADRs in risk groups using VigiBase, the WHO global database of individual case safety reports.

Methods

**Dataset:** 15.4 million reports retrieved on 28 August 2017 from VigiBase

Disproportionality analyses performed for drug-adverse event (AE) pairs (1) in the entire database and (2) across a range of data subsets. Drug-AE pair disproportionality overrepresented in such subsets but not in the whole data were identified.

Prioritization
Identified drug-AE-subset associations ordered by (1) vigiRank [2] for strength of evidence, and (2) weighted random sampling for subset balancing.

**Initial review**
Manual review of top-ranked drug-AE-subset associations, including review of the reports and consultation of literature in search for support for possible risk group.

**In-depth review**
In-depth review of potential signals performed by clinical experts.

**Signals of ADRs in risk groups**

Example of a subset disproportionality analysis
Information Component (IC) measures of disproportionality for a specific drug and adverse event, across different data subsets, with 99% credibility intervals for the overall analysis and 99% credibility intervals for the subsets to avoid highlighting spurious associations [1]

Example of a subset disproportionality analysis on 28 August 2017 from VigiBase
Dataset: 15.4 million reports retrieved not in the whole data were identified.

Disproportionality analyses performed for drug-adverse event (AE) subset balancing. For strength of evidence, and (2) weighted random sampling for association potential signals described in seven signals describing potential risk groups for ADRs [3].

Signals of ADRs in risk groups

**Out of 386 manually reviewed drug-AE-subset associations, 18 (4.6%) were classified as potential signals. The highest yield was identified in females (5), underweight adults (3), and the elderly (3).**

**As of August 2018, in-depth clinical reviews have been completed for 14 out of 18 potential signals, reflecting potential risk groups for ADRs [3].**

**The drug-AE pair was disproportionally overreported in the elderly subgroup and the case series (n=67) suggested causality through:**
1) plausible time to onset (n=52), 2) recovery upon withdrawal (n=47), and 3) ceftriaxone reported as the only suspected drug (n=27). Ceftriaxone is known to cause raised liver enzymes, and the elimination half-life of the drug in patients over 75 years is increased [4,5].

**Conclusions**
Signals of ADRs in risk groups can be identified from a global database using subset disproportionality analysis. Continued development of statistical screening methodologies to highlight potential signals within subgroups could usher in a new era of “precision pharmacovigilance”.

References
[5] References Disclosure

Disclosure
The authors are indebted to the national centres that contribute data to the WHO Programme for International Drug Monitoring. However, the opinions and conclusions in this study are not necessarily those of the various centres, nor of WHO.

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