Why Adverse Drug Events occur and what can be done to avoid them.

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Why Adverse Drug Events occur and what can be done to avoid them.

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Abstract

This article reviews the prevalence and importance of adverse drug events. The mechanisms that lead to ADE are explored and strategies to prevent them are discussed.

Introduction

An adverse drug event (ADE) is any injury resulting from the use of a drug.[1] ADE are an important problem in healthcare, only patient accidents cause more harm to patients in NHS hospitals.[2] The incidence of ADE reported in the USA is 6.5% in adult inpatients, 27.4% in outpatients and 2.3% in paediatric inpatients.[3] However, up to 50% of admissions due to medications may be avoidable.[4] The high prevalence of ADE and their negative consequences for the patient, the healthcare provider and the economy[3] has prompted research to try and identify their causes[5,6] so that they may be prevented.[7] Unfortunately study findings can be difficult to compare and interpret because different definitions for drug related incidents are commonly used.[8]

Methods

Mechanisms of ADR

The mechanisms of a large number of ADR have been elucidated. However, many other ADR are still poorly understood. This is unsurprising as the action of drugs are affected by a wide variety of individual factors such as body weight, body composition, sex, age, dosage forms, delivery systems, time of administration and co-ingestion of other drugs.[11,13] Physiological or pathological states can also predispose individuals to ADR. Risk groups include those who are pregnant, lactating, children, elderly, or patients who have decreased renal clearance or haemodialysis.[4,11,13] Clinical trials are unlikely to identify these ADR in specific populations due to ethical exclusion from the trials. The teratogenicity of thalidomide is an obvious example.[4] Other methods of detection are therefore necessary.

Pharmacological

Pharmacological ADR can be divided into direct effects and collateral effects. Direct ADR occur via the intended therapeutic action of the drug, for example hypoglycaemia with insulin use.[13] The usual dose can cause hypoglycaemia if food intake is reduced or exercise increased. Collateral effects occur as a consequence of the drugs action at receptors in other locations or multiple receptors. For example ?–adrenoreceptor antagonists are used following myocardial infarction to reduce heart rate and the risk of arrhythmias. They are also used to reduce blood pressure but their non-specific action means that they also act upon the ?–adrenoreceptors in the peripheral arteries, which can worsen peripheral vascular disease. The action of drugs at more than one receptor type is also a mechanism for ADR to occur. For example the therapeutic effects of tricyclic antidepressants are derived from their ability to stimulate the monoaminergic pathways by reducing monoamine re-uptake. These drugs also have antimuscarinic activity which inhibits the activity of the parasympathetic pathways causing dry mouth, constipation, long sightedness, urine retention and impotence.
Toxicity

The toxic effects of drugs are either due directly to the drug or a toxic metabolite produced by enzymes, reactive oxygen species (ROS) or by light.[11] Toxicity occurs when the amount of toxic molecules becomes too great for the body’s defences. For example, paracetamol is metabolised by enzymes in the liver to the highly reactive N-acetyl-P-benzoquinoneimine, which binds to glutathione. If too much paracetamol is taken or the glutathione stores become depleted, N-acetyl-P-benzoquinoneimine binds cellular macromolecules killing liver cells. Few therapeutic drugs induce toxicity via ROS but halothane, phenytoin and some antiepileptic drugs such as methyldopa may produce ROS capable of binding to DNA causing cell toxicity or carcinogenicity. Light radiation is also capable of inducing drug toxicity. Tetracyclines, chlorpromazine, sulfonamides and quinolones are examples of drugs that can undergo phototoxic reactions to produce toxic metabolites.

Genetic susceptibility to ADR

Genetic differences in an individual’s response to a drug can increase their susceptibility to an ADR. Altered drug metabolism can change the amount of drug available, the extent and duration of effects or produce toxic metabolites all of which can increase the likelihood of an ADR.[13] Genetic explanations have been discovered for many of the ADR which were previously thought to be type B idiosyncratic ADRs. Examples of abnormal drug metabolism are given below:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD is an enzyme that oxidises glucose-6-phosphate to the corresponding gluconolactone.[11,13] This reaction produces NADPH that maintains the antioxidant glutathione in its reduced form to prevent damage from ROS. G6PD deficiency is an X-linked defect common to African-Americans, Mediterranean and some Filipino populations. A G6PD deficient individual is at an increased risk of haemolysis from oxidising agents such as sulphonamides, aspirin, and quinine which in severe cases can be fatal.

Porphyria

Acute intermittent porphyria is characterised by recurrent attacks of abdominal pain, neurological disturbances and excessive amounts of δ-aminolevulinic acid and porphobilinogen in the urine.[11,13] Different forms exist but it is an autosomal dominant disorder of the haem biosynthetic pathway due to an enzymatic error. Acute crisis can be provoked by exposure to drugs such as barbiturates, corticosteroids, oral contraceptives, ethanol, sulphonamides, anaesthetics and oral antidiabetics.

