REVIEW ARTICLE

Why and how? Addressing to the two most pertinent questions about pharmacovigilance in Ayurveda

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ABSTRACT

Pharmacovigilance is the outcome of a natural and implied willingness of a physician to ensure safety to his patient. This is a discipline in medicine which pragmatises the principle of *first do no harm* towards a wider and systematic application in clinical practice. It is however important to understand that despite of its huge potential in ensuring a safe practice of medicine through knowledge of avoidable causes of adversities, its path has never been easy. Applying principles of pharmacovigilance into the realm of traditional medicine particularly to Ayurveda is even more difficult for the issues of why and how of pharmacovigilance in light of historical practice and anecdotal evidences of safety in Ayurveda. Application of pharmacovigilance in Ayurveda thereby demands a careful and thoughtful observation of its needs and its methods of application in order to to maximize its impacts to ensure the patient safety to every extent possible.

Key words: *Adverse drug reaction, drug safety, pharmacovigilance*

INTRODUCTION

Pharmacovigilance was born of a need felt by the medical fraternity striving to save their patients from preventable causes of drug adversities. Preventing untoward and unwanted effects of medical interventions that are primarily designed to cure, treat, or diagnose morbidities are the primary concerns of pharmacovigilance.[1] Most national programs make an effort to expand the horizons of pharmacovigilance by including blood transfusion, vaccination, and traditional health care within its realm.[2]

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The application of pharmacovigilance in Ayurveda has come as an eventuality to the repeatedly felt need of making drug safety a universal concept further to its augmentation by an observation of ever escalating global growth of the traditional health care market.[3] It was also a public health issue considering the substantial human population getting exposed to traditional health care.[4] Multiple adverse reaction reports[5-7] and an increasing global concern about the safety of *Ayurvedic* drugs paved the final way to launch the National Pharmacovigilance Programme in India about 2 years ago. A National Pharmacovigilance Resource Center (NPRC-ASU) was set up in 2008 as its executive body and many regional and peripheral centers as its working arms and legs.[8]

During this period exhaustive campaigning was conducted throughout the country to promote awareness among various stakeholders about drug safety and adverse drug reaction (ADR)-reporting issues in Ayurveda. Thus, over 50 awareness programs and a few brain-storming sessions were conducted throughout the country (at peripheral and regional centers for pharmacovigilance of ASU drugs) with a primary objective to increase the awareness about pharmacovigilance in Ayurveda, discuss various ways and modalities to make it operational, and create an awareness about ADR reporting among physicians, and promote a culture for reporting regularly to the respective peripheral or higher centers.

Though it is too early to evaluate the success or failure of pharmacovigilance in the Ayurveda campaign, we need to understand that the pharmacovigilance movement has not been an unqualified success in India and elsewhere despite consistent efforts by WHO and respective national authorities. Among many reasons leading to the underperformance of the program, the important ones are poor appreciation of idea and use of pharmacovigilance at various levels, especially among the prescribers where a physician fails to link ADR reporting to any tangible benefits to his own.[9] At the same time while transposing the idea of pharmacovigilance in Ayurveda, we often fail to address the needs which are adherent to the style and intricacies of *Ayurvedic* clinical practice.

It is therefore necessary to realize that the future success of the pharmacovigilance program in Ayurveda will largely depend on how we address two primary questions referring to its need and application. Among these two, the former is mandatory to generate a genuine interest about ADRs and the latter is essential to define and design a smooth operational mechanism which can make way to achieve the ultimate objective of pharmacovigilance.

Why Pharmacovigilance in Ayurveda?

Addressing the classical and contemporary relevance

Ayurveda has described situations of drugs not utilized optimally (according to their order, proportion, combinations, or indication required as per the individual needs).[10] The *Charaka Samhita* beautifully elaborates three essential points to ensure safe use of medicines, including knowledge about the name of the drug, its physical identification, and its properties. We all know that these points remain relevant to ensure a drug safety in whatever system of medicine.[10]

Besides the knowledge about drug identification and properties, Ayurveda puts further stress upon its use in clinical situations. While describing rational medicine use Ayurveda mandates knowledge of *yoga* (a single drug or a combination of more than one) and *mana* (dose) and its individualization as per patient's needs.[11] *Yukti* (tactful use of medicine as per individual needs also called *yuktivyapasharaya chikitsa*)[12] is possibly the biggest tool of Ayurveda which renders a safe and effective use of a medicine possible in routine clinical practice. Ayurveda provides flexibility about the choice of drugs, their doses, combinations, and duration of therapy according to the patient's sensitivity to a drug as well as the seriousness of the disease. Hence, practising Ayurveda in the way it is taught in the classical texts can minimize adverse reactions greatly.

Often because of this, the need for pharmacovigilance in Ayurveda is questioned. The view is that if *Ayurvedic* medicines are used as described there will not be any ADRs. The adverse reactions, if noted, are believed to be due to improper use or poor quality of medicines.[13] It is in this context that pharmacovigilance, in the way it is applied in contemporary medicine, is considered to be neither essential nor applicable to the basic needs of Ayurveda.

