A Qualitative and Quantitative Comparison of Adverse Drug Reaction Data in Different Drug Information Sources

Abstract

Background: For safe use of medicines, awareness regarding the existing knowledge of adverse drug reactions (ADRs) is essential to prevent, identify, and manage them. Aim: The present study is planned to assess variation in documented ADRs of antihypertensive drugs in various sources of drug information. Material and Methods: A cross-sectional, observational study was undertaken to analyze the different sources of ADRs-related information. Textbooks, National Formulary India (NFI), Drug Today (DT), and Current Index of Medical Specialties (CIMS) were analyzed for ADRs pertaining to nine antihypertensive groups comprising a total of 44 drugs. ADRs were categorized according to body systems, tabulated, and compared. Quantitative and qualitative analyses of ADRs and serious ADRs were done. Results and Discussion: Textbooks mostly provided ADRs of drug groups as a whole and not of individual drugs. None of the analyzed sources mentioned all antihypertensive drugs. DT contained information for the maximum number of drugs studied (81.8%) and NFI gave information for 29.7% drugs only. There was a wide variability among various resources while listing ADRs. NFI listed the maximum number of total ADRs, and least ADR information was provided by DT. NFI mentioned the maximum number of serious ADRs (47) for prototype drugs followed by CIMS (36) and DT (8). The quality of data was better in NFI, but none of the resources studied were found to be complete. Conclusion: No source of information was complete in providing wholesome information of ADRs studied, and there was a wide variability in describing them.

Keywords: Adverse drug reactions, Pharmacovigilance Programme of India, safety profile, VigiAccess, VigiBase

Introduction

All medicines are associated with adverse drug reactions (ADRs) which may be minor, severe, or even life-threatening. The World Health Organization (WHO) defines ADR as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.”[1] The Food and Drug Association categorizes a serious adverse event (events relating to drugs or devices) as one in which “the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.”[2] ADRs are not rare; an incidence of 10%–25% has been documented in different clinical settings.[3] For safe use of medicines, awareness regarding the existing knowledge of ADRs is essential to identify and manage them. Often, complete information regarding ADRs is lacking/variable in different sources of information in literature, and a single credible benchmark is lacking. The paucity of complete information may lead to all ADRs being not identified and/or could be mistaken as a new disease or ignored. This can lead to unsafe use of medicines.

The WHO Drug Dictionary Enhanced Terminology is assessed by the national regulatory authorities, who have an interest in the fast, safe, and correct communication of clinical and drug safety data collected from trials and reports from around the world, but not for the general prescriber.[4] The WHO Adverse Reaction Terminology has been developed for over more than 30 years to serve as a basis for rational coding of adverse reaction terms only and does not serve as an ADR database for

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the prescriber.[5] The Pharmacovigilance Programme of India (PvPI) under the Central Drugs Standards Control Organization (CDSCO) is a source of ADR reporting and collection of ADR data. VigiAccess database, under PvPI, is only a repository of Individual Case Safety Reports and is not a systematic register of ADRs that have occurred or may occur.[6] Pharmacovigilance is the science related to detection, assessment, understanding, and prevention of adverse effects of prescription medicines. The word “pharmacovigilance” is derived from “pharmakon” (Greek word for “drug”) and “vigilare” (Latin word for “to keep watch”).[7] Continuous monitoring of unwanted effects, safety-related aspects of marketed drugs, and safety alerts regarding drug use are under purview of the PvPI.[8] Although envisaged as a 2-way flow of information, PvPI has not yet been established as a key resource for day-to-day ADR assessment and safety decisions taken by prescribers.

Availability of clinically relevant, contemporary, and unbiased drug information goes a long way in promoting the rational use of drugs. Various sources of drug information are utilized by physicians for accessing relevant drug information such as indications, ADRs, contraindications, and special precautions. Drug information is usually sourced from medical textbooks, medical journals, National Formularies, drug compendia like Current Index of Medical Specialties (CIMS), Monthly Index of Medical Specialties, and Drug Today (DT).[9,10] The 5th edition of National Formulary of India (NFI) 2016 has been released on November 14, 2015.[11] The criteria for inclusion of drugs in the NFI are drugs from the National List of Essential Medicines 2011, India, drugs used in national health programs, drugs listed in Indian Pharmacopoeia, drugs not covered but recommended by a panel of experts, and any drug (s) considered appropriate by the International Patent Classification. Therefore, all drugs of a class may not find mention in the NFI. The Indian Pharmacopoeia 2014 with 2015 and 2016 addendums are available,[12] but it provides only pharmaceutical details of individual drugs and not clinical data. Drug information available in various sources should be uniform, reliable, and conforming to the regulatory label of the drug.

