Background

Medicines Information Centres receive many enquiries specifically about adverse drug reactions (ADRs), as well as a large number featuring related patient safety issues (e.g. contraindications). Annual statistics collated by Regional MI Centres suggest that on average about 15% of their enquiries fall into the ADR category. Statistics from pharmacy patient helplines show that a high proportion of their calls are also concerned with side effects.

ADRs occur in 10-20% of hospitalised inpatients and may be responsible for 1 in 1000 deaths on medical wards. Studies in hospitals suggest about 5% of all admissions are due to ADRs. The epidemiology of ADRs in primary care is less well studied, but as many as 2% of GP consultations may be due to suspected ADRs.

ADRs are great mimickers of disease, causing diagnostic confusion and resulting in unnecessary referral and investigation.

Certain disorders are commonly drug-induced and a thorough assessment of drug exposure is particularly important in these cases. Examples include rashes, electrolyte disturbances, postural hypotension, confusion, constipation, renal or liver dysfunction, and gastrointestinal haemorrhage. Less common examples include blood dyscrasias.

Some patients have an increased susceptibility to ADRs including the elderly, neonates and children, patients with multiple disease states (e.g. ICU patients, HIV patients), those with impaired kidney or liver function, and patients receiving polypharmacy. Ignoring manufacturers’ contra-indications or failing to monitor the patient adequately are also common methods of increasing the likelihood of known ADRs.

Definition

What are the essential features of an ADR?

- There is some evidence that at least one medicine is responsible.
- The effect is unintended.
- It is harmful, or potentially harmful.
- The reaction is seen at normal doses used clinically (to distinguish ADRs from ‘toxicity’ which is used to describe the symptoms of overdose or poisoning).

Types Of Adverse Drug Reaction Enquiry

- Can drug X cause symptom Y? How common is this side effect? Is it reversible?
- Which of drugs A, B or C is the most likely cause of symptom Y?
- How should I manage a suspected ADR in this patient?
- This patient has experienced a suspected reaction to drug X. Is it safe to use another drug from the same or related therapeutic class?
- What are the long-term risks of drug X?
- Prescribing information (or patient information leaflet) mentions side effect Y. Why is this listed – more information required.
- More information on the incidence or characteristics of a specific side effect (e.g. pulmonary reactions to amiodarone, methotrexate-induced liver disease etc.).
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Factors To Take Into Account When Assessing Causality

When assessing whether a causal relationship between the drug and an event exists, the enquirer often expects an opinion or advice on the likelihood that a particular problem or symptom is drug-induced. Sometimes it is relatively easy to do this, if, for example, the patient is taking only one medicine and no evidence is found to implicate the drug as the cause of the suspected reaction. However, when asked about a patient taking more than one medicine and who has several concurrent medical conditions, it can be very difficult to distinguish which, if any, of the medicines is causative.

The TRIP system can be used to help determine whether an ADR has occurred. TRIP stands for Timing, Recovery, Independent evidence, Predictability:

1. **Timing**
   Depending on the type of reaction, time to onset can vary from minutes to months. For example, anaphylaxis to IV drugs can begin almost immediately after administration, whereas drug-induced Parkinsonism may take several months to develop. An understanding of the pharmacokinetics and pharmacodynamics of the drug is required, as well as the mechanism of the ADR, when considering the time interval between drug exposure and onset of symptoms. For withdrawal reactions, the duration of administration and the length of the interval since stopping therapy are important timing considerations.

2. **Recovery**
   Do symptoms improve/resolve when the suspect drug is stopped? This is called dechallenge. Many reactions will resolve on stopping the drug; this supports cause and effect but could be coincidental. Does the reaction improve when a specific treatment is given? (e.g., procyclidine for oculogyric crisis caused by metoclopramide).

3. **Independent Evidence**
   Is there another possible non-drug cause for the problem? The clinical picture may be a manifestation of an underlying disease. For example, before attributing disturbed liver function to drug therapy, other causes must be excluded such as viral hepatitis or biliary obstruction.