Analyzing the classical needs for pharmacovigilance in Ayurveda

The success of *Ayurvedic* therapy largely depends upon the choice of drugs and their doses with reference to an individual's needs. This clinical decision making relies upon the skills of the physician to make and use minute observations about the sickness (*roga*) and the sick (*rogi*).[14] Other factors that determine the choice of drug and dose include geographical (*desha*) and seasonal (*kala*) specifications at the time of actual management. It is thus clear that success in *Ayurvedic* therapy is primarily a net outcome of a thorough decision-making process based upon multiple factors. If this process is not followed, not only are the expected benefits jeopardized, but adverse effects could also occur. Interestingly, as there are no objective tools in Ayurveda to help make the choice of drug, the chances of subjective variations are fairly large.[15]

Pharmacovigilance can be projected as a great tool to help decision making with reference to adverse drug reactions in Ayurveda. A subsequent causality analysis would allow us to identify the possible underlying reason for the adverse effect in an *Ayurvedic* context and therefore ultimately to prevent such adverse reactions eventually.

Contemporary needs of pharmacovigilance in Ayurveda

A recent sample survey conducted among institutionally qualified *Ayurvedic* physicians from Uttar Pradesh and Bihar revealed the marked ignorance among most physicians about issues related to *Ayurvedic* drug safety and concurrent adversities.[16] Most physicians in the survey, however, agreed upon the possibility of adverse reactions to *Ayurvedic* drugs attributing variable causes to their occurrence. Most labeled counterfeit drugs and inappropriate use as the most important causes of ADRs associated with *Ayurvedic* drugs. It is interesting to note that most physicians accepted their ignorance about pharmacovigilance and admitted that there was a need for better training.

This survey was in accordance with the findings seen at another survey conducted among *Ayurvedic* physicians from Maharashtra.[17]

The thought that ADRs are associated with *Ayurvedic* medicines is no more a vested thought of the occident. Increasingly, we have started accumulating reports of ADRs from the *Ayurvedic* fraternity including frequent Indian ADRs reports associated with aconite and lead which form an essential component of many *Ayurvedic* drugs.[5,6,18]

It is important to note that *Ayurvedic* drugs are inadequately tested for their safety in vulnerable populations like the elderly, children, pregnant and lactating women, and seriously ill patients.[19] Absent pharmacokinetic data and possibility of drug--herb, herb--herb, and herb--food interaction further make it difficult to predict the safety of various *Ayurvedic* combinations prescribed or incidentally consumed.

Pharmacovigilance practice, through reporting of ADRs and subsequent causality analysis in terms of contemporary pharmacological as well as *Ayurvedic* principles, can give us an excellent opportunity to learn from our mistakes and avoid repetition in future. Besides making our patients safe through a wide range of interventions, this is also going to make Ayurveda grow in terms of rationality and accountability.

Besides these benefits, the practice of pharmacovigilance also helps us differentiate genuine drug reactions from those occurring due to drug adulteration, contamination, or poor quality of drugs.

Pharmacovigilance in Ayurveda: Benefits for stakeholders

The success of the pharmacovigilance movement largely depends upon active involvement of its stakeholders operating at various levels starting from drug manufacturing to its consumption. As the ADR report is the primary unit of information coming from stakeholders at different levels, the success of a pharmacovigilance program is a direct reflection of ADR reporting culture at stakeholder levels. A poor response to ADR reporting call, however, is a global experience in pharmacovigilance.[9]

Due to the lack of visibility of any tangible and immediate benefits of reporting, stakeholders do not respond to calls for ADR reports. ADR reporting therefore is striving hard to find a momentum among stakeholders so much to generate substantial data to reach at a conclusion about drug safety or otherwise.

How can a physician benefit through a pharmacovigilance initiative?

This is the primary question which needs to be honestly answered before a physician is asked to get involved and to report. Perhaps the most "instant" benefit a physician may receive through ADR reporting is a better knowledge about the cause and effect of an ADR of a drug. While reporting, one is required to give details about the clinical condition, the suspect drug, its dose, effects of de-challenge and re-challenge (if possible), treatment given, and any investigations done to detect the levels of the suspect agent in tissue or body fluid. These details would give insight to the treating physician about the drug use in a specified condition. Acquiring a better knowledge about drug safety through self-experience is a definitive way of learning which eventually leads to more precise and objective decision making. This is how a physician can directly learn from his own ADR reporting.

Besides this, as a collective effort, the acquired ADR data from various sources would become a dependable repository of information for peers, paramedics or consumers. Processed information may also lead to the development of protocols to manage such adverse reactions in routine clinical practice. Together, the practice will lead to better patient care as its primary gains and a better clinical practice for physician as its dividends.

How to Practice Pharmacovigilance in Ayurveda?

Addressing the issue of the *modus operandi* to maximize the impact

Many plans and protocols, despite their proven benefits, face failures when are transposed to the situations different to the primary ones for which they were originally designed. A difference among needs, resources, and objectives warrants a revisit and subsequent indigenization of the plan to ensure its success in the local environment.

