Novel integrated pharmacovigilance score to prioritize torsadogenic signals: the experience of the ARITMO project

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Background. Different automated approaches are under development to support signal detection and to complement case-by-case analysis, but they are usually performed on a single database and, most importantly, do not take into account other variables such as extent of consumption and time on the market of the drugs under scrutiny.
Aim. Within the ARITMO project (www.aritmo-project.org), we developed an integrated pharmacovigilance score to improve the efficacy of traditional disproportionality approaches for prioritization of signals of Torsades de Pointes (TdP).
Methods. 11 criteria were defined to detect TdP signals for antipsychotics, H1-antihistamines and anti-infectives. Both qualitative (e.g., number of cases of TdP without concomitant cardiovascular drugs) and quantitative parameters (e.g., disproportionality measures using different denominators) were used. These criteria were weighted through a Delphi-like approach and converted into different scores using FAERS, EudraVigilance, France, German and Italian databases. These scores, previously normalized to the 0-1 range, were aggregated calculating the mean value to obtain an integrated torsadogenic score. We also separately computed information on 1) drug consumption (DDD/TID obtained from various European Countries, as a measure of drug exposure), 2) time on the market (in years, from year of first marketing to 2011), 3) consistency among archives (mean difference across scores). These three continuous parameters were converted to the 0-1 range and aggregated to obtain a measure of the uncertainty (from low to high).
Results. Out of 482 analyzed agents, 169 received an integrated score: 53 antibacterials, 38 antipsychotics, 29 antivirals, 20 H1-antihistamines, 12 antimycotics, 10 antiprotozoals, 6 antimycobacterials. Thirty drugs were retrieved only in one single database (54 in FAERS, 12 in Eudravigilance, 6 in Italy, 5 in France, and 3 in Germany). Eighteen of the top-50 ranked agents were labeled by AZCERT lists as being potentially torsadogenic (www.azcert.org, as of May 15th 2013). Twenty-three agents received a high score (>0.20), 41 an intermediate score (0.10-0.20), 98 a low score (0.01-0.10). Rupatadine and oxatomide ranked first (score=1), although with different degree of uncertainty: 0.64 and 0.94, respectively. Among antipsychotics, 28 agents were ranked among top-50 drugs. Pimozide showed the highest score (score=0.47; uncertainty=0.63), haloperidol showed intermediate score (0.16; 0.42), clotiapine the lowest (0.02; 0.93). Among other pharmaco-therapeutic classes, first-ranked drugs were halofantrine (antiprotozoals; score=0.63; uncertainty=0.71), ganciclovir (antivirals; score=0.51; uncertainty=0.84), cefalotin (antibacterials; score=0.26; uncertainty=0.81), and posaconazole (antimycotics; score=0.24; uncertainty=0.56).
Conclusion. This score attempts to integrate different indicators of torsadogenic risk through multiple sources and provides initial elements to provisionally rank drugs for their torsadogenic potential by highlighting inter- and intra-class differences. Calibration is required to identify optimal thresholds for signal prioritization, both in terms of score and its uncertainty.
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