   Is there objective evidence of a link with drug therapy? A rechallenge will cause symptoms to recur if the suspect drug is restarted. Positive rechallenge is strongly suggestive that the drug was responsible. Although deliberate rechallenge is seldom justifiable, in clinical practice it can occur by mistake (e.g., patient with known penicillin allergy given co-amoxiclav). There are other types of independent evidence such as plasma levels of drugs or measures of drug activity (e.g., INR).

4. **Predictability**
   Are the characteristics of the adverse event consistent or inconsistent with the known pharmacology of the drug? For example, many adverse reactions are dose-related and may be avoided by using a reduced dose. Have similar events been reported previously with the drug or a related drug? (e.g., in textbooks, clinical trials, spontaneous reporting schemes).

These criteria provide useful general guidance but they have some drawbacks. For example, with new medicines there may be only very limited data available. Due to the limited size and controlled nature of pre-marketing clinical trials, only the most common adverse events will be observed and subsequently listed in the SPC at the time of approval. Rare events, if described, may only be encountered by chance. In this situation you would attach less weighting to known experience with the drug. A positive dechallenge (resolution of symptoms on stopping the suspect drug) is usually a strong indication of iatrogenic disease but coincidences can occur (e.g., rash in a child taking antibiotics may be viral). Failure of symptoms to resolve quickly may not always count against the possibility of an ADR (e.g., regrowth of hair following drug-induced alopecia will take weeks or months).
**Expressing Incidence**

The EU has a classification system which is used in SPCs and patient information leaflets:

- **Very common** ≥ 1 in 10  
  e.g. cough with ramipril

- **Common** ≤ 1 in 10 but ≥ 1 in 100  
  e.g. epistaxis with dabigatran

- **Uncommon** ≤ 1 in 100 but ≥ 1 in 1000  
  e.g. pathological gambling with pramipexole

- **Rare** ≤ 1 in 1000 but ≥ 1 in 10000  
  e.g. rhabdomyolysis with simvastatin

- **Very rare** ≤ 1 in 10000  
  e.g. Stevens-Johnson syndrome with ciprofloxacin

**Information from Published Studies**

Remember to assess the relative importance of different sources of information on adverse reactions:

**Clinical trial data**

These give a helpful indication of common reactions with a guide to incidence, but:

- The comparatively small patient population involved means that serious, but uncommon, reactions are unlikely to be discovered.

- The patients involved in clinical trials are highly selective and not representative of the real patient population.

- The procedures for ADR monitoring and reporting in clinical trials are variable and may not be sufficiently robust.

**Case reports**

Case reports can be useful in raising suspicion but in most cases they are insufficient to establish a causal association for the following reasons:

- There is no comparison group not exposed to the drug to allow for a quantitative estimate of risk.

- There is no reliable denominator of drug-exposed patients from which an incidence rate can be estimated.

- Prone to bias. A single case report linking a reaction to a drug could be just coincidence, or due to one of a large number of confounding influences.

**Epidemiological studies**

Given the limitations of clinical trials and case reports, post-marketing epidemiological studies generally provide the best source of quantitative information on ADRs. These fall into two broad categories:

- **Follow-up (cohort) studies.** Groups defined by exposure status to a particular drug are followed and subsequent events recorded and compared. For example, 750 patients on leflunomide are scrutinised for adverse events.

- **Case-control studies.** Groups defined by their outcomes are enrolled and prior drug exposures ascertained and compared. For example, 4000 patients with upper GI bleeding are investigated in an attempt to identify factors that may have caused it.
Adverse Drug Reactions

**Reporting to the CHM**

Many health professionals have a poor understanding of the yellow card scheme and its role in pharmacovigilance, and so pharmacists should ensure that they are familiar with it. If the outcome of an MI enquiry indicates that an ADR may have occurred, it is worth suggesting that a yellow card be submitted to the Commission on Human Medicines (CHM) if the reaction meets their reporting criteria. For healthcare professionals the CHM request that they report:

- All reactions to new drugs (they have an inverted black triangle next to them in the BNF or their SPCs).
- Any serious reaction to all other drugs including prescription and OTC medicines, vaccines and herbal products.