The idea of pharmacovigilance in Ayurveda also requires to be revisited in this spirit to underline its own needs, resources, and objectives. It is only then that the policy of implementation can be framed with a view to achieve the targets.

As the fundamental objective of pharmacovigilance is to ensure a safe medical practice by preventing drug-related harms to the patients, by increasing awareness and channelizing feedbacks, reporting of ADRs can be increased.

Contrary to the pharmacovigilance with conventional medicines, where a constant watch upon drug behavior is required, for drugs which are newly introduced and where there are no safety data available,[20] in Ayurveda we need to work with known drugs which are in use for long periods and are believed to be safe when used as per the *Ayurvedic* principles of their preparation and use. Pharmacovigilance in Ayurveda needs to identify contemporary causes for ADRs with *Ayurvedic* medicines. A growing demand and subsequent exploitation of herbal drugs in general and *Ayurvedic* drugs in particular however are posing some new and yet to be answered propositions. There are new proprietary medicines in the market, about which data are not available. There are suggestions that allow any herbal drug to be mixed up with a new drug which can be marketed without any clinical trial. There are extracts of the herbs being marketed without clinical trials. There are also new drugs not reported in *Ayurvedic* classics. These issues are also required to be dealt in depth through pharmacovigilance in Ayurveda.

ADR reporting in pharmacovigilance of Ayurvedic medicines

The ADR reporting form developed by NPRC-ASU[21] beautifully blends the need of Ayurveda with that of conventional ADR reporting practice as is envisaged by CDSCO in India.[22] Obviously, this ADR form deals with various reasons of possible ADR peculiar to the current *Ayurvedic* practice.

One of the important causes of ADRs to *Ayurvedic* medicines is their deterioration upon storage. This is especially true for powders containing salts or sugar. Salt-containing powders are prone to liquifaction upon absorption of water and similarly sugar-containing powders adsorb water upon exposure and pose a threat of being contaminated with fungi.[23] Drug dispensing in Ayurveda has also been a matter of great variation. Even if the drug is prescribed in milligrams or grams conventionally the doses are dispensed empirically through the use of spoons. Thus, the actual amount of a drug dispensed and thereby consumed in individual cases may not be precisely what was prescribed. Besides this a phenomenon called bulk dispensing also requires attention. At most state-run hospitals of Ayurveda, a lump sum amount of prescribed drugs is dispensed to the patient with an instruction to make required doses at their own as per the duration of therapy.[13] Any inappropriate dose formation at home may lead to adversity where the reason for this is not really the drug but the way it was taken. Different sizes of *vati* (tablet) preparations in Ayurveda and different formulations with the same name as described in different *Ayurvedic* texts are another problem which need attention.

ADR reporting in Ayurveda should essentially address these situations, paying attention to the peculiarities characteristic of its practice style and therefore additions to the ADR reporting form are essential. NPRC-ASU (NPRC-Ayurveda, Siddha, and Unani) has worked in this direction by adding specific features in its ADR reporting form. Besides enquiring about drug dose, its indication, and the method of administration, it also enquires about dietary history, *anupana*, of the drug and also asks for collection of remains of the incriminated drug if can be made possible.

It is important that therapeutic procedures practised in Ayurveda should also be brought under the ambit of pharmacovigilance. *Panchakarma, Ksharasutra, Rakta mokshana* are few such procedures. In these cases, the procedure-related harm needs documentation and discussion. It is heartening to note that a consensus has arrived to include adverse events caused by medical devices and therapeutic procedures under the purview of pharmacovigilance.[1]

Causality analysis in Ayurveda

As discussed earlier, safe use of *Ayurvedic* medicine is entirely dependent upon its quality and appropriate uses. Any ADR therefore is an opportunity to learn about the possible causes. Causality analysis is one of the ways to find links between the drug in question and the adverse events that have occurred. From the *Ayurvedic* perspective, this causality analysis would be a definitive guide to find deficiencies in either drug quality or in its use.

Every ADR in Ayurveda should be analyzed in terms of drug properties (*rasa, guna, virya, vipaka, and prabhava*), the dose consumed singly or cumulatively, coadminstered drugs, herbs or food, *prakriti* of patient, vital status of the patient (*sara pariksha*), coexisting illness, pregnancy, lactation, and age (elderly or infancy).

The ADR reported and analyzed in Ayurveda may finally be reduced to two inferences: (1) *Prakriti sama samaveta* -- where the inference can be drawn by applying *Ayurvedic* principles of pharmacology, (2) *Prakriti vishama samaveta* -- where results cannot be drawn by applying the conventional *Ayurvedic* principles.

The latter example may come as a signal to *Ayurvedic* pharmacovigilance and asks for a constant pharmacoepidemiologic monitoring to incriminated drug uses in diversified human population.[24]

Conclusions

Pharmacovigilance is the process of constant monitoring upon adverse drug reactions with the objective to learn from experiences and subsequently to reduce further adversities. Applying pharmacovigilance in Ayurveda gives us an opportunity to understand the relevance of ADRs in Ayurveda with special reference to the *Ayurvedic* fundamental principles and of its current practice style.

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