Adverse drug reaction

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Summary
An adverse drug reaction (ADR) is an unwanted, also an undesirable effect of a drug medication that occurs during usual use in the clinic. It is an unintended noxious response which occurs after the normal use of a drug, which is suspected to be associated with the drug. Every drug that can produce the therapeutic effect on the body can also has the ability to produce unwanted side effects. Health professionals should all be well grounded in the knowledge and awareness that these unwanted effects pose to the health care system and very importantly ways to avoid these adverse drug reactions. These adverse drug reactions' occurrence is almost daily in the institution that provides health care and it can adversely affect a patient's quality of life, often causing considerable morbidity and mortality. It is said to be responsible for an approximate of 1 in 20 admissions in the hospital. The aim of this study is to briefly discuss some facts about ADR's and their prevention, and their diagnosis.
Abbreviations: ADR -adverse drug reaction. ACE -angiotensin-converting enzyme. UK-United Kingdom. NSAID- non -steroidal anti-inflammatory drug.
Kew words: Pharmacovigilance, drug, adverse reactions, treatment, clinical.

Introduction

An adverse drug reaction (ADR) is 'an harmful or irritating reaction resulting from an intervention related to the use of a drug medication; adverse effects usually predict hazard from administration that would be given in the future and warrant prevention, or specific treatment, or change of the regimen of dosage, or product withdrawal. [1].

A lot of research work has been conducted in the identification of the patient populations that have high risk potentials, the medications that are commonly the cause, and the potential causes of ADRs. The regular rise in the number of drugs on the market, in an aging population, and an upward trend in polypharmacy contributes to factors causing the prevalence of ADRs worldwide.

"Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice", they have also been found to be the cause of emergency admission in the hospital and these adverse drug reactions might also occur during the use of the medication or after the use of the medication.[2].

The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. Inevitably, the event frequency is associated with the method used to identify such events and the majority of ADRs do not cause serious systemic manifestations. Nevertheless, this frequency of potential harm needs to be considered carefully because it has associated morbidity and mortality, can be financially costly and has a potentially negative effect on the prescriber-patient relationship. [3,4].

Medicines that have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics. Fatal ADRs, when they occur, are often attributable to haemorrhage, the most common suspected cause being an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory drug (NSAID).[5].

Classification of adverse drug reactions

Classification systems for ADRs are useful for educational purposes, for those working within a regulatory environment and for clarifying thinking on the avoidance and management of ADRs.

Rawlins-Thompson Classification

Adverse drug reactions initially was classified into two sub -types. Type A ADRs that are dose-dependent and are predictable; they are augmentations of pharmacologic effects of the drug that is already known, such as that of orthostatic hypotension with antihypertensive medications. Type B ADRs are the uncommon and unpredictable adverse reaction, depending on the pharmacology of the drug which is known; they do not depend on dose and they affect a small population, which suggests that the individual patient host factors are important. Allergic reactions or hypersensitivity to drugs are examples of type B ADRs. Type A reactions later, were called augmented, and type B reactions, bizarre. Also two further types of reactions were eventually added: chronic reactions, relating to both dosage and the time (type C), and delayed reactions (type D). Withdrawal later became the next (fifth) category (type E), and most

recently, unexpected failure of therapy then became the sixth (type F).There are almost 80% of ADRs in the hospital setting causing admission to a hospital are type A. These ADRs are potentially avoidable and often predictable.

Table1.Drug dose and features

Type of reaction	Features	Examples	Management
A: Dose related (Augmented)	Common Related to the pharmacologic action of the drug- exaggerated pharmacologic response. Predictable Low mortality	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, serotonin syndrome with SSRIs, digoxin toxicity	Reduce dose or withhold drug Consider effects of concomitant therapy
B: Non- dose related (Bizarre)	Uncommon Not related to the pharmacologic action of the drug Unpredictable High mortality	Immunologic reactions: anaphylaxis to penicillin Idiosyncratic reactions: malignant hyperthermia with general anesthetics	Withhold and avoid in future
C: Dose related and time related (Chronic)	Uncommon Related to the cumulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates	Reduce dose or withhold; withdrawal may have to be prolonged.
D: Time related (Delayed)	Uncommon Usually dose related Occurs or becomes apparent sometime after use of the drug	Carcinogenesis Tardive dyskinesia Teratogenesis Leucopenia with lomustine	Often intractable
E: Withdrawal (End of use)	Uncommon Occurs soon after withdrawal of the drug	Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety)	Reintroduce drug and withdraw slowly
F: Unexpected failure of therapy (Failure)	Common Dose related Often caused by drug interactions	Inadequate dosage of an oral contraceptive when used with an enzyme inducer Resistance to antimicrobial agents	Increase dosage Consider effects of concomitant therapy

The DoTS system

The DoTS classification is based on the Dose relatedness, and the Timing and Susceptibility of the patient. DoTS first considers the doses of the drugs, as many adverse effects are related obviously to the dose of the drug used. In DoTS, reactions are divided into toxic effects (effects related to the use of drugs outside of their usual therapeutic dosage), collateral effects (effects occurring within the normal therapeutic use of the drug) and hyper-susceptibility reactions (reactions occurring in sub-therapeutic doses in susceptible patients).

