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REVIEW ARTICLE

CHRONOPHARMACOVIGILANCE: TIME-DEPENDENT PATTERNS OF ADVERSE DRUG REACTIONS AND THEIR REGULATORY IMPLICATIONS

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Abstract

Chronopharmacology is the study of the effects of biological rhythms, especially circadian rhythms, on pharmacokinetics and pharmacodynamics of drugs and their therapeutic efficacy and safety. The rhythmic nature of physiological functions like hormone secretion, enzymatic activity, gastrointestinal function, renal clearance, cardiovascular function, and immune response plays an important role in governing the temporal profiles of absorption, distribution, metabolism, and excretion of drugs. There is increasing evidence that adverse drug reactions (ADRs) are not randomly timed but rather follow a predictable pattern with a close association with biological clocks. Therefore, the onset of medication can have a profound effect on either the occurrence or intensity of ADRs. This review focuses on the issue of time-dependent patterns of ADRs in the integrated framework of chrono-pharmacology and chronopharmacovigilance. It outlines the mechanistic explanations provided by circadian biology to time-dependent patterns of drug safety and clinical evidence of time-dependent differences in the occurrence of ADRs in a broad range of therapeutic classes. The data underscores the challenges of conventional pharmacovigilance where biological timing is not considered as a drug-related risk factor. The review also delves into the implications that time-dependent patterns of ADRs have on pharmacovigilance and regulation. The use of time-dependent variables in drug safety monitoring, trial designs, and risk management plans may enable better signal detection and improved benefit-risk assessments. The use of chronopharmacological concepts in regulatory science can, therefore, facilitate the development of personalized medicine, where the dosing regimen will be optimized for safety. It can, therefore, be concluded that the appreciation of temporal variability in ADRs is an important milestone in more accurate drug safety profiling.

Keywords: Adverse drug reactions, chronopharmacovigilance, circadian rhythm, drug safety, pharmacovigilance, regulatory science.

INTRODUCTION

Adverse drug reactions (ADRs) remain one of the major health concerns worldwide, contributing largely to patient morbidity, unnecessary hospitalization, hospital stay, and rising healthcare costs. ADRs remain among the list of reasons for treatment-related harm despite advancements in drug development, regulation, and post-marketing surveillance[1]. The conventional pharmacovigilance approach has largely focused on a set of known variables such as the dose of a drug, the duration of therapy, patient demographics, associated diseases, genetic susceptibility, and interactions between multiple drugs[2,3]. Although these factors are of utmost importance, they fail to incorporate an essential aspect of drug exposure: administration of drugs in the context of their endogenous rhythms[2].

Chronopharmacology provides a strong scientific basis to explain the temporal differences in the efficacy and toxicity of drugs by correlating pharmacological response with circadian biology[4,5]. The circadian rhythms, controlled by the central biological clock and peripheral clocks in the principal organs of the body, are characterized by predictable changes in physiological and biochemical functions on a 24 hrs cycle[5]. Secretion of hormones, gastrointestinal motility, expression of hepatic enzymes, renal blood flow, the immune system, and repair mechanisms in cells vary in a time-dependent manner[6]. Circadian rhythms have a direct effect on the pharmacokinetics of drugs and tissue sensitivity to drugs. This means that the same drugs taken at different times of the day can have a vastly different safety profile[7].

Increasing clinical and experimental evidence has shown that ADRs do not occur in a random fashion over time but, rather, follow predictable patterns of time. For instance, sedative response, hypotensive reactions, gastrointestinal intolerance, and immunologically mediated responses may be enhanced or reduced based on the circadian rhythm. The assumption of a time-invariant risk of drugs is thus challenged[8]. It is this awareness that has led to the development of chronopharmacovigilance a relatively new branch that involves time factors in pharmacovigilance practice[9]. The aim of chronopharmacovigilance is to discover, analyze, and interpret time-series data of ADRs by evaluating the timing of drug administration in relation to the circadian rhythm and periodic physiological variations, in addition to the traditional risk factors. This method has the potential to optimize signal detection and help resolve inconsistencies in ADR reports[10].

In terms of regulatory science, the implications of identifying time-dependent ADRs are far-reaching. It leads to more accurate assessments of benefit and risk, and it is consistent with regulatory visions of patient-centered and precision medicine[10]. This review article brings together the collective knowledge that exists concerning the nature of ADRs in terms of time and focuses on the role of chronopharmacovigilance as an emerging area of research for improving drug safety surveillance and decision-making[11].

Concept and scope of chronopharmacovigilance

Chronopharmacovigilance may be defined as the scientific evaluation of the changes in the number of adverse drug reactions that follow a circadian, diurnal, and seasonal pattern[12]. Clock time, as opposed to the calendar time mentioned in traditional pharmacovigilance, becomes an important concern in chronopharmacovigilance[13].