Cytochrome P450 system

Genetic polymorphisms within the population cause variations between individuals in their abilities to metabolise drugs. An important example is the polymorphisms in the cytochrome P450 system. The population can be divided into 3 groups: slow, medium and fast metabolisers.[11] Approximately 8% of the UK, 30% Hong Kong Chinese and 1% of Arabs populations are slow metabolisers;13 at increased risk of adverse effects from drugs which rely on this system. The two main groups of drugs which are affected by these polymorphisms are those that act on the CNS (e.g. metoprolol, propranolol) and those that act on the CVS (e.g. haloperidol, amitriptyline, nortriptyline, flecainide and propafenone).[11,13]

Review

Drug interactions

Interactions may increase or decrease the action of a drug causing unexpected ADR or ineffective treatment.[14] Important examples are drugs which induce or inhibit liver enzymes (table 1a & 1b). Enzyme inducers increase the metabolism rendering some other drugs less effective. Conversely, enzyme inhibitors will slow down metabolism increasing the plasma concentrations of other drugs and make ADR more likely. Prescribers should be aware of this and avoid this situation if possible or consider changing the dosages accordingly.

Immunological ADRs

Immunological ADR include all ADR involving the immune system and they are commonly described according to the Gell and Coombs classification[13,15] (table 2).

Type I

Mast cell mediated immediate hypersensitivity. The interaction between the drug and native proteins produces antigenic complexes. The complexes stimulate specific IgE receptors on the surface of mast cells causing degranulation and the release of inflammatory mediators.[15] Clinical manifestations include: urticaria, rhinitis, asthma, angio-oedema and anaphylactic shock. The most frequently involved drugs are penicillin, neuromuscular blocking agents
and local anaesthetics.[11,13] Anaphylactoid reactions differ in that they involve the direct release of inflammatory mediators and can occur at the first contact. They are unpredictable and often serious.[11]

**Type II**

Cytotoxic antibody reactions occur when a drug alters a membrane bound protein or acts as a hapten.[11,13] The binding of antibodies to the altered proteins causes a conformational change in the structure of the antibody tail region (Fc region) which can then trigger complement-mediated cell lysis. Examples include haemolysis with methyldopa and thrombocytopenia with quinine.

**Type III**

Drugs can alter native proteins to become antigens stimulating antibody synthesis. If the ratio of antigens to antibodies becomes high enough cross linking of antigens and antibodies results in large complexes. These large immune complexes can become deposited in membranous filtration systems and activate the complement system resulting in damage to the tissue.[11] The classic example is serum sickness with horse-derived anti-tetanus serum and snake antivenins characterised by fever, arthragias, skin reactions and enlarged lymph nodes.[13,15]

**Type IV**

A hepten-protein complex sensitises a T lymphocyte.[13] The T-lymphocytes that recognise the complex undergo clonal expansion.[15] Then if the complex is encountered in future the sensitised T-lymphocytes secrete cytokines (e.g. interleukin 12 and interferon gamma) that initiate an inflammatory response and cause an accumulation of activated macrophages. Contact dermatitis from antihistamine cream and Stevens-Johnson syndrome with carbamazepine are examples of delayed cell-mediated ADR.

**Discussion**

**Medication errors**

The prescription process relies on the complex interaction of health professionals from different disciplines and errors which lead to ADE can occur at any stage in the prescription process.[16,17] Research has identified the most common errors in the prescription process and when they are most likely to occur[5,6] from this data a generic model of medication error has been developed see Karnon et al.[7]

**How prescribers can minimise ADE**

A variety of factors have been identified which can occur in isolation or in combination to contribute to ADE. As shown in table 3 the different factors can be broadly classified under four headings: organisational factors, communication factors, knowledge deficits, and lapses (failure to follow procedure). Not all of the factors in table 3 can be solved by the prescriber alone, systems and education also need to be improved to reduce errors.[16,17] However, significant steps can be taken by the prescriber to minimise medication errors. For example, there are more than 10 000 abbreviations commonly used in medicine but with more than 16 000 meanings[19] which is an obvious route to confusion, misinterpretations and medication errors. When prescribing writing should be legible and abbreviations avoided. Especially as the use of similar product labelling and packaging was found to be most commonly reported reason for medication error (approximately 53% of reports) in the USA Medication Error Reporting Program.[20] This is something to be addressed by regulating agencies and manufactures as clear labelling is essential. Prescribers can help to avoid errors by organising the products so that easily confused products are not stored together. But the most important method of avoiding medication error for health professionals is diligence when prescribing. The correct procedures should be followed at all times. Labels should be read carefully and recognition of products should not rely upon their location or packaging, which can both change. A clear understanding of the product should be attained before its use which will allow the proper administration and facilitate the identification of unusual usage, which can be checked. This requires knowledge of the product, its indications and contraindications as well as the patient’s condition. The prescriber must be vigilant and select the most appropriate drug for a patient; always considering if there is a better option with a smaller potential for adverse effects. ADE occurring as the result of genetic or immunological ADR can be hard to prevent if individual susceptibility is unknown. However, the prescriber can be aware of the drugs most likely to cause these ADR and their common manifestations. A high level of suspicion can then be maintained so that if they do occur they can be quickly diagnosed, managed and documented so that they are avoided in future.

