EDITORIAL

Drug Saf 2012; 35 (2): 87-90
0114-5916/12/0002-0087/$49.95/0

Prevention and Pharmacovigilance
What Should We Do, What Can We Do?

I. Ralph Edwards

Uppsala Monitoring Centre, Uppsala, Sweden

1. Background

The last annual International Society of Pharmacovigilance (ISoP) meeting, held in Istanbul from 26–28 October 2011, was a well organized and run occasion with a potpourri of topics that must have provided something for everybody. They certainly allowed me many opportunities for thought after the meeting. I find it is often the way that, during and after a meeting, perhaps while walking around beautiful and interesting cities like Istanbul, I subconsciously connect lecture contents in a way that was probably not meant, and might not even be logical.

I would like to meander through the streets of Istanbul with you and share some loosely connected thoughts, which were interrupted by sightseeing and chatting to friends.

There were four papers that particularly caught my attention because, not only were they each masterly presentations of their topic, but also they caused me to reflect (yet again) on the purpose of pharmacovigilance. These were:

- Dr Mary Mease on 'Measuring REMS effectiveness: time for a program overhaul' (abstract OP03 *Drug Safety*);
- Professor Joerg Hasford on 'Ethics in clinical research and pharmacovigilance';
- Professors Robin Ferner and Jeffrey Aronson who did a double act called 'Better than cure';
- Professor Valerie Beral on 'Long-term effects of medicines commonly used in women'.

I very much hope that each of these presentations will be available on the ISoP website (available to members).

2. Risk Management Plans

It is relatively recently that risk management plans have come to be, but already we were told by Dr Mease that "… around three-quarters of healthcare stakeholders believe that the REMS program needs a major overhaul …" and "… it is virtually impossible to measure the benefits of a REMS, compared to its burdens on patient access and cost of health care delivery, for a newly approved drug, and that even for an already-approved drug, it would likely require two years or more to effectively conduct such an assessment."[1] Apparently there were also issues with medication guides not getting to patients, or not being comprehensible. A plea was made to involve more healthcare stakeholders; this seemed a shame, since I had hoped that risk evaluation and mitigation strategies (REMS) would be a major safety breakthrough.

3. Ethics

Professor Hasford mentioned the utilitarian ethics usually associated with Jeremy Bentham and John Stuart Mill. These philosophers focus on the idea, at the most simple level, that our aim must ultimately be to maximize benefits and well-being for the majority, with as little harm as possible. In pharmacovigilance, this translates to preventing harm to patients or, at the very least, to minimize the numbers harmed and the degree of harm in individuals. Whilst I doubt if anyone would disagree with this aim, we spend most of our time working on how we find out about harm

that has occurred and, to a less extent, why and how to deal with it or prevent it.

Professor Hasford demonstrated that we might have conflicting ethics in relation to testing drugs on humans when we are unsure of the harm that they may cause. Experimenters have to weigh this notion of theoretical or unknown risk against a vision that doing their experiment may save many more people from damage. Other examples of ethical dilemmas showed that the utilitarian view of ethics does have limitations. One much debated issue is whether a public concern about confidentiality should be allowed to prevent the collection and use of anonymized information in epidemiological studies. Given the extremely small chance of identifying an individual (and any harm being caused) from such data versus the great value of this information to illuminate serious issues in public health, the utilitarian view seems correctly and overwhelming 'yes'.

Back to pharmacovigilance. Our concern usually focuses on the minority of people who are harmed by drug products, but if this concern causes the drug to be withdrawn it may lead to greater harm to those who are taking the drug with good effect. Dr Mease also makes the point that patients might even be exposed to more serious harm from alternatives, by REMS being an obstacle to access. Neither are good utilitarian outcomes.

Withdrawing a drug is a very crude tool to prevent harm. Prevention of harm for a minority whilst maintaining a useful drug for the rest should be our ethical objective. So *targeted* prevention perhaps gives us a good ethical way forward.

4. Prevention

As might be expected, prevention has been identified as a major goal for regulatory pharmacovigilance.[2] The main way we think we do this is by the provision of information in the Summary of Product Characteristics (SPC) and various publications, but it appears that communications about potential harm and how to avoid it are not very effective, and the issues are much more complicated anyway. The reasons for failure in healthcare communication are frequently debated and, whilst it is important to deal with these reasons, this is not the main path I want to pursue.

Professors Aronson and Ferner took us down a more profound path and gave an erudite presentation on how we can easily be mislead by the use of the concept of prevention, producing eight different ways in which the term has been used differently in medical literature that mentions the topic.[3,4]

I do not intend to go into the details of the different views on 'prevention', but again to highlight some points that came from thinking back on the presentation. Many will assume that if an adverse reaction to a drug is mentioned in the SPC it is preventable – certainly if there is an explicit warning. It is common knowledge that drug administration to children is commonly off-label, there being no suitable dosage form for some drugs. Often children are not properly dosed by their parents. Can this situation be realistically avoided by not prescribing the drug? Here the practical challenge is how to prevent harm. Apart from not using the drug, or using a similar, better formulation, other strategies such as better education of health professionals and parents in how to manage the dosage form (such as how to split tablets, and not to give double doses after missed doses which can be a very common problem with children) and to make a paediatric formulation, are options that might be considered. Each of these options has different consequences. This kind of prevention is not often considered to be part of pharmacovigilance. When considering 'preventable' adverse reactions in a study, any off-label use of drugs that causes an adverse effect might be just accepted as 'preventable'.