Preventing Adverse drug reactions

Even though there are ADRs that are unpredictable – such as anaphylaxis in a patient after one previous uneventful exposure to a penicillin-containing antibiotic – many are preventable with adequate prior knowledge and monitoring. The ability to prevent ADRs usually entails when the drug treatment plan is inconsistent with current evidence-based practice or is unrealistic when taking known circumstances into account.

There are two steps to be followed in order to prevent an ADR occurring:

1. Identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly.

Age. Elderly patients may be more prone to ADRs, with age-related decline in both the metabolism and elimination of drugs from the body. Children differ from adults in their response to drugs. Neonatal differences in body composition, metabolism and other physiological parameters can increase the risk of specific adverse reactions. Higher body water content can increase the volume of distribution for water-soluble drugs, reduced albumin and total protein may result in higher concentrations of highly protein bound drugs, while an immature blood–brain barrier can increase sensitivity to drugs such as morphine.

◊ Gender. Women may be more susceptible to ADRs. For example, impairment of concentration and psychiatric adverse events associated with the anti-malarial mefloquine are more common in females.

◊ Ethnicity has also been linked to susceptibility to ADRs, due to inherited traits of metabolism. Examples of ADRs linked to ethnicity include the increased risk of angioedema with the use of ACE inhibitors in black

patients.

◊ Pharmacogenetics is concerned with studying genetic variations which influence the individual's response to drugs, and also examines multiple forms of a single gene that exists in an individual or among a group of individuals (polymorphism) that codes for drug transporters, enzymes that metabolizes drugs and the receptors for drugs.

2. Ensure the treatment plan mitigates any possible adverse effects.

Treatment plan

Prudent, safe prescribing is key to reducing errors that can contribute to ADRs. Treatment plans should consider and mitigate for any possible adverse effects. For example, co-prescription of folic acid with methotrexate will reduce the incidence of adverse effects associated with folate deficiency; and monitoring electrolytes and renal function when treating with renally active drugs or diuretics. These examples can all prevent treatment-emergent adverse effects although may be limited because monitoring recommendations are often inadequate or ambiguous. It is important to remember that prudent prescribing may also avoid the use of drugs altogether and the treatment plan should always consider non-pharmacological or conservative options.

Diagnosing Adverse drug reactions

Treatment related problems that occurs in patients that are admitted to hospitals might manifest in many different ways, such as drowsiness or weakness, biochemical or haematological derangements (including acute kidney injury, electrolyte imbalance or anaemia), bleeding, gastrointestinal disturbances. A comprehensive medication history is fundamental in identifying any possible connection between a presenting complaint or subsequent finding and an ADR, as well as preventing future ADRs. In some cases, specific investigations can assist in the diagnosis of an ADR by providing objective evidence of the reaction and confirming a drug-induced disease. For example, organ-specific damage accompanied by intracellular tissue deposition of the drug or a metabolite.

Pharmacovigilance

Pharmacovigilance is concerned with identifying, evaluating, and understanding and the prevention of adverse drug events and any other problems that are related to drugs.

A new legislation was introduced in the European Union in 2012 which ensures good vigilance practice for pharmaceutical companies and the medicines regulators also. This new guidance clearly identifies the roles and responsibilities of relevant stakeholders in terms of drug safety. Notably, the guidance has introduced a programme of more intensive surveillance for new pharmacological agents and biological agents with black triangle status (i.e. those requiring additional monitoring).

Reporting Adverse Drug Reactions

The mainstay of detecting potential ADRs over the last half a century has been spontaneous reporting systems such as the Yellow Card Scheme in the UK, operated by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). The scheme was founded in 1964 following the thalidomide disaster in the late 1950s. Through spontaneous reporting, the scheme collects data on suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued on prescription or purchased over the counter. For a report to be valid, only four items of information are required: an identifiable patient, a reaction, a suspected medicinal product and an identifiable reporter. However, reporters are encouraged to provide as much information as possible, i.e. to provide additional data and clinical context for assessors.

Spontaneous reporting systems, while widely adopted for pharmacovigilance, are most effective when the adverse events are rare and uncommon (less than 1% of treated patients) and when the event is typical of a drug-induced condition. Their use is more limited in identifying a small increase in the rate of common events, such as myocardial infarction or stroke. This is the reason why recent drug safety scandals, such as thiazolidinedione-induced and rofecoxib-induced cardiovascular events, remained undetected despite widespread use of these agents.

There are many other methods and data streams used in pharmacovigilance, including formal drug safety studies, published data, and pharmaceutical company data from periodic safety update reports (PSURs) and shared international data. However, regulators and scientists are also looking at the ability of other ‘big data’ sources, such as social media, to detect early signals; this remains an exciting and largely unexplored area of research.

Conclusion

In the above article, we have carefully discussed the identification, prevention and reporting of ADRs, and also how steps are being taken to improve on the awareness of adverse drug reactions. It would make the healthcare institution a better place in future years to come if this topic can be tackled without rest. Drug medication efficacy would be greatly improved, and clinical practice would be more efficient.

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