Review

Adverse drug reactions

Saima Parveen[1]

Abstract

Adverse drug reactions are a common clinical problem. They are diagnosed on clinical grounds from the temporal relation between the start and finish of drug treatment and the onset and offset of the reaction. Pharmacological adverse reactions are generally dose-dependent, related to the pharmacokinetic properties of the drug, and resolve when the dose is reduced. Idiosyncratic adverse reactions are not related to the known pharmacology of the drug, do not show any simple dose-response relation, and resolve only when treatment is discontinued .Vigilance by clinicians in detecting, diagnosing, and reporting adverse reactions is important for continued drug safety monitoring.

Key words : Adverse, drug reactions

Introduction

An adverse drug reaction is any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use. In contrast, an adverse drug event is an untoward occurrence after exposure to a drug that is not necessarily caused by the drug[1].

When a drug is marketed little is known about its safety in clinical use because only about 1500 patients are likely to have been exposed to it[1,2]. Thus drug safety assessment should be considered an integral part of everyday clinical practice since detection and diagnosis often depend on clinical acumen.

In this article we review the current status of adverse drug reactions, briefly describing the complexity of the more bizarre reactions and outlining a strategy to eliminate serious adverse drug reactions.

Adverse drug reactions are a major clinical problem, accounting for 2-6% of all hospital admissions[3-6]. Recent surveys in the United States have indicated that adverse drug events increase the length of hospital stay and costs[5,6].

1. Associate Professor
Department of Pharmacology &Therapeutics
Holy Family Red Crescent Medical College

Correspondence : Saima Parveen
E-mail : dr.shireenayeshasiddiqua@gmail.com

Importance of adverse drug reactions

Adverse drug reactions:

- Account for 5% of all hospital admissions
- Occur in 10-20% of hospital inpatients
- Cause deaths in 0.1% of medical and 0.01% of surgical inpatients
- Adversely affect patients' quality of life
- Cause patients to lose confidence in their doctors
- Increase costs of patient care
- Preclude use of drug in most patients, although they may occur in only a few patients
- May mimic disease, resulting in unnecessary investigations and delay in treatment

Types of adverse drug reactions

Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic)[7]. Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are therefore readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

A) Pharmacological adverse drug reactions

Type A adverse drug reactions are more common than type B reactions[3] accounting for over 80% of all reactions. They can be divided into those due to the primary

pharmacology of the drug' that is, augmentation of the drug's therapeutic actions, and Those due to the secondary pharmacology of the drug, that is, an action different from the drug's therapeutic actions but still rationalizable from the known pharmacology of the drug.

Thus, for β blockers, bradycardia and heart block are primary pharmacological adverse effects while bronchospasm is a secondary pharmacological adverse effect. More emphasis is now placed on the secondary pharmacology of new drugs during preclinical evaluation to anticipate problems that might arise once the drug is given to human.

Recent experience with fialuridine, an experimental drug for hepatitis B, highlights the need for continued development of appropriate in vivo and bridging in vitro test systems to predict secondary pharmacological adverse effects in humans. In June 1993, during phase II trials, 5 out of 15 patients died while two others required emergency liver transplantation for liver and kidney failure[8]; this effect had not been observed in four animal species. On the basis of results from in vitro studies in cultured hepatoblasts, the toxicity may be due to inhibition of mitochondrial DNA polymerase γ by fialuridine and its metabolites[9].

Factors predisposing to pharmacological adverse reactions include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug-drug interactions. Some drugs, including captopril, were introduced into clinical practice at a dose that was subsequently shown to be associated with an unacceptable frequency of toxicity and for which a lower dose was found to be both safe and effective. Elderly people and patients with diseases such as renal failure which affect drug handling are more likely to have type A reactions. The likelihood of developing an adverse interaction also increases with the number of drugs prescribed; for example, if five drugs are given simultaneously the chance of an adverse interaction occurring is 50%[10]. To date, this has largely been a problem in elderly people but it is becoming increasingly common in younger patients with chronic diseases such as AIDS, who may be taking[6-10] different drugs[11].