The present study is planned to assess variation in documented ADRs of antihypertensive drugs in various sources of drug information.

Material and Methods

A cross-sectional, observational study was undertaken to analyze and compare the different sources of information regarding ADRs. Latest editions of Goodman and Gilman’s Pharmacological Basis of Therapeutics (GG),[12] Harrison’s Principles of Internal Medicine,[13] Rang and Dale’s Pharmacology,[14] NFI,[15] DT,[16] and CIMS[17] were analyzed for ADRs pertaining to nine antihypertensive groups comprising a total of 44 drugs. Antihypertensive agents were selected for the study as these are commonly prescribed and used drugs. All the antihypertensive drugs mentioned in the target sources of information were made part of the study. The ADRs were categorized according to body systems such as the cardiovascular system, central nervous system, respiratory system, and gastrointestinal system. ADRs of each drug were compared among the various drug information sources. Parameters assessed were: (i) number of drugs out of the 44 drugs studied that were not mentioned at all in various sources, (ii) average number of ADRs mentioned for all drugs in various sources, (iii) total ADRs of prototype drugs from each antihypertensive group, (iv) serious ADRs of the prototype drugs mentioned, and (v) qualitative analysis of serious ADRs among different sources.

Results

NFI, DT, and CIMS were analyzed for provided ADR information of 44 antihypertensive drugs belonging to nine drug groups [Figure 1]. Pharmacology textbooks[12,14] provided ADRs of drug groups as a whole and not of individual drugs. Medicine textbook[13] mentioned various drug therapies and regimens and did not deal with the details of drugs (like ADRs) in detail. Therefore, data from these textbook sources of information were not included in the final analysis.

The information was analyzed according to drug groups such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, beta blockers, and various numbers of drugs present per group. The maximum number of drugs (10 each) for ACEIs and beta blockers and minimum for vasodilators, diuretics, and central sympatholytics (2 each) were mentioned in NFI, DT, and CIMS [Figure 1].

The maximum number of antihypertensive drugs was mentioned in DT (36 out of 44 studied), it being deficient in only 8 drugs. CIMS listed 31 drugs followed by NFI (16 drugs). NFI enumerated a total of 395, DT listed 330,

![Figure 1: Number of drugs studied per group. ACE I: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blocker; CCBs: Calcium channel blockers; Misc.: Miscellaneous](image-url)
while CIMS enumerated 650 ADRs for the antihypertensive drugs studied in all.

The total ADRs of prototype drugs listed in NFI, DT, and CIMS were 218, 63, and 184, respectively. None of these sources of information was complete in providing wholesome information regarding ADRs of antihypertensive drugs and there was variability in description [Table 1].

NFI mentioned the maximum number of serious ADRs (47) of the prototype drugs followed by CIMS (36) and DT (8). DT is deficient in elaborating the serious ADRs [Table 2].

**Qualitative analysis**

Serious ADRs were analyzed in these sources of information. Data were incomplete in all sources of information; NFI does not mention all the drugs and is silent on few of the serious ADRs. DT does not mention all the drugs and is silent on most of the serious ADRs. CIMS does not mention all the drugs either and is silent on most of the serious ADRs, but does report few ADRs which are not mentioned in either DT or NFI [Table 3]. NFI seems the best source as far as serious ADRs information is concerned; however, a few serious ADRs were not mentioned even in NFI. DT reported serious ADRs for only a few of the drugs overall, most of which are cardiovascular events. It is deficient in information regarding serious events other than cardiovascular ADRs in all drugs studied except for one (Eplerenone). CIMS mentions only a few of the serious ADRs for some drugs and not all [Tables 3 and 4]. NFI also provided more elaborated information about the reported ADRs compared to the other two resources.

