

## Drugs can harm

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Adverse drug reaction is a major clinical problem. Many patients present to hospitals because of the drugs they take. Case history of four such patients seen at an Accident & Emergency department in Hong Kong over the last three months are presented. The definition, classification and clinical implication of adverse drug reaction are reviewed. Preventive strategies with reference to the local scenario are discussed. (*Hong Kong j.emerg.med.* 2000;7:169-172)

**Keywords:** Adverse drug reaction, emergency department

### Case 1

A 25-year-old female patient was brought to the Accident & Emergency department (A&E) because of acute psychosis. She was previously well and had no known history of drug allergy. About three months before presentation she consulted a general practitioner (GP) for weight reduction. She was prescribed phentermine, a catecholaminergic drug, together with a laxative and multivitamin. After taking the drug for about 2 months, she developed palpitation and dizziness. She consulted the same GP and was prescribed propranolol and cinnarizine. She became agitated and had auditory hallucination, a few days before presenting at A&E. On presentation, she was restless and confused and haloperidol was required to calm her down. After one day in hospital with cessation of the GP's medication, her mental state normalised. She probably suffered from phentermine-induced psychosis.

### Case 2

A 57-year-old female doctor who is a general practitioner presented with malaise, decreased appetite, generalised pruritus and jaundice. She diagnosed herself to have fungal infection on her

face and took oral terbinafine. She took the drug for 2 weeks before she became unwell and sought medical attention at A&E. She was admitted and investigation revealed that her total bilirubin was 291  $\mu\text{mol/L}$ , alkaline phosphatase 220 U/L, gamma glutamyl transpeptidase 636 U/L, alanine aminotransferase 1794 U/L, aspartate aminotransferase 2332 U/L. Her liver function gradually improved after withdrawal of terbinafine. The culprit for her hepatitis was terbinafine.

### Case 3

A 79-year-old lady presented with tremor of her limbs for three weeks. She had hypertension and anxiety neurosis and was followed up by a GP. Her medications included spironolactone, cisapride, domperidone, citalopram, lorazepam, omeprazole and oscar. The duration that she had been on these drugs was unknown. On examination in A&E, she was tremulous. Gait was unsteady because of the tremor. After staying in hospital without taking her usual medications, her tremor subsided. On review, citalopram, a selective serotonin reuptake inhibitor, is likely to be the cause of her tremor.

### Case 4

A 35-year-old man attended the A&E because of dizziness. He had diarrhoea one day before and was seen by a GP who prescribed dimenhydrinate, promethazine, terfenadine, betahistine, lomotil<sup>®</sup>, hyoscine butylbromide, and paracetamol in 2

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different coloured tablets. After exclusion of any serious pathologies, he was asked to stop all his medications. His dizziness improved.

## Discussion

In our daily clinical practice as Emergency physicians (EP), it is not uncommon to see patients presenting with illnesses resulting from the drugs prescribed by their doctors. In parallel to the large number of drugs available in the market, the presentations of drug-related illness are also highly variable. It ranges from self-limiting dizziness to life-threatening toxic epidermal necrolysis. The aforementioned cases illustrate how diverse these reactions may manifest. If it goes unrecognised, further intervention and treatment only add harm to patients.

When drug-related illness is encountered, three aspects should be considered i.e. a drug-drug interaction (DDI), an adverse drug event (ADE) and an adverse drug reaction (ADR). DDI results when one drug affects the pharmacological properties of another. The clinical efficacy of one or both drugs can be altered and unwanted events can occur. Ventricular arrhythmia as a result of co-administration of erythromycin and terfenadine is one of the many examples of DDI. ADE is a broad term. It encompasses any unwanted occurrences following the exposure to a drug but not necessarily caused by the drug. For instance, damage to the sciatic nerve during an intramuscular injection at the buttock is an ADE. An ADR is an unwanted or unintended effect of a medicine which occurs during its proper use.<sup>1</sup> In general, it excludes those events due to an overdose or lack of efficacy. It can be classified in terms of severity, individual susceptibility or its clinico-pharmacological characteristics.