B) Mechanisms of idiosyncratic adverse drug reactions

- Pharmaceutical variation: eosinophilia-myalgia syndrome with l-tryptophan
- Receptor abnormality: malignant hyperthermia with general anaesthetics
- Abnormal biological system unmasked by drug: primaquine induced haemolysis in patients deficient in glucose 6-phosphate dehydrogenase
- Abnormalities in drug metabolism: isoniazid induced peripheral neuropathy in people deficient in the enzyme N-acetyl transferase (those who are slow acetylators)
- Immunological: penicillin induced anaphylaxis
- Drug-drug interactions: increased incidence of hepatitis when isoniazid is prescribed with rifampicin
- Multifactorial: halothane hepatitis

Idiosyncratic adverse drug reactions

Idiosyncratic adverse reactions are less common than pharmacological adverse reactions, but they are as important because they are often serious and account for many deaths. Mechanisms of idiosyncratic adverse effects[12] are listed in the box.

The body's drug metabolising system has been implicated in the pathogenesis of many idiosyncratic reactions[13]. Drug metabolism is conventionally divided into phase I and phase II[14]; it acts as a defence mechanism by facilitating excretion of the parent drug and its metabolites, limiting their ability to accumulate within the body and cause dose-dependent toxicity. Metabolic processes may also prevent accumulation of some drugs within particular cells or cellular compartments, which would eventually lead to toxicity. The best example of this is perhexilene, an antianginal agent, which caused hepatotoxicity and peripheral neuropathy in people deficient in the CYP2D6 (debrisoquine hydroxylase) isoform of cytochrome P-45015.

Paradoxically, drug metabolising enzymes, particularly the phase I cytochrome P-450 enzymes, may also cause the formation of chemically reactive metabolites, a process termed bioactivation[12,13,16]. Such metabolites may be toxic. In most people the formation of chemically reactive metabolites is counterbalanced by detoxification mechanisms' a process termed bioinactivation. In susceptible people the usually favourable balance between bioactivation and bioinactivation may be perturbed by either genetic or host factors such as age, enzyme induction, and disease, all of which allow the toxic metabolites to escape detoxification. Under these circumstances, the toxic metabolites may bind covalently to various cellular macromolecules and cause toxicity. With most drugs, however, the factors which cause this imbalance are unknown, which explains why such

reactions continue to occur. In some cases chemically reactive metabolites will be formed irrespective of the dose[16]. At therapeutic doses any toxic metabolite formed will be detoxified by cellular defence mechanisms, but an imbalance between bioactivation and bioinactivation may result after overdoses. This will lead to the formation of large amounts of chemically reactive metabolite, which will overwhelm cellular detoxification capacity and lead to cell damage.

The clearest example of this occurs in paracetamol overdose, which causes hepatotoxicity and kills about 160 people each year in the United Kingdom[17]. Paracetamol hepatotoxicity should not be classed as an adverse reaction since the hepatic injury occurs when the drug is used inappropriately. However, the occurrence and severity of liver damage with paracetamol is a function not only of the dose but also of various host factors[13]. Indeed, paracetamol hepatotoxicity has been reported with therapeutic drug use. For example, a recent study in 67 alcoholic patients with paracetamol hepatotoxicity showed that 40% had taken less than 4g/day (the recommended therapeutic dose) and 20% had taken 4-6 g/day (a non-toxic dose)[18]. Paracetamol is largely metabolised by phase II processes (glucuronidation and sulphation) to stable metabolites, with 5-10% undergoing P-450 metabolism to the toxic quinoneimine metabolite[19]. This is detoxified by cellular glutathione. At overdose, saturation of the phase II pathways results in a greater proportion of the drug undergoing bioactivation. This leads to glutathione depletion and allows the toxic metabolite to bind to proteins, resulting in hepatocellular damage[19]. The use of N-acetylcysteine to treat paracetamol overdose shows that elucidation of the mechanism of drug toxicity can lead to the development of rational treatments that will prevent toxicity. Alcoholic patients show increased susceptibility to paracetamol because excess alcohol consumption depletes glutathione20and induces the CYP2E1 isoform of cytochrome P-450[21], the primary enzyme concerned with paracetamol bioactivation[22].