The field of chronopharmacovigilance encompasses:

- Circadian pattern identification in the reporting of ADRs
- Evaluation of dosing-time-related risk factors
- Optimization of Risk Minimization Measures
- Informing Regulatory Decision-Making and Labeling

Such an approach is in line with the general shift towards personalized and precision medicine, where the treatment not only targets the patient but also the timing of the biological processes[13,14].

Biological basis of time-dependent adverse drug reactions

1. Circadian regulation of drug metabolism

Circadian expression and activity of drug-metabolizing enzymes like cytochrome P450 have been noticed[15]. The level of expression and availability of the hepatic enzyme varies from day to night. This results in variations in the plasma levels of drugs, giving higher peaks of exposure and toxicity[16,17].

2. Variability in drug transport and distribution

Membrane transporters which play a role in the absorption and excretion of drugs, such as P-glycoprotein and organic anion transporters, have a circadian rhythm. Other factors like gastrointestinal motility and gastric pH also change daily, influencing drug absorption and potentially giving a time-dependent gastrointestinal ADR[18,19].

3. Circadian sensitivity of target organs

The rhythmic responsiveness of organ systems to pharmaceutical provocations also exists. For example:

- Cardiovascular events reach peaks during early morning hours
- Reactivity of the airway increases at night
- Pain sensation and inflammation show diurnal variation

These rhythms can accentuate or ameliorate drug-induced adverse reactions depending on the timing of their administration[20,21,22].

Clinical evidence for time-dependent ADRs

There is cumulative evidence for the importance of chronopharmacovigilance. Antihypertensive drugs can cause excessive nighttime hypotension when given at night[23]. Nonsteroidal anti-inflammatory drugs show time-dependent gastrointestinal and renal toxicity. Central nervous system drugs can cause increased sedation or dizziness when given during the night[24].

In the post-marketing environment, the clustering of ADR reports at certain times of day has been noted in spontaneous reporting databases. However, this information is not commonly analyzed systematically, indicating an opportunity to improve the analysis of safety signals by considering times of day[25].

Challenges in chronopharmacovigilance

However, chronopharmacovigilance has some challenges despite its potential:

- Incomplete reporting of time of administration in spontaneous ADR reports[26].
- Standardized terminology is not used for time variables[27].
- Confounding due to patient behavior, comorbidities, and polypharmacy[27].
- Limited awareness among healthcare professionals[28].

However, these approaches have some limitations that could be overcome by the use of advanced analysis techniques such as time-stratified disproportionality analysis and the integration of real-world evidence[29].

Regulatory Implications

1. Impact on PSURs and signal detection

The effect of the regulations in this section on the preparation of PSURs has been described above[30]. The regulations about the content of the PSUR have implications for signal detection, since they contain requirements regarding the presentation of information on the submission documentation in the Master File[30,31].

The use of time variables in PSUR evaluation may help to improve the detection of safety signals and benefit-risk profiles. Time trends in ADRs can explain discrepancies observed between populations and studies[32].

2. Risk management plans and labeling

Results from chronopharmacovigilance may help illuminate specific risk minimization actions, including the timing of doses to avoid risks of adverse drug reactions. Future product labeling by regulatory

agencies may include aspects of time of administration, not only in efficacy but in safety as well[33].

3. Relevance for low- and middle-income countries

In resource limited settings, where the pharmacovigilance system is still in its developing stages, chronopharmacovigilance can be done in a cost-effective manner to improve safety outcomes through the optimization of existing therapies rather than new ones[34].

Future directions

The future of chronopharmacovigilance is in:

- Electronic health records and digital health technologies[33].
- Real-time physiological rhythms recorded by wearable devices[34].
- Temporal signal detection using artificial intelligence[35].
- Education of healthcare professionals on time-based drug safety[36].

The integration of chronopharmacovigilance into regulatory science could be a paradigm shift in the post-marketing surveillance of drugs[37].

CONCLUSION

Chronopharmacovigilance adds a crucial time factor to pharmacovigilance. This new field takes into account the fact that adverse drug reactions are not randomly distributed in time. Chronopharmacovigilance is a new field that improves current knowledge about drug risk profiles and contributes to making more accurate decisions. The integration of the concept of biological time into pharmacovigilance systems could improve the safety of patients, provide optimal results, and advance the development of personalized medicine. With the evolution of pharmacovigilance regulations, chronopharmacovigilance should be considered an integral part of pharmacovigilance.

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AUTHOR'S CONTRIBUTIONS

Salim S: writing the original draft, methodology, investigation. **Rashid SS:** literature survey, data processing. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

None to declare.

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