Patients, carers or parents are asked to report any side effect that they, or a person in their care, may have experienced from a medicine.

Yellow cards may be completed on paper, electronically via the MHRA’s dedicated yellow card website, or via MiDatabank – ask your tutor to show you how this works.

**Questions to Ask an Enquirer**

- Establish patient’s age if relevant.
- Ask about the diagnosis and relevant past medical history.
- List all current and recent medication (including OTC products, complementary medicines and potential substance misuse).
- Ask about relevant biochemistry (e.g. renal function, liver function).
- Consider any history of ADRs and/or allergies.
- Ask for the details of the suspected reaction including signs and symptoms, and severity.
- Establish when the suspected reaction began (especially in relation to starting drug treatment) and whether the drug has been stopped.
- Ask how the patient has been managed and how he/she is now.

**Example Sources to Use in Answering Enquiries**

- Most SPCs include details of adverse events reported during clinical trials and their frequency. They sometimes include information about side effects detected after the product has been launched.
- MiDatabank can be helpful for questions about more common adverse drug reactions (such as statin-induced myopathy).
- Martindale and AHFS (through Medicines Complete), and Lexicomp or Micromedex (if your centre has them), are very useful places to look for information on ADRs. References are usually provided so you can follow these up if necessary.
- The CHM’s yellow card data is available at www.mhra.gov.uk but make sure you’ve read the detailed interpretation guide first. Drug Safety Update, the MHRA’s current awareness publication, is also available electronically here.
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- Expert clinicians can often give valuable advice on complex cases. (such as a dermatologist’s opinion on a skin reaction).
- Consider using Medline and Embase but choose your search terms carefully.
- Manufacturers’ Medical Information Departments can sometimes help but be aware that there is a requirement for telephone enquiries about suspected ADRs to be followed up (by sending out adverse event reporting forms).
- Your centre may have access to the current edition of Meyler’s Side Effects of Drugs.

Further Reading

- There is a helpful Clinical Knowledge Summary on adverse drug reactions (January 2012) available from Evidence Search. Go to [www.evidence.nhs.uk](http://www.evidence.nhs.uk), click on Clinical Knowledge Summaries, and then use the A-Z listing.
- Try the MHRA’s learning module on pharmacovigilance which has been developed with BMJ Learning at [www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON228754](http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON228754)

Exercises

- If you have the MiCAL programme, have a go at question nos. 3 and 9.
- Attempt the ‘Test Yourself!’ questions on page 2.6 and read the example enquiry on page 2.8.
- There are some real enquiries to try with your tutor on page 2.9.
Adverse Drug Reactions

Test Yourself!

1. A GP telephones you to ask whether gold can cause pulmonary fibrosis. What further information do you need to find out before answering this enquiry?

2. Where would you look to find out how to minimise withdrawal symptoms upon discontinuation of paroxetine?

3. Give two limitations of the CHM collated yellow card data (Drug Analysis Prints) in answering adverse reaction enquiries.

4. List three predisposing factors to the development of an ADR.

5. Finding out about the presentation of drug-induced skin reactions can be difficult, and yet they are commonly encountered clinically. Why is the information available so limited?
6. What are the limitations associated with using the BNF to answer enquiries about adverse drug reactions?

7. The CHM encourages reporting of ADRs by pharmacists. Would you report constipation with amitriptyline? How about a gastrointestinal bleed which was suspected to be caused by diclofenac? Justify your answers.