An ADR is considered mild when it does not require antidote treatment or prolong hospitalisation. It is of moderate severity if it needs a change in but not necessarily cessation of the drug; or it prolongs hospitalisation and requires specific treatment. It is a severe reaction when it becomes life-threatening and the drug has to be discontinued. If a patient dies directly or indirectly from the drug, it is a lethal

ADR.<sup>2</sup> This classification is simple and easy to understand. But it does not tell the cause or the mechanism of the ADR. In fact, for the same reaction, it may occur in one individual but not another, even though they may have taken the same drug in the same manner. Therefore individual susceptibility plays a role in the development of ADR. The side effect of a drug is a reaction that may occur in anyone. It is defined as an undesirable pharmacological effect at recommended doses. Dry mouth and blurred vision after hyoscine are common side effects seen in the A&E setting. Some reactions, however, only occur in some individuals. A patient is said to be intolerant to a drug when the person has a low threshold to the normal pharmacological action, that is, drug intolerance. Drug idiosyncrasy is an abnormal reaction to a drug with a genetically determined basis. For example, peripheral neuropathy associated with isoniazid occurs in genetically predisposed individuals who are slow acetylators of isoniazid. Drug allergy, on the other hand, is an immunologically mediated reaction. It is specific and reproducible on re-exposure to the same drug. The skin rash that develops after beta-lactam antibiotics should be familiar to the emergency physicians. Pseudoallergy mimics an allergic reaction,<sup>3</sup> but it lacks immunological specificity. The development of urticaria after morphine is one such example. Another classification system is to categorise ADR into type A (pharmacological) or type B (idiosyncratic) reaction.<sup>4</sup> Type A reactions are commoner, dose-dependent, related to the pharmacokinetics of the drug and resolved with reduction in dosage. A primary type A reaction refers to an augmentation of the drug's therapeutic action whereas a secondary reaction is unrelated to its therapeutic action but still deducible from its pharmacology. Atropine in the treatment of heart block, for example, causes tachycardia, which is a primary reaction. Glaucoma, if precipitated, is then a secondary reaction. An idiosyncratic reaction is not related to the pharmacology of the drug. The manifestation is usually bizarre and is not dose-dependent. It is not as common but usually more serious.

An understanding of the issue of ADR is essential to emergency medical practice. A significant proportion of patients were admitted to hospitals

with conditions that were related to drug reactions. The figure varies from 2%-12%.<sup>5-8</sup> Citing Australia as an example, a recently published study found that there were at least 80000 medication-related hospitalisations each year and between 32%-69% were avoidable.<sup>9</sup> Another study in Europe showed that ADR caused about 64% of drug-related visits to the emergency department.<sup>10</sup> The more important data to know is the incidence of ADR in the community. These data, however, are difficult to obtain for the degree of drug exposure in the community is unknown.

For the EP, recognition of ADR is of particular importance. Given the diverse manifestation, ADR is a great mimic of disease. This often leads to delayed diagnosis and as a result, unnecessary investigation and treatment. In the emergency medicine setting, there are several steps to aid the diagnosis of an ADR. Firstly, it should be confirmed that the suspected medication was in fact administered. Secondly, a clear temporal sequence of drug administration and occurrence of the reaction should be verified. Most ADR occur soon after the administration of the drug, but it can be delayed for months or years. Thirdly, the response after withdrawal or reduction in dosage of the drug should be noted. One should also check if the reaction has been reported before.<sup>11,12</sup> Above all, a high index of suspicion is needed. Basically, diagnosis of ADR is clinical and by exclusion as there is no specific laboratory test.

To avoid ADR, the EP should pay more attention when prescribing to the high risk groups. Those at the extreme of age constitute a significant risk. Owing to the immature enzyme system in drug metabolism and elimination, neonates and infants are more prone to ADR. The grey baby syndrome caused by chloramphenicol is a well known example. For the elderly, ADR is a major clinical problem.<sup>13</sup> This is related to the impairment of renal and hepatic function, multiple pathologies and poor reserve in old people. Following this, the underlying medical diseases also contribute to the development of ADR. Diseases of the liver and kidney need no further explanation. Concurrent infection sometimes leads to ADR as well. This is exemplified by the development of morbilliform rash in Epstein Barr virus-infected patients who are given ampicillin.

