World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:12, No:10, 2018

A Multifactorial Algorithm to Automate Screening of Drug-Induced Liver Injury Cases in Clinical and Post-Marketing Settings

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Abstract : Background: Hepatotoxicity can be linked to a variety of clinical symptoms and histopathological signs, posing a great challenge in the surveillance of suspected drug-induced liver injury (DILI) cases in the safety database. Additionally, the majority of such cases are rare, idiosyncratic, highly unpredictable, and tend to demonstrate unique individual susceptibility; these qualities, in turn, lend to a pharmacovigilance monitoring process that is often tedious and time-consuming. Objective: Develop a multifactorial algorithm to assist pharmacovigilance physicians in identifying high-risk hepatotoxicity cases associated with DILI from the sponsor's safety database (Argus). Methods: Multifactorial selection criteria were established using Structured Query Language (SQL) and the TIBCO Spotfire® visualization tool, via a combination of word fragments, wildcard strings, and mathematical constructs, based on Hy's law criteria and pattern of injury (R-value). These criteria excluded non-eligible cases from monthly line listings mined from the Argus safety database. The capabilities and limitations of these criteria were verified by comparing a manual review of all monthly cases with system-generated monthly listings over six months. Results: On an average, over a period of six months, the algorithm accurately identified 92% of DILI cases meeting established criteria. The automated process easily compared liver enzyme elevations with baseline values, reducing the screening time to under 15 minutes as opposed to multiple hours exhausted using a cognitively laborious, manual process. Limitations of the algorithm include its inability to identify cases associated with non-standard laboratory tests, naming conventions, and/or incomplete/incorrectly entered laboratory values. Conclusions: The newly developed multifactorial algorithm proved to be extremely useful in detecting potential DILI cases, while heightening the vigilance of the drug safety department. Additionally, the application of this algorithm may be useful in identifying a potential signal for DILI in drugs not yet known to cause liver injury (e.g., drugs in the initial phases of development). This algorithm also carries the potential for universal application, due to its product-agnostic data and keyword mining features. Plans for the tool include improving it into a fully automated application, thereby completely eliminating a manual screening process.

Keywords : automation, drug-induced liver injury, pharmacovigilance, post-marketing
Conference Title : ICPDS 2018 : International Conference on Pharmacoepidemiology and Drug Safety
Conference Location : Chicago, United States
Conference Dates : October 10-11, 2018