If an ADE, medication error or a potential medication occurs it is important that it is identified and reported. The Medicines and Healthcare products Regulatory Agency[21] runs the yellow card scheme in the UK for
both Healthcare professionals and patients to report suspected ADR and the National Patient Safety Agency[22] has a reporting system for medication errors and potential medication errors occurring in the UK. The data collected is analysed in an attempt to identify the causes of error and ADE so that they may be prevented in the future.

Conclusion(s)

ADE are a common occurrence but up to 50% may be avoidable.[4] Avoiding ADE is important not only to prevent patient harm but also to save the extra resources and money needed to treat them. This has led researchers to try and identify the numerous mechanisms behind ADE and ways to reduce their incidence. Improved medications and safer prescription systems are being designed. However, knowledge of the mechanisms of ADE and diligence on the behalf of the prescriber is essential to reduce avoidable ADE. The patient’s diagnosis, medications and any other factors that might affect drug action should be considered and the most appropriate drug based on these considerations selected. Only drugs that are familiar to the prescriber should be used and the mechanisms of common and important complications should be known. These methods will reduce ADE, but some will still occur and these should be reported to aid future developments in drug safety.

References

Illustrations

Illustration 1

Table 2

<table>
<thead>
<tr>
<th>Immunological reaction</th>
<th>Important Examples</th>
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<tr>
<td><strong>Type I – immediate hypersensitivity</strong> (e.g. interaction between drug and native protein produces a new, antigenic molecule)</td>
<td>Anaphylaxis and urticaria with penicillins</td>
</tr>
<tr>
<td><strong>Type II – cytotoxic antibody</strong> Drug alters a membrane-bound protein; cytotoxic antibodies bind to the altered protein and complement-mediated cell lysis occurs</td>
<td>Haemolysis with methyldopa Thrombocytopenia with quinine</td>
</tr>
<tr>
<td><strong>Type III – immune complex</strong> Persistent foreign protein molecules cause antibody synthesis; immune complexes are formed and damage tissues</td>
<td>Serum sickness with horse-derived antitetanus serum and snake antivenins</td>
</tr>
<tr>
<td><strong>Type IV – delayed hypersensitivity</strong> Delayed cell-mediated reactions</td>
<td>Erythema nodosum with sulphonamides</td>
</tr>
<tr>
<td></td>
<td>Stevens–Johnson syndrome with carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin hypersensitivity</td>
</tr>
</tbody>
</table>
Illustration 2

Table 3

<table>
<thead>
<tr>
<th>Commonly reported reasons for medication error[13,16]</th>
</tr>
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<tr>
<td><strong>Communication</strong></td>
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<tr>
<td>Poor handwriting</td>
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<tr>
<td>Similar sounding/ looking product names</td>
</tr>
<tr>
<td>Drug product abbreviations</td>
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<td>Lack of information about the patient</td>
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1a. Drugs capable of inducing hepatic enzymes and the drugs affected.

<table>
<thead>
<tr>
<th>Hepatic enzyme inducers</th>
<th>Drugs metabolised more rapidly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Hydrocortisone</td>
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<tr>
<td>Carbamazepine</td>
<td>Oral Contraceptive Pill</td>
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<td>Barbiturates</td>
<td>Phenytoin</td>
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<td>Rifampicin</td>
<td>Warfarin</td>
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<td>Alcohol (chronic excess)</td>
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<tr>
<td>Sulphonylureas</td>
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</table>
Table 1b. Hepatic enzyme inhibitors and drugs that can be affected.

<table>
<thead>
<tr>
<th>Hepatic enzyme inhibitors</th>
<th>Drugs metabolised more slowly</th>
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</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Carbamazepine</td>
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<tr>
<td>Omeprazole</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Theophyllines</td>
</tr>
<tr>
<td>Valproate</td>
<td>Warfarin</td>
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<tr>
<td>Isoniazid</td>
<td></td>
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<tr>
<td>Cimetidine</td>
<td></td>
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<tr>
<td>Acute ethanol intoxication</td>
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<tr>
<td>Sulphonamides</td>
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</table>
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