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Drug Safety of Antihypertensive Medicines Using Pharmacovigilance Data: Signal Management Through Traditional Methods Versus Process Automation

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Abstract

Hypertension remains a leading etiological agent of cardiovascular morbidity and mortality worldwide, thus requiring vigorous marketing pharmacovigilance of anti-hypertensive drugs. In the current study, the conventional approaches of signal detection used manually were compared with the processing automation procedure using extensive actual data accumulated using the FDA Adverse Event Reporting System (FAERS) during the past years, especially selected representative therapeutics, amlodipine, ramipril, and minoxidil. The old paradigms were based on manual case assessments together with disproportion measures (mainly the Reporting Odds Ratio (ROR)) and supplemented with expert clinical adjudication. Conversely, the automated model used a scripted pipeline, which included data cleaning, natural-language processing, automated codification and derivation of statistical signals. A mixed system was employed, combining a pre-screening with an expert validation as a requirement.

The automated approach increased the range of detections and the efficiency of operations and, at the same time, increased sensitivity, but at the cost of a higher rate of possible false-positive indications. The hybrid scheme was the most balanced, which offered the maximum credible signal capture, better sensitivity on genuine pharmacological matters, high specificity persistence, and equal accompanying noise decrease.

These results support the idea that hybrid signal management systems, which consist of automated routine and high-volume processes with domain knowledge to make conclusive judgments, is optimal, scalable, and regulatory compliant to the current condition of pharmacovigilance, especially in resource-limited environments.

Conclusion: This comparative evaluation of the signal detection methodologies of anti-hypertensive drugs gives a clear outline of the supplementary benefits of both the traditional and automated application techniques. Hybrid models are therefore an evidence based and pragmatic step towards modern signal management especially relevant in the changing pharmacovigilance set ups of India and other regions that face similar data and resource bottlenecks.

Keywords: pharmacovigilance; signal detection; anti-hypertensive drugs; process automation; artificial intelligence; FAERS database; hybrid system; disproportionality analysis; drug safety monitoring; post-marketing surveillance

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1. Introduction

Hypertension can be described as a state of situation where blood pressure in the arteries is regularly close to, or higher than 140/90mmHg. According to the World Health Organization, hypertension affects about 1.285 billion persons aged 30-79 years old including about 46 percent of the same population who are unaware of their status; only 42 percent of the same population are treated. In turn, hypertension is one of the main factors that contribute to early death in the world. (1) The most important issues in lifestyle, such as tobacco consumption, alcoholism, high sodium, obesity, and mental stress, play a major role in the pathogenesis of the diseases . Heart, brain, kidney, and eye tissues are typically vulnerable organs that hypertension would damage when left unchecked. The preventive measures then focus on balanced and low sodium eating, avoidance of tobacco and alcohol, proper management of stress, and good weight of the body. (2) Severe hypertension (systolic or diastolic blood pressure greater than 180mmHg or 120mmHg) can be clinically observed as chest pain, breathlessness, acute cephalalgia, a-fibrillation, and anxiety . There is a wide range of

antihypertensive pharmacotherapies available such as diuretics, 2-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, calcium-channel blockers, 2-blockers, 2-receptor agonists as well as vasodilators. (3,0) The benefit-risk profile associated with every therapeutic class is unique, and thus the pharmacovigilance (PV) monitoring should be performed carefully.

Pharmacovigilance can be defined as the science and activities pertaining to the realization, examination, comprehension, and aversion of adverse effects or any other issue of medicine or vaccine-related violence by World Health Organization. The tragedies with drugs in the past (mostly the thalidomide tragedy in Europe) led to the introduction of planned PV to the whole world. In 1962, the United States passed the Kefauver-Harris Drug Efficacy Amendments which required evidence of safety and efficacy, informed consent, ethics review control, reporting of adverse events, compliance with Good Manufacturing Practices, as well as appropriate advertisement and labelling policies. PV is an essential part of drug safety surveillance where core functions include case handling, signal identification and benefit-risk assessment. A modern PV system is often designed with three main parts, including input (adverse drug reaction reports by consumers or health-care professionals), process (entry of data, analytical evaluation), and output (benefit-risk judgments and signal reports).