Importance of the immune system

Many idiosyncratic adverse reactions are thought to be mediated by the immune system on the basis of clinical criteria[12,13,23]. The mechanism by which a drug leads to an immune mediated adverse reaction is explained by the hapten hypothesis[24]. Central to the hypothesis is the assumption that small molecules such as drugs can be recognised as immunogens, that is, a substance capable of eliciting a specific immune response only when they become covalently bound to macromolecules such as proteins (to form haptens)[24]. The type of hypersensitivity is partly determined by the nature of the immune response and the site of antigen formation. The best understood reactions are the type I hypersensitivity reactions induced by penicillins and mediated by IgE antibodies directed against a drug hapten conjugated to protein[13,25]. Severe anaphylactic reactions occur in only 1 in 2000 patients; the genetic basis of the IgE response to penicillins remains unclear.

Less well understood are the immunological mechanisms underlying severe reactions such as the Stevens-Johnson syndrome and immunoallergic hepatitis. In vitro studies have shown that drugs causing these reactions undergo oxidative metabolism to chemically reactive metabolites that can form haptens with proteins[26]. Both humoral and cell mediated responses directed against drug induced antigen have been detected in patients. For example, in halothane hepatitis[27]. With some compounds the immune response is directed predominantly towards an autoantigen. For example, in hepatitis induced by tienilic acid patients have circulating autoantibodies directed against the P-450 isoform (CYP2C9) that is responsible for bioactivation of the drug[28]. However, whether such autoantibodies are pathogenic or represent an epiphenomenon (their appearance is secondary) needs further study. The role of T cells in drug induced tissue injury is also poorly understood, although recent immune histochemical studies, particularly of skin reactions, suggests that they subserve a pathogenic role[29].

Host factors and adverse drug reactions

Genetically determined alterations in drug metabolising enzymes can predispose to both pharmacological and idiosyncratic toxicity[26]. Single gene defects account for only a minority of adverse drug reactions. For most adverse reactions, particularly the idiosyncratic drug reactions, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infection[13,26]. Most work has focused on enzyme polymorphisms in drug oxidation and conjugation as risk factors for drug toxicity, but this search for genes affecting susceptibility needs to be extended to include cell repair mechanisms, elaboration of cytokines, and immune responsiveness. Such investigations may in the future provide us with the capability to predict a person's susceptibility to the different forms of drug toxicity.

Concomitant host disease may also influence

susceptibility to adverse reactions. The best recent example is HIV disease, which increases the frequency of idiosyncratic toxicity with anti-infective drugs such as co-trimoxazole[30]. Around 50% of patients receiving high doses of co-trimoxazole for Pneumocystis carinii pneumonia and 30% receiving prophylactic doses develop skin rashes[31]. This contrasts with a frequency of 3% in people who are negative for HIV infection[31]. Glutathione deficiency has been suggested by some[32,33] but not all[34,35] investigators to be responsible for the increased frequency of reactions[30,31]. The reasons are likely to be more complex and to include not only changes in drug metabolising capacity (bioactivation and bioinactivation) but also immune dysregulation.

Spontaneous reporting schemes

The exposure of 1500 patients to a drug by the time of licensing[1,2] will allow the more common adverse reactions to be detected but not necessarily characterized. At least 30 000 people need to be treated with a drug to discover, with a power of 0.95, at least one patient with an adverse reaction which has an incidence of 1 in 10 00036. Thus, postmarketing surveillance is important to permit detection of less common adverse effects.

Spontaneous adverse drug reaction reporting schemes, as exemplified by the yellow card system in the United Kingdom, form the cornerstone of post marketing drug safety surveillance. Indeed, spontaneous reporting schemes remain the only way of monitoring the safety of a drug throughout its marketed life. The yellow card scheme is important in identifying previously undetected adverse reactions[37] and over the years has provided many early warnings of drug safety hazards, for example, remoxipride and aplastic anaemia to allow appropriate drug regulatory action to be taken. A problem with spontaneous reporting is that less than 10% of all serious and 2-4% of non-serious adverse reactions are reported[2,38]. All doctors need to be aware that adverse drug reaction reporting is part of overall patient care and is not simply an afterthought. Since 1964 reporting in the United Kingdom has been restricted to doctors, dentists, and coroners, although more recently a reporting scheme for pharmacists has been introduced. In some European countries all healthcare professionals are allowed to report adverse drug reactions, while in the United States patients can also report through the MED Watch scheme[39].