**Discussion**

To promote the rational and scientific use of drugs, it is important that relevant information about any drug, namely, its indications, dosage, ADRs, contraindications, and precautions is readily available to the prescribing physicians. Various sources of information available for the assessment of ADRs and prescribing decisions are the standard textbooks, National Formularies, drug information compendia, drug advertisement brochures, and online search engines. Textbooks provide ADR information of drugs as a class only and not individually. Online search is easily accessible but with doubtful authenticity, and advertisement brochures are usually biased. Prescribers usually tend to consult the commercially available drug information compendia which need to be accessed for completeness and quality of data.

We undertook this cross-sectional observational study to assess the quantity and quality of drug information about ADRs available in various sources and compared it with NFI, as a standard. DT and CIMS are commercially available drug information compendiums and were found to contain variable ADR information.

ADRs are an important health issue due to their being a factor in morbidity and mortality of patients. The safety of patients and the safe use of medicines are crucial for optimum use of medicines and delivery of health care. Safety issues related to drugs are regulated by the CDSCO, and PvPI deals with reporting and collection of ADR data in India. PvPI is an integral component of the WHO collaboration for International Drug Monitoring. The WHO database could become an important source of ADR-related information in due course of time. Various online tools under this program such as VigiBase, VigiAccess, and VigiMine are designed for global data collection, data mining, or retrieval. But as of now, it has a limited base and access. Physicians at large are not just aware of it. It is envisaged to be a 2-way flow of ADR-related information, but is still in a consolidation phase.
Table 3: Variability in mentioning serious cardiovascular adverse drug reactions of antihypertensive drugs

| Serious ADR          | Drug   | Whether Mentioned NFI | Whether Mentioned DT | Whether Mentioned CIMS |
|----------------------|--------|-----------------------|----------------------|------------------------|
| Hemolytic ADRs       | Ramipril | No                    | No                   | Yes                    |
|                      | Captopril | Yes                  | No                   | No                     |
|                      | Losartan | Yes                  | No                   | No                     |
|                      | Propranolol | Yes               | No                   | No                     |
|                      | Metoprolol | Yes              | No                   | No                     |
|                      | Methyl dopa | Yes            | No                   | No                     |
|                      | Hydrochlorothiazide | No | Yes                   | Missing               |
|                      | Hydralazine | Yes              | No                   | Missing               |
|                      | Terazosin | Yes                  | No                   | No                     |
| Cardiovascular events| Enalapril | Yes                  | No                   | No                     |
|                      | Captopril | No                   | No                   | Yes                    |
|                      | Trandolapril | Missing    |Yes                   | Missing               |
|                      | Fosinopril | Missing            | Yes                  | No                     |
|                      | Atenolol | Yes                  | No                   | No                     |
|                      | Metoprolol | Yes               | No                   | No                     |
|                      | Esmolol | Yes                  | No                   | Missing               |
|                      | Bisoprolol | Missing         | Missing              | Yes                    |
|                      | Amlodipine | Yes                | Yes                  | No                     |
|                      | Felodipine | No                | Missing              | Yes                    |
|                      | Verapamil | No                   | No                   | Yes                    |
|                      | Diltiazem | No                   | No                   | Yes                    |
|                      | Clonidine | Yes                  | No                   | No                     |
|                      | Methyl dopa | Yes            | No                   | No                     |
|                      | Hydrochlorothiazide | Yes | No                   | No                     |
|                      | Sodium nitroprusside | Yes | Missing       | Missing               |
|                      | Terazosin | Yes                  | No                   | No                     |
|                      | Doxazosin | Missing             | Yes                  | Missing               |
|                      | Eplerenone | Missing        | Yes                  | Missing               |

Yes: ADR mentioned; No: ADR not mentioned; Missing: Drug not mentioned in the source of information; NFI: National Formulary of India; DT: Drug Today; CIMS: Current Index of Medical Specialties; ADRs: Adverse drug reactions

Table 4: Analysis of other serious adverse drug reactions of antihypertensive drugs

| Serious ADR          | Drug   | NFI | DT | CIMS |
|----------------------|--------|-----|-----|------|
| Pancreatitis         | Enalapril | Yes | No  | No   |
|                      | Methyl dopa | Yes | No  | No   |
|                      | Hydrochlorothiazide | Yes | No  | No   |
|                      | Prazosin | Missing | No  | Yes  |
| Renal impairment     | Enalapril | Yes | No  | No   |
|                      | Lisinopril | No  | No  | Yes  |
|                      | Olmesartan | Missing | No  | Yes  |
|                      | Hydrochlorothiazide | No  | No  | Yes  |
| Fatal hepatic necrosis| Methyl dopa | Yes | No  | No   |
| Bronchospasm         | Enalapril | Yes | No  | No   |
|                      | Atenolol | Yes | No  | No   |
|                      | Metoprolol | Yes | No  | No   |
|                      | Esmolol | Yes | No  | Yes  |
| Laryngeal stridor    | Ramipril | No  | No  | Yes  |
| Bone marrow depression| Methyl dopa | Yes | No  | No   |
| Anaphylactic reactions| Captopril | No  | Yes | No   |
|                      | Eplerenone | Yes | Missing | Missing |

