Adverse drug reactions

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Abstract

Adverse drug reactions (ADRs) are a common and important cause of morbidity and mortality. They occur frequently in patients undergoing anaesthesia or in Intensive Care. ADRs occur by a number of mechanisms, some of which remain unclear, but several risk factors have been identified. It is increasingly recognized that pharmacogenetic factors are important in determining susceptibility to ADRs. Medical practitioners should be aware of their responsibility to report ADRs and know how to report them.

Keywords Adverse drug event; adverse drug reaction; drug reaction classification; drug reaction mechanism; Medicines and Healthcare products Regulatory Agency

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- classify adverse drug reactions
- list the risk factors and describe common mechanisms associated with adverse drug reactions
- describe the process of recognizing and reporting any adverse drug reaction to the MHRA

An adverse drug reaction (ADR) is described by the World Health Organization as a 'response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'. ADRs are relatively common being responsible for approximately 6.5% of all hospital admissions with a projected annual financial cost to the NHS of £466 million and a mortality of 2%,[1] although it is recognized that admissions related to ADRs are under-reported.[2]

Anaesthesia-associated ADRs represent a significant cause of mortality and morbidity. One review of all Medicines and Healthcare products Regulatory Agency (MHRA) data up to 2005 revealed some 11,199 reactions for common anaesthetic agents, 9% of which were fatal. The majority of ADRs in this report was not allergic and generally associated with induction of anaesthesia.[3] However, allergic reactions are generally under-reported, particularly for older drugs. Whilst anaphylaxis is thought to have an incidence of 1:5000 to 1:20,000, more accurate data is expected from the 6th National Audit Project led by the Royal College of Anaesthetists, specifically targeted at perioperative anaphylaxis.

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Adverse drug events are subtly different from ADRs. Adverse drug events (ADEs) occur when there is a reaction associated with exposure to a drug but not necessarily caused by that drug. ADEs occur frequently, particularly after the introduction of a new therapeutic agent, and are important as the reporting of ADEs helps identify ADRs associated with new drugs.

Classification

The traditional classification for ADRs comprises Type A (augmented) reactions and Type B (bizarre or idiosyncratic) reactions and generally encompasses most observed ADRs. Subsequently four further divisions were added to produce a six category classification (A–F) (Table 1). A more recent classification (Table 2) accounts for the **d**ose relatedness, **t**ime course and **s**usceptibility of the patient (DoTS)[4] to a reaction and this classification is increasingly used. Malignant hyperpyrexia, for example, occurs at any dose in susceptible individuals (**Do**), occurs on first dose (**T**), and individual susceptibility factors are an inherited mutation for the ryanodine receptor (**S**).

Type A and B reactions

The MHRA continues to refer to the simple, 'classical' classification, and this suits discussion of drug reactions occurring in anaesthesia and intensive care. In general, Type A reactions are those in which the adverse reaction occurs in proportion to the dose of the administered drug and tend to be related to pharmacokinetics. Thus the hypotension associated with propofol administration is a dose-related and predictable adverse reaction to increasing amounts of propofol. Fasciculations associated with suxamethonium is another such Type A reaction, but so is the subsequent rise in intra-ocular pressure – a secondary adverse reaction occurring as a consequence of an initial reaction. Such reactions are usually revealed in developmental clinical trials and so are already well recognized before the marketing of a new drug.

In contrast, Type B reactions tend to be unpredictable ('bizarre'), and unrelated to the known pharmacology of the drug in question. The reactions tend to be more severe and potentially fatal but remain relatively rare. The most familiar examples in anaesthesia are anaphylaxis, suxamethonium apnoea and malignant hyperpyrexia (MH). These reactions are idiosyncratic, infrequent and influenced by immunological and genetic factors. Some Type B reactions present less dramatically (e.g. halothane hepatotoxicity or fluoride nephrotoxicity). For all these reasons Type B ADRs are often missed in clinical trials, being discovered during post-marketing surveillance often some years later.

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Classification of drug reactions

	Type of reaction	Mnemonic	Features	Examples relevant to anaesthesia/Intensive Care
A	Dose-related	Augmented	Common Related to pharmacological action of drug Predictable Low mortality	Hypotension after propofol, fasciculations with suxamethonium
B	Non-dose-related	Bizarre	Uncommon Unrelated to pharmacological action of drug Unpredictable High mortality	Anaphylaxis, suxamethonium apnoea, malignant hyperpyrexia
C	Dose-related and time-related	Chronic	Uncommon Related to cumulative dose	Propofol infusion syndrome
D	Time-related	Delayed	Uncommon Usually dose-related Occurs or becomes apparent some time after use of drug	Tricholorethylene carcinogenesis, fluoride nephrotoxicity
E	Withdrawal	End of use	Occurs soon after drug withdrawal	Rebound hypertension with clonidine cessation Opioid withdrawal syndrome
F	Unexpected failure of therapy	Failure	Common Dose-related Often caused by drug interactions	Rifampicin (or other enzyme inducing drug) associated therapeutic failure of oral contraceptive

Adapted with permission (Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000; 356(9237): 1255–1259[10])

Table 1

Risk factors for ADRs

One of the difficulties in understanding ADRs is that the mechanisms by which they occur are largely unknown. However, some predisposing factors have been identified.

Age

Patients at the extremes of age are at increased risk of ADRs for several reasons. In the elderly, multiple medications are commonly taken to treat co-existing pathologies. Therefore the risk of an ADR arising *per se* or from drug interactions is increased. Ageing is also associated with impaired drug metabolism, decreased physiological reserve (especially renal hepatic and cardiovascular function) and nutritional deficiency. Therefore elderly patients are more susceptible and less able to tolerate the adverse effects of a given drug. Of those drugs relevant to anaesthesia, hypnotics, anti-hypertensives, anticoagulants and NSAIDs are particularly associated with adverse events in the elderly.

Children, and particularly neonates, have other physiological differences including a greater proportion of extravascular total body water, immature renal and hepatic function, reduced plasma protein concentrations and a relatively permeable blood–brain barrier. These factors contribute to susceptibility to ADRs. Furthermore, children unwell enough to require hospitalization usually require multiple drug therapy, which increases the risk of adverse events. For some reactions the mechanism is unclear, e.g. the association of aspirin with Reye's syndrome. Of concern to anaesthetists is that of the 331 deaths in children reported to the MHRA via the Yellow Card scheme in the UK before the year 2000, 30 were attributable to anaesthetic agents.[5]

Polypharmacy

Multiple drug therapy is an independent risk factor for the development of an ADR, with as few as five separate drugs being associated with an ADR. A prospective analysis of in-hospital ADRs in a UK centre demonstrated that each addition of a drug was independently associated with a 1.14 times increased hazard of an ADR.[6] Importantly, additional medication was the only significant predictor of an ADR in this study, and was most frequently associated with diuretics, opioids and anticoagulants. The risks associated with polypharmacy are probably due to drug interactions or are related to altered pharmacokinetics, as well there being an association with age and disease state.

Disease

The nature or severity of a disease influences the pharmacodynamic effects of a drug e.g. the administration of a given dose of propofol in a patient with systemic sepsis is more likely to result in hypotension; respiratory depression is more likely after morphine in a patient with renal disease compared with the same doses in healthy individuals. This is important in the critically ill population where life-threatening adverse drug events are estimated as occurring in over a fifth of patients. Recent evidence suggests that kidney injury and thrombocytopenia are particularly associated with an increased risk of an ADE. Since intravenous drugs are also associated with increased risk, it is clear

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