Until recently, another commonly quoted example is the higher frequency of hypersensitivity reaction to co-trimoxazole in patients affected by human immunodeficiency virus.<sup>14</sup> Genetic constitution is another risk factor. For the local Chinese population, glucose-6-phosphate dehydrogenase deficiency is a prevalent problem. Its association with drug-induced haemolysis is a topic which every EP should know. Women, interestingly, are more likely to develop ADR than men.<sup>15</sup> This can be seen in cases of drug-induced lupus erythematosus.

ADR is common and can be lethal and its prevention is of utmost importance. In Hong Kong, the situation is more complicated. Patients here can obtain drugs from various sources, namely the Government or Hospital Authority clinics, the GP, drug stores, the Chinese traditional medicine practitioners and other practitioners of alternative medicine. Worse still, self-medication is common in Hong Kong.<sup>16</sup> Many types of drugs sold to the public are not under any regulations. The presence of polypharmacy and overprescription are important problems.<sup>17</sup> Hence, patients are exposed to various types of drugs which are potentially dangerous.

EP, as the medical professionals in the forefront, can play a pivotal role in the prevention of ADR. Apart from recognising and treating patients with ADR, patient education on drug safety is indispensable. Another way is to actively report, collate and analyse ADR in patients presenting to the emergency department. This is essential for appropriate action to ban certain drugs with serious or dangerous unwanted effects. EP, as a group, can give opinions to the authority on legislation governing the sale and use of certain drugs. Finally, we as emergency physicians should always be careful in prescribing. The simple rule is to treat with drugs only when necessary, to limit the number of drugs used, to adopt a simple regime as much as possible and above all, be sure you understand the drug you use.<sup>18</sup>

## References

1. Asscher AW, Parr GD, Whitmarsh VB. Towards the safer use of medicines. *BMJ* 1995;311:1003-5.

2. Vervloet D, Durham S. Adverse reactions to drugs. *BMJ* 1998;316:1511-4.
3. Drug toxicity. Chapter 302. Merck Manual of diagnosis and therapy. <http://www.merck.com/pubs/manual/sections.htm>
4. Pirmohamed M, Breckenridge AM, Kitteringham NR, et al. Adverse drug reactions. *BMJ* 1998;316:1295-8.
5. Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993;27:832-40.
6. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug interaction - implication for prevention. *JAMA* 1995;274(1):29-34.
7. Burkholder DF. Adverse drug effects and their impact on patient care: a review of the problem. *Drug Intel Clin Pharm* 1979;13:421-4.
8. Miller RR. Hospital admissions due to adverse drug reactions. *Arch Intern Med* 1974;43:219-23.
9. Roughead EE. The nature and extent of drug-related hospitalization in Australia. *J Qual Clin Pract* 1999;19(1):19-22.
10. Raschetti R, Morgutti M, Menniti-Ippolito F, et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. *Eur J Clin Pharmacol* 1999;54(12):959-63.
11. Gleckman RA, Borrego F. Adverse reactions to antibiotics. *Postgrad Med* 1997;101(4):56-61.
12. Pirmohamed M, Park BK. The adverse effects of drugs. *Hosp Med* 1999;60(5):348-52.
13. van Kraaij DJ, Haagsma CJ, Go IH, et al. Drug use and adverse drug reactions in 105 elderly patients admitted to a general medical ward. *Neth J Med* 1994;44(5):166-73.
14. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992;5(12):1237-57.
15. Siedl LG, Thornton GF, Cluff LE. Epidemiological studies of adverse drug reactions. *Am J Public Health* 1965;55:1170.
16. Lau LK, Tse HW, Munro C. A study on the practice of self-medication in Hong Kong. *HK Pract* 1989;2(6):272-86.
17. The drug utilisation review committee, Hospital Authority. Polypharmacy. *Drug Education Bulletin* 1997 Jun; 11.
18. Watson DS. Strategies to contain misuse and abuse of pharmaceuticals. *HK Pract* 1991;13(2):1318-21.