If a patient has an allergy to penicillin, then on the whole we believe that anaphylaxis or urticaria was preventable if a patient who has previous allergy to penicillin is given a cephalosporin. It is the circular argument – if it can be prevented, it is preventable. What if this imaginary patient had a serious infection with an organism only sensitive to a cephalosporin? Then the use of a cephalosporin is dictated by the clinical situation, and the relevant consideration for preventability ceases to be the SPC alone but the standard of care,

however that is decided. At a recent PhD defence there was a dramatic debate in the audience provoked by a finding in the thesis of concurrent use of aspirin and warfarin in Individual Case Safety Reports (ICSRs); a combination that is known to produce bleeding via interaction because of the antiplatelet effect of aspirin, its gastric irritation and (at higher doses) an increase in prothrombin time potentially causing an increase in stroke and gastrointestinal bleeding. For years it has been known that this drug combination should not be used, yet it was strongly argued that the two drugs are often used in patients with atrial fibrillation to avoid embolism. Again, the standard of practice has been based on a consideration of relative clinical risks, and the risk of embolization at the time of decision overcomes the need to prevent bleeding by avoiding the combination.

If we talk of medication error we might superficially think that all are preventable. However, error is not avoidable; people will always make mistakes but systems can be made to stop an error causing harm, *if they are adhered to*. This is not the place to discuss safety theory and root cause analysis, but any discussion of preventability needs of adverse drug effects must include the concept of the 'error-proofness' of systems of use. If we think of the examples given above relating to standard of care, how should we ensure that those difficult decisions are properly informed? Clinicians need to have access to information systems and other support at the time the decision is made, and this is challenging. Anyone who remembers their days as a junior doctor will remember how nerve-wracking it can be not to have that support, and we know that mistakes are made because of it. So the degree of preventability should also take into account the context of a decision.

Another matter of context is the diagnosis and full clinical appraisal of the patient. It may be that the drug, its prescription and dispensing are not the issue, but that a missed clinical predisposition to an adverse drug reaction (ADR) is the fault. Preventing wrong medical assessment is another kind of activity to be assessed.

No more examples need to be given to understand that the label 'preventable ADR' covers many aspects of clinical practice, and to label ADR in this simple way is not useful in tackling this ethical imperative.

5. Final Complexity

Professor Beral produced excellent data and compelling analysis on a variety of drug problems that have been seen during the use of medicines in women. From the perspective of prevention of harm, the most fascinating information she gave was around the use of the oral contraceptive.

We have known for some time that mortality in young women who start 'the pill' is very small but increases with age, mainly because the risk of cardiovascular events increases with age and that there is a persistent reduction in the risk of ovarian and endometrial cancers, which continues into the postmenopausal years. Apparently there is sufficient long-term information now to allow us to look more closely at both the short-term relatively small increase in cardiovascular mortality and the long-term reduction in mortality from ovarian and endometrial cancer. It seems that, after women have stopped taking the pill and as they get older, there is a net benefit from having used the pill, with the net benefit being greater the longer each woman took the pill.

In terms of prevention, this knowledge is going to be difficult to manage for any of us. The longer women use the pill they will increase their mortality slightly in the short term, which is then a trade-off for a potentially greater reduction in mortality afterwards. In order to get the benefit after, it seems that women must take a small risk in the short-term because the longer-term benefit is greater with long-term use. The net benefit seems to be greater if women take the pill at relatively young ages.

In the examples of prevention mentioned above, we have to deal with a contemporaneous trade-off between risk and benefit; this is a common situation. Currently, we believe the way forward for prevention of harm from the pill is to exclude any woman with cardiovascular (including venous thromboembolic) risk factors from long-term use. Now, if we consider the data on lifetime mortality together it seems that preventing early cardiovascular mortality by not using (or reducing the duration of use) could remove (or reduce) a

protective side effect for ovarian cancer later in life. As we have more information to consider in an already fairly complicated clinical decision about what a healthy woman should use for contraception, where the preventable risks are context dependent, it will increase the challenge of giving good clinical advice – to have a dialogue with a young person about the preventable risks of venous thromboembolic disease and other vascular disease, as well as the beneficial effects on ovarian cancer later in life, is quite a task!

6. Conclusions

Perhaps the familiar top-down approach to medicines regulation hampers the development of REMS. In any case, key success factors for REMS would seem to be good communication with all stakeholders, and agreed, clear, audited endpoints, which are regularly monitored.

It seems quite clear that the ways we might consider for prevention are many more than taking a drug off the market, and we must at least find out what happens to patients when we do take preventative actions. Root cause analysis should become a more familiar tool in considering preventable drug effects.

The more we find out about the factors that alter the risks and effectiveness of drugs, the more and more complex it will be to advise patients about prevention of harm, in the context of possible benefits. On the other hand, we must be more successful in finding those people with particular risk factors, for example genetic risk factors and many others.

Acknowledgements

The author has no conflicts of interest, financial or otherwise, that have any bearing on the content of this paper.

References

1. Mease M. Measuring REMS effectiveness: time for a program overhaul? [abstract]. Drug Saf 2011; 34 (10): 887
2. Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003 Jan-Feb; 12 (1): 17-29
3. Ferner RE, Aronson JK. Preventability