Conclusion

The importance of adverse drug reactions is often underestimated. They are common and can be life threatening and unnecessarily expensive. The measures outlined in the box above are important to improve the benefit to risk ratio of drug treatment by reducing the burden of drug toxicity. Because of the wide range of drugs available, the manifestations of toxicity may vary and affect any organ system. In fact, adverse reactions have taken over from syphilis and tuberculosis as the great mimics of other diseases. The pattern of toxicity is likely to change with the introduction of new biotechnology products. It is therefore important for prescribing clinicians to be aware of the toxic profile of drugs they prescribe and to be ever vigilant for the occurrence of unexpected adverse reactions.

Strategy to improve drug safety

- Avoidance of chemical functional groups that are well recognized to cause toxicity during drug design, for example, aromatic amines, phenols, epoxides, and quinones.
- Development of metabolically inert drugs to avoid metabolic interactions and prevent formation of toxic metabolites. For example, vigabatrin and gabapentin.
- Development of suitable in vitro and in vivo systems to elucidate the role of shortlived, potentially toxic metabolites in the pathogenesis of idiosyncratic toxicity.
- Increased use of in vitro systems, such as cell lines expressing drug metabolising enzymes, to predict the potential for adverse drug interactions and polymorphic routes of metabolism.
- Study of high risk patients during the premarketing drug development phase to identify pharmacokinetic and pharmacodynamic factors that influence susceptibility to drug toxicity.
- Development of computer based schemes to monitor for adverse reactions and adverse events in primary and secondary care.
- Encouragement to report adverse drug reactions to regulatory agencies
- Identification of risk factors for different types of drug toxicity by using pharmaco-epidemiological approaches.
- Identification of multi-genetic predisposing factors to allow the prediction of individual susceptibility.

References

1. Asscher AW, Parr GD, Whitmarsh VB. Towards the safer use of medicines. BMJ. 1995;311:1003–1005.
2. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? J R Coll Physicians Lond. 1995;29:41–49.
3. Einarson TR. Drug-related hospital admissions. Ann Pharmacother. 1993;27:832–840.]
4. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events—implications for prevention. JAMA. 1995; 274:29–34.
5. Bates DW, Spell N, Cuilen DJ, Burdick E, Laird N, Petersen LA, et al. The costs of adverse drug events in hospitalized patients. JAMA. 1997;277:307–311.
6. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277:301–306.
7. Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford: Oxford University Press; 1991. pp. 18–45.
8. McKenzie R, Fried MW, Sallie R, Conjeevaram H, Dibisceglie AM, Park Y, et al. Hepatic-failure and lactic-acidosis due to fialuridine (fiau), an investigational nucleoside analog for chronic hepatitis B. N Engl J Med. 1995;333:1099–1105
9. Lewis W, Levine ES, Griniuviene B, Tankersley KO, Colacino JM, Sommadossi J-P, et al. Fialuridine and its metabolites inhibit DNA polymerase gamma at sites of multiple adjacent analog incoroporation, decrease mtDNA abundance, and cause mitochondrial structural defects in cultured hepatoblasts. Proc Natl Acad Sci USA. 1996;93:3592–3597.
10. Atkin PA, Shenfield GM. Medication-related adverse reactions and the elderly: a literature review. Adverse Drug Reactions Toxicol Rev. 1995;14:175–191.
11. Harb GE, Jacobson MA. Human immunodeficiency virus infection: does it increase susceptibility to adverse drug reactions? Drug Safety. 1993;9:1–8.
12. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. Br J Clin Pharmacol. 1992;34:377–395.
13. Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. Drug Safety. 1994;11:114–144.
14. Williams RT. Detoxication mechanisms. New York: Wiley; 1959. The metabolism of foreign compounds and the detoxication mechanisms; pp. 717–740.
15. Shah RR, Oates NS, Idle JR, Smith RL, Lockhart JDF. Impaired oxidation of debrisoquine in patients with perhexilene neuropathy. BMJ. 1982;284:295–298.
16. Pirmohamed M, Madden S, Park BK. Idiosyncratic drug reactions: metabolic bioactivation as a pathogenic mechanism. Clin Pharmacokinet. 1996;31:215–230.
17. Bray GP. Liver failure induced by paracetamol. BMJ. 1993;306:157–158.
18. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology. 1995;22:767–773.
19. Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. Semin Liver Dis. 1990;10:267–278.
20. Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. Gut. 1988;29:1153–1157.
21. Raucy JL, Lasker JM, Lieber CS, Black M. Acetaminophen activation by human liver cytochromes P-45011E1 and P-4501A2. Arch Biochem Biophys. 1989;271:270–283
22. Lee SST, Buters JTM, Pineau T, Fernandezsalguero P, Gonzalez FJ. Role of cyp2e1 in the hepatotoxicity of acetaminophen. J Biol Chem. 1996;271:12063–12067
23. Pohl LR, Satoh H, Christ DD, Kenna JG. Immunologic and metabolic basis of drug hypersensitivities. Ann Rev Pharmacol. 1988;28:367–387.
24. Park BK, Coleman JW, Kitteringham NR. Drug disposition and drug hypersensitivity. Biochem Pharmacol. 1987;36:581–590.
25. Weiss ME, Adkinson MF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy. 1988;18:515–540.
26. Park BK, Pirmohamed M, Kitteringham NR. The role of cytochrome P450 enzymes in hepatic and extrahepatic human drug toxicity. Pharmacol Ther. 1995;68:385–424.
27. Pohl LR. Drug-induced allergic hepatitis. Semin Liver Dis. 1990;10:305–315.