8. What problems do you foresee in answering questions about the risks associated with chronic treatment with a drug?

9. Give an example of a dose-related side effect and one which is not dose-related.
Adverse Drug Reactions

**Example Enquiry**

The following is a written response to a letter received by Medicines Information from a GP enquiring about the risk of proton pump inhibitors and hypomagnesaemia. Where would you have looked for the information?

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**University Hospital Southampton**

NHS Foundation Trust

Dr Glanville
Waterside Medical Practice
Bouremouth Road
Chandlers Ford
Hampshire

Wessex Drug & Medicines Information Centre
Pharmacy Department
Southampton General Hospital
Southampton SO16 6YD
Tel (023) 8120 6908/9 Direct
Fax (023) 8120 4467
Email: medicinesinformation@uhs.nhs.uk

18th December 2013

Dr Glanville,

Re: Alex Green DOB 04.11.1951 Hospital no. 3472198

Thank you for your enquiry concerning an alternative proton pump inhibitor (PPI) in a patient with PPI-induced hypomagnesaemia. I understand that a switch to ranitidine has led to a loss of symptom control.

Unfortunately hypomagnesaemia appears to be a class effect with the PPIs (1,2). The precise mechanism is unknown but several theories have been put forward including impaired intestinal absorption of magnesium (1). It is generally reported in patients taking PPIs for at least three months, with the majority of cases occurring after a year’s treatment (1,2).

In a safety review by the US FDA, approximately a quarter of PPI-induced hypomagnesaemia cases required discontinuation of treatment in addition to magnesium supplementation. Some cases reported both positive de-challenge and positive re-challenge (i.e. resolution of hypomagnesaemia with PPI cessation and recurrent hypomagnesaemia with PPI resumption). In terms of resolution of symptoms, the median time required for the magnesium levels to normalise was one week. After re-starting the PPI, the median time to develop hypomagnesaemia again was two weeks and in the majority of cases reviewed, the patients did not continue on PPI therapy after the hypomagnesaemia was treated (1).

There have been a couple of strategies put forward to manage PPI-induced hypomagnesaemia. For example one study suggested that esomeprazole was associated with the lowest risk of hypomagnesaemia and pantoprazole with the highest, but there were some significant limitations to the authors’ calculations (2).

In contrast, a second paper that studied the course of severe PPI-induced hypomagnesaemia in a small group of patients found that the use of pantoprazole with magnesium supplements actually resulted in effective control of dyspepsia without a recurrence of their low magnesium (3). The authors attributed this finding to pantoprazole being the least potent PPI (3).

Finally we identified one further case where a patient with PPI-induced hypomagnesaemia was successfully maintained on pantoprazole (Mondays, Wednesdays, Fridays) and an H2 antagonist (famotidine) on the remaining days of the week (4).

We have included these final 2 papers for your information. Please do not hesitate to contact us again if you require further assistance.

Yours sincerely,

Gurpreet Kaur
Medicines Information Pharmacist

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**References**


Real Enquiries

This section helps you to think about the enquiry answering process. Below are given the details of three real enquiries, as received by a regional MI centre. Decide with your tutor which of these enquiries to do. Then for each one describe:

(a) Any further questions you would like to ask the enquirer.
(b) The top sources that you would use to answer the enquiry.

Your tutor will go through these with you when you have finished. If you like, research a full answer using the MiDatabank Trainer on MiCAL to document it, but discuss this with your tutor first.

1. Drug-induced hyponatraemia

A junior pharmacist drops into your office to find out whether paroxetine, digoxin, or ramipril can cause hyponatraemia. A consultant has asked her to check this out for an elderly female patient who currently has a low plasma sodium.

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<th>Further questions for enquirer</th>
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Adverse Drug Reactions

2. **Cross-sensitivity between antimalarials**
   A GP asks you about this. He wants to know if a patient who developed an allergic reaction on chloroquine can be safely given mefloquine.

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3. **Antidepressants and epilepsy**
   A GP telephones you to ask which antidepressant is recommended in patients with epilepsy.

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