

IMPROVEMENTS NEEDED IN RISK COMMUNICATION

Issues surrounding the best ways to communicate the risk of side effects to patients were presented to delegates at the 33rd European Symposium on Clinical Pharmacy held from 20–23 October in Prague, Czech Republic. Christine Clark reports

Communicating the risk of the side effects of drugs to patients is often poorly done, according to Theo Raynor, professor of pharmacy practice, University of Leeds.

For example, the side effect sections of patient information leaflets generally just provide a list of possible side effects with no indication of the levels of individual risk.

Even when information on risks is given, patients often misunderstand this, Professor Raynor said. In particular, one recent study showed that people routinely over-estimated the probability of side effects. Study participants estimated a 26 per cent chance of getting a side effect from penicillin (compared with the actual value of 18 per cent) and a 15 per cent probability of kidney damage with ibuprofen (compared with the actual value of 0.1 per cent).

Professor Raynor pointed out that patients often had a poor understanding of relative and absolute risk. A case in point was the news, in 1995, that third generation combined oral contraceptives had double the risk of thrombosis of the first or second generation. As a result, many women stopped their contraceptive tablets and there was a sharp rise in terminations and unwanted pregnancies. However, the absolute risk of thrombosis is 5–10 per 100,000 users per year, and so doubling of this figure still represents a small risk. Moreover, the risk of thrombosis associated with pregnancy is actually four to five times higher.

In the light of this experience, the Department of Health recommended new wording for leaflets based on frequency descriptions (eg, 15 per 100,000 women per year). When this type of wording was tested on female students at the University of Leeds, there was still a significant level of misunderstanding, with less than 12 per cent of those surveyed understanding the absolute level of risk.

How risks are presented (or framed) can also be important, Professor Raynor continued. For example, “90 per cent fat-free”, sounds different to people from “10 per cent



Theo Raynor: risks of side effects are communicated poorly to patients

fat”. Similarly, people are more likely to undergo treatment with a drug if told that it is 99 per cent safe than if told that it causes side effects in 1 per cent of cases.

People also have difficulty balancing the benefits and harm caused by a medicine, he explained. European guidelines recommend the terms, “very common”, “common”, “uncommon/rare” and “very rare” to describe risk. However, studies show marked discrepancies between people’s understanding of the terms and the levels of risk that they had originally been intended to describe (see Panel 1). This suggests that such terms can be misleading, he said.

Percentages can also be misunderstood by the public, Professor Raynor continued. One study showed that “40 per cent” was variously interpreted to mean one in four, four out of 10 or every 40th person. Frequency statements are generally better understood. When comparisons are made, however, it is better to keep the denominator constant, otherwise studies have shown that there is a tendency to associate a bigger denominator with a bigger risk, he warned. There are always particular difficulties with the appreciation of very small risks. Here analogies can be helpful — for example, the risk of being struck by lightning.

Another issue associated with advising patients about side effects is that of explaining to them what action they should take if a side

effect occurs, Professor Raynor explained. The same European guidelines as above recommend that patients be advised to report side effects “immediately”, or “as soon as possible” for less urgent episodes. However, studies have shown that the terms “immediately” and “as soon as possible” are generally interpreted as meaning the same thing. “The EU guideline was clearly not researched in patients,” he noted.

Instead, a helpful way to present side effect information is to categorise it clearly according to severity and the action required, Professor Raynor suggested. For example, patients should be advised that if they suffer a “serious side effect” they should “stop treatment and see a doctor”. For “less serious side effects” they should “tell the doctor [about the side effect] when [they] next see him or her”. For “minor side effects” patients should be advised that the details provided to them are “for information only”.

By way of an overall guideline for communicating risk information, Professor Raynor recommended using a list of five points compiled by Diane Berry, professor of psychology, University of Reading. These are that:

- Numerical rather than verbal descriptors should be used
- Frequencies should be cited in preference to percentages
- A consistent denominator should be used
- Both positive and negative frames should be applied (see above)
- Baseline risks should be set out when presenting increases or decreases in risk

Panel 1: Interpreting EU risk terms¹

EU terminology	Level of risk	Level of risk understood by readers
Very common	>10%	54%
Common	1–10%	34%
Uncommon	0.1–1%	11%
Rare	0.01–0.1%	8%
Very rare	<0.01%	4%

Dr Clark is a freelance medical writer and consultant pharmacist

Adopt a 3D approach to classifying ADRs

The accepted classification of adverse drug reactions (ADRs) does not help practitioners or patients to assess individual risks, Robin Ferner, director of the West Midlands Centre for Adverse Drug Reaction Reporting, told delegates.