Yes: ADR mentioned; No: ADR not mentioned; Missing: Drug not mentioned in the source of information; NFI: National Formulary of India; DT: Drug Today; CIMS: Current Index of Medical Specialties; ADR: Adverse drug reaction

Serious ADRs increase morbidity, hospital stay, loss of working days, and also contribute to increased financial burden. These sources of information were not up to the mark for mentioning the serious ADRs. NFI mentioned the maximum number of serious ADRs (47) for the prototype drugs followed by CIMS (36) and DT (8). For enalapril, NFI mentioned 10 serious ADRs while only 4 ADRs were mentioned in CIMS and none of the ADRs were mentioned in DT. Similar number (9) of serious ADRs was mentioned in NFI and CIMS while only 1 was mentioned in DT for hydrochlorothiazide. In general, DT is deficient in elaborating the serious ADRs for prototype drugs, a dangerous pitfall for the prescriber.

Quantitative analysis

DT contains information for a maximum number of drugs, i.e., 36 out of the total of 44 antihypertensive drugs (81.8%), belonging to nine antihypertensive classes studied and NFI gave information for 16 drugs only. On the other hand, NFI listed the maximum number of total ADRs (218) and the least number was provided by DT (63). None of the sources of information mentioned all the antihypertensive drugs studied.

Total ADRs of prototype drugs listed in NFI, DT, and CIMS were 218, 63, and 184, respectively. There was a wide variability while listing ADRs, for example, 54 ADRs were mentioned for enalapril in NFI, but only 11 ADRs were mentioned in DT. For hydrochlorothiazide, CIMS mentioned 42 ADRs while DT mentioned only 3 ADRs. No source of information was complete in providing wholesome information regarding the type of ADRs of antihypertensive drugs and there was also variability in describing them.

Qualitative analysis

Qualitative analysis of serious ADRs was undertaken in these sources of information. Information for cardiovascular events such as arrhythmias, myocardial infarction, chest pain, aggravation of angina, cardiac blocks, and congestive heart failure was not symmetrical across all sources of information. Cardiovascular ADRs were not mentioned in different sources for many drugs such as verapamil, diltiazem, captopril, and felodipine, a serious lacuna.

No hemolytic ADR was mentioned in DT. NFI mentioned hemolytic ADRs for captopril, losartan, propranolol, metoprolol, methyl dopa, hydralazine, and terazosin, while CIMS mentioned them for only ramipril and hydrochlorothiazide.

Some data regarding serious ADRs are not mentioned in NFI such as renal impairment with lisinopril, laryngeal stridor.
with ramipril, and anaphylactic reactions with captopril. DT failed to mention serious ADRs other than cardiovascular ones except for eplerenone for which it mentions anaphylactic reactions. A known serious ADR, bronchospasm of beta blockers, and fatal hepatic necrosis, and bone marrow depression for methyldopa are mentioned only in NFI and neither of the other two sources of information. CIMS mentions only a few of the serious ADRs with some drugs.

Since these sources of ADR information are commonly utilized for seeking drug information, such variability may lead to unsafe use of drugs. This study highlights the discrepancies in drug information available in various sources by taking a representative sample of antihypertensive drugs. To the best of our knowledge, this study is the first such attempt to address this issue. It will be helpful in making the prescriber aware of the pitfalls of depending on only one source of information for ADRs.

Conclusions

Different data sources covering ADRs have their strengths and limitations, and selection of appropriate source of information is often difficult. Variation exists in the quantity and quality of information on ADRs of drugs available in various sources. The field of comprehensive ADR resource is not appropriately addressed in the medical literature. Academicians and policymakers can work toward more robust ADR information with updated information from time to time.

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Conflicts of interest
There are no conflicts of interest.

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