28. Beaune PH, Bourdi M. Autoantibodies against cytochrome P-450 in drug induced autoimmune hepatitis. Ann N Y Acad Sci. 1993;685:641–645.

29. Friedmann PS, Strickland I, Pirmohamed M, Park BK. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. Arch Dermatol. 1994;130:598–604.

30. Koopmans PP, van der Ven AJAM, Vree TB, van der Meer JWM. Pathogenesis of hypersensitivity reactions to drugs in patients with HIV infection—allergic or toxic. AIDS. 1995;9:217–222.

31. Van der Ven AJ, Koopmans PP, Vree TB, van der Meer JW. Adverse reactions to co-trimoxazole in HIV infection. Lancet. 1991;ii:431–433.

32. Roederer M, Staal FJT, Osada H, Herzenberg LA, Herzenberg LA. CD4 and CD8 T cells with high intracellular glutathione levels are selectively lost as the HIV infection progresses. Int Immunol. 1991;3:933–937.

33. Buhl R, Holroyd KJ, Mastrangeli A, Cantin AM, Jaffe HA, Wells FB, et al. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. Lancet. 1989;ii:1294–1298.

34. Aukrust P, Svardal AM, Muller F, Lunden B, Berge RK, Ueland PM, et al. Increased levels of oxidized glutathione in CD4+ lymphocytes associated with disturbed intracellular redox balance in human immunodeficiency virus type 1 infection. Blood. 1995;86:258–267.

35. Pirmohamed M, Williams D, Tingle MD, Barry M, Khoo SH, O'Mahony C, et al. Intracellular glutathione in the peripheral blood cells of HIV-infected patients: failure to show a deficiency. AIDS. 1996;10:501–507.

36. Stricker BHC. Drug-induced hepatic injury. 2nd ed. Vol. 5. Amsterdam: Elsevier Science; 1992.

37. Belton KJ, Lewis SC, Payne S, Rawlins MD. Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. Br J Clin Pharmacol. 1995;39:223–226.

38. Smith CC, Bennett PM, Pearce HM, Harrison PI, Reynolds DJM, Aronson JK, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol. 1996;42:423–429.

39. Kessler DA. Introducing MEDWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA. 1993;269:2765–2768.