ADRs are conventionally divided into two main types. Type A ADRs are predictable, dose-related, “augmented” pharmacological effects of the drug involved, such as a brain haemorrhage caused by a warfarin treatment. Type B ADRs are those that are bizarre, not easily predictable and rare, an example being an instance of increased libido in a patient taking the dopamine agonist quinagolide to treat a prolactin-secreting tumour.

However, this classification does not work well in all circumstances. For example, the gingival hypertrophy caused by phenytoin is fairly common but is not an augmented pharmacological effect. In addition, bone marrow suppression caused by azathioprine used to be described as a type B event until the discovery that genetic variations in the levels of thiopurine methyl transferase were responsible, making it a predictable event.

Instead, a three-dimensional model of ADRs that takes into account issues such as



Grapefruit juice can affect drugs metabolised by cytochrome P3A4

dose, timing and patient susceptibility is useful for predicting, preventing and palliating ADRs, Dr Ferner said. Such a system has been described as the DoTS (dose, time, susceptibility) model.²

Dr Ferner went on to give examples of dose-related effects that can occur in all regions of the dose-response curve — toxic effects are seen at the top, collateral effects in

the rising portion and “hyper-susceptibility” reactions at the bottom of the curve.

Turning to timing, Dr Ferner explained that ADRs can occur with the first dose, early or late during treatment, on withdrawal and even after withdrawal of the drug. Others are time-independent, for example, the risk of bleeding with warfarin is constant, as is the risk of gastrointestinal haemorrhage with non-steroidal anti-inflammatory drugs.

Susceptibility to an ADR is governed by a number of factors, including genetics, age, gender and co-existing diseases. In addition, altered physiology or exogenous factors can play a role. Cytochrome P450 polymorphisms and propensity to develop malignant hyperthermia are examples of genetic factors. Grey-baby syndrome associated with chloramphenicol and the greater sensitivity of elderly people to hypnotics are examples of age-related factors. Women are more easily intoxicated with alcohol than men and more likely to develop a cough with ACE-inhibitors. The volume of distribution changes for some drugs during pregnancy, altering a woman’s susceptibility to ADRs. An example of an exogenous factor is the way in which grapefruit juice can affect drugs metabolised by cytochrome P3A4.

Failure to prescribe treatment causes preventable ADEs

Not prescribing appropriate drug treatment for patients during their hospital stay is just as much a medication error as prescribing the wrong dose or drug, according to Almut Winterstein, assistant professor, department of pharmacy health care administration, University of Florida. And such a failure to prescribe can lead to a preventable adverse drug event (pADE).

Dr Winterstein explained that a recent systematic review of pADEs shows that they occur with a median frequency of 1.8 per cent. Moreover, the average pADE increases the length of hospital stay by 4.6 days at a cost of \$4,685. Dr Winterstein said that high priority areas for pADEs were currently hyperglycaemia and hypoglycaemia, acute renal impairment, thromboembolic and haemorrhagic events, respiratory depression, uncontrolled pain and allergic and anaphylactic reactions.

Turning particularly to preventing the ADE of loss of glycaemic control, Dr Winterstein told delegates that a prospective study of adult medical and surgical patients had shown that the most common cause for hypoglycaemia is failure to adjust a patient's treatment to match the reduced food intake or changes in their eating schedule that



CHRISTINE CLARK

Almut Winterstein: not prescribing appropriate drug treatment is a medication error

often accompany a hospital stay. Hyperglycaemia, the study says, is most commonly caused by a lack of ownership among clinical staff of the patient's diabetes management and excessive use of sliding-scale insulin. One way of preventing hypoglycaemic events is to insert "flags" into the computerised patient record to alert staff when "nil

by mouth" orders were entered. "Flags" to provide recommendations when the blood glucose level exceeds twice 160mg/dL (8.9mmol/L, upper limit of normal) could help prevent hyperglycaemic events, she added.

Dr Winterstein went on to say that delays in implementing evidence could also constitute errors and cause pADEs. For example, the results of the first International Study of Infarct Survival (ISIS-1) trial established the efficacy of beta blockade after acute myocardial infarction back in 1986. However, in 1996, a US study of more than 45,000 patients, who had no contradictions to beta blockade, showed that only 50 per cent had received beta-blockers as discharge medication, although there were significant variations (from 30 to 77 per cent) between states.

REFERENCES

1. Berry DC, Knapp P, Raynor DK. Provision of information about drug side effects to patients. *Lancet* 2002;359:853-4.
2. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003;327:1222-5.