Signal detection is chiefly tailored at recognition of infrequent and unforeseen Adverse Drug Reactions (ADRs). Signal detection is identified as an analysis activity undertaken during pharmacovigilance to determine an unanticipated outcome concerning the safety profile of a drug. (4) The pipeline of the methods goes through consecutive steps, which are signal identification, validation, prioritization, risk, action to be taken as a mitigation measure, and findings dissemination . The evidence sources are clinical trial data, spontaneous reporting systems, peer-reviewed literature, or regulatory agency data. In the past, signal detection was very much manual intensive but it is quite clear that the number of ADR reports is growing exponentially over the past few years and hence manual works was too cumbersome. The possibility of obtaining clinically relevant information in the presence of a lot of background noise can be likened to the one concerning the identification of actual safety indicators within a large body of data, thus, the use of artificial intelligence (AI) tools in PV is necessary. (5)

To overcome the objections of the manual approaches, the introduction of AI in PV is being actively sought. The PV platforms with AI can process enormous volumes of data, such as the results of a clinical trial, or cases of spontaneous cases, faster and more accurately than ever. By using natural language processing (NLP), machine learning algorithms, and advanced analytics, AI contributes to the scenario in which ADR patterns are identified more effectively. Benefits include eliminating recurrence of manual procedures, MedDRA automated coding and digitizing of handwritten or unstructured data, gathering a report out of Individual Case Safety Reports (ICSRs) and standard literature, detecting the ADR patterns and duplicates, and systematically categorizing a report according to drug class and severity. Therefore, these technologies save time, labour, financial resources but increase efficiency in processing cases. (6)

Despite the advantages, AI-based PV is a challenging phenomenon. Complete automation of the signal recognition can give false results especially during challenging ADR patterns. Sub-optimal sensitivity or specificity of the algorithm is associated with the risk of missing of important safety signals. Such terminological differences as drug names or descriptions of diseases add to the problems in data-processing. Additionally, the use of patient data without their informed consent causes certain ethical and privacy issues, and therefore, to verify AI tools, promote their compliance, and patient safety, a regulatory control should be strengthened. (6)

Incorporation of AI/automation in PV systems can correspond to the actual decrease in the time, labor intensity, and economic cost of case processing, but will not be able to replace the factual role of a qualified medical opinion and competent decision-making by experienced PV specialists in determining final causality and signals. Full automation of PV processes brings a high-risk level; hence, many tests, validation, and regulatory acceptance are conditions before the implementation of fully AI-driven systems. A hybrid PV model of the type where AI supports and bridges human expertise, without replacing it, should therefore be recommended. (6)

2. Background

The high mortality burden of hypertension in the world makes the need to exercise close, continuous safety monitoring of anti-hypertensive drugs imperative due to the large populations that face the risk of exposure and the duration of therapy, which increases the likelihood of occurrence of any rare or latent adverse drug reactions (ADRs) that cannot be detected without the aid of post-marketing surveillance.

All major anti-hypertensives classes have a unique ADR profile that directs specific signal-detection regimens: ACE (cough, angioedema, hyperkalaemia), ARBs (angioedema, although less common), calcium-channel blockers (peripheral oedema, gingival hyperplasia), diuretics (electrolyte imbalance), beta-blockers (bradycardia, drowsiness), and vasodilators (reflex tachycardia, pericardial effusion with minoxidil.

The modern pharmacovigilance models, ICH, EMA GVP Module IX, WHO are focused on organized signal management that includes the detection, validation, confirmation, prioritisation, assessment, and recommendations to action. Disproportionality approaches are also framework rather than dispensing and would be supported by clinical assessment to eliminate confounding, reporting bias and the lack of denominator data.

Recent FAERS-based and national-database studies have discovered or strengthened signals that are relevant to anti-hypertensive therapy, such as, hyponatraemia with amlodipine and renin-angiotensin system blockers, angioedema signals with amlodipine mono- or combination therapy and with RAAS blockers, possible

urinary retention with amlodipine, gingival overgrowth or bleeding with amlodipine and other cardiovascular agent, hepatotoxicity signals in ramipril, strong angioedema signals.

These studies confirm further usefulness of the disproportionality analysis methodology, together with the challenges of working with very large datasets at the level of manual work.

Literature of AI applications in pharmacovigilance reports significant improvements in efficiency, including automatic MedDRA coding, narrative generation, duplicate identification, seriousness triage, literature mining and initial signal flagging.

Challenges and limitations that persist are that large, representative, population-specific training datasets are needed; linguistic diversity, synonyms, misspellings, and incomplete reporting need to be addressed; algorithmic bias can be a problem; nuanced clinical judgment is not easily automated (temporality, dechallenge/rechallenge, alternative causes) but rather is a resistance; false-positives may happen or a lot; ethical and privacy concerns; they need to run on infrastructure; and many adaptive AI tools are not yet supported by strong regulatory frameworks.

All the available information points to the fact that automation should be implemented only in a cautious and hybrid manner as opposed to being swamped by it in full.

3. Signal Detection and Analysis

Signal management Information Signal management was undertaken in accordance with EMA Good Pharmacovigilance Practices (GVP) Module IX (Rev 1), consisting of signal detection; validation; confirmation; analysis; prioritisation; assessment; recommendation of action.

The most significant source of data was an open access database FDA Adverse Event Reporting System (FAERS), including a long duration of recent years. The report included only those in which amlodipine, ramipril or minoxidil came up as primary suspect drugs. They were filtered out by deleting duplicates, and non-serious (non-serious) non-full-scale reports that were incomplete or unambiguously irrelevant were removed. MedDRA terminology was applied in standardising adverse events.

The conventional part involved a manual case-level review in addition to disproportionality analysis using Reporting Odds Ratio (ROR). The signals were considered as the positive ones when the ROR was greater than 2, the lower limit of the 95 percent confidence was also greater than 1 and a minimum number of cases were met. A special clinical examination was conducted to measure temporality, de-challenge/re-challenge, alternative explanation, dose-response, biological plausibility, severity, and anticipatedness compared to labelling of products. (7)

The automated method included a specific pipeline which was created in Python, including libraries used to organize data, clean it, and to compute statistics and natural-language processes free-text narratives. The automated processes included the following: duplicate detection, MedDRA mapping, seriousness detection, narrative extraction, and disproportionality measurement (ROR and confidence intervals). The thresholds were worked out in accordance with those which are used in the traditional arm.

An automated output was used as an early triage step in the hybrid approach. All the possible signals were subject to mandatory expert manual verification to ensure clinical relevance, determine causality, as well as make regulatory judgment before final classification. (7)

Qualitative and comparative performance was assessed in terms of breadth of performance across the three strategies in terms of detection as well as sensitivity at exhibiting true signals and in terms of specificity or a false positive load and their ability to conform to the expected clinical and regulatory performance of a strategy.

4. Comparative Results and Insights

The traditional manual approach provided a high level of specificity and strong clinical basis (8,9) as well as offered several potential associations with new literature. Automation significantly increased the range of signal detection and sensitivity with the ability of auto detection to capture associations that had previously been ignored as part of manual review such as some dose related associations. (10)

The hybrid model, consisting of automated initial screening and expert validation was the most favourable: it produced the largest reliable signals, the highest sensitivity to detect the real safety issues, without compromising on specificity, and the minimum overall noise. Within the hybrid system, dose-dependent patterns (e.g., increased association of pericardial effusion with higher dose of minoxidil) were also better defined. (11)

4.1 Discussion – Opportunities and Challenges of Automation in Pharmacovigilance

a) Opportunities

- Massive automatic recession of redundant manual documentation and coding functions is implemented through the deployment of advanced automation methods.
- Regular assigning of the MedDRA terms with the help of computers facilitates terminological precision between datasets.
- Maximum use of data is made possible through the effective extraction and organization of the information when presented in unstructured narrative.
- Improving the soundness and timeliness of the pharmacovigilance processes, rapid duplicate detection, triage of seriousness, and filtering of non-serious reports.
- Very large volumes of reports can be processed with scalability and hence have the ability to withstand high volume requirements.
- The possibilities of linking to literature and electronic health records materials provide the

possibilities to enrich the data and conduct cross-source analyses.

b) Challenges

- Large-scale expression of complex clinical patterns and heterogeneous data is a tremendous problem.
- Reliability of models depends on availability of large, representative and population specific training datasets.
- The risk is both low sensitivity, which is missing the few serious events that occur, and subjects, which causes the creation of too much background noise.
- Linguistic variability: This includes the presence of synonyms, misspelling, jargon, partially documented language, and so forth. This is an overwhelming challenge.
- Response: The automation of fine-tuning of judgments about causality is still weakly developed. Ethical, privacy, bias, transparency, and accountability issues are still considered the top priorities. Request Infrastructure requirements, training documentations, validation procedure, and acceptance regulative requirements are all necessary to deploy in practice.

5. Conclusion

This comparative evaluation of the signal detection methodologies of anti-hypertensive drugs gives a clear outline of the supplementary benefits of both the traditional and automated application techniques. Although automation significantly increases the scale of processing, consistency, and ability to derive a larger number of potential signals, it cannot reproduce the profundity of clinical reasoning that makes it a dependable tool in assessing causality, prioritising, and making regulatory decisions. Alone automation, however, is more likely to produce more false-positive signals, thus generating alert fatigue and the misidentification of resources.

The development of a hybrid system, where high-throughput routines (data cleaning, coding, preliminary disproportionality screening, extraction of narratives and the like) are reinforced by automation, but one of the key tasks, signal validation, assessment of clinical context, elimination of all possible alternative causes, and recommendation of actions, remain the prerogative of a trained, certified human being, helps to communicate a greater overall effectiveness. It provides the greatest detection sensitivity without reducing specificity, ensures compliance with the regulations and patient-safety focus besides presenting realistic and resource-efficient trajectory, given the growing volumes of data on pharmacovigilance.

Hybrid models are therefore an evidence based and pragmatic step towards modern signal management especially relevant in the changing pharmacovigilance set ups of India and other regions that face similar data and resource bottlenecks. Any future work needs to be investigating validation, standardisation and gradual introduction of such hybrid workflows to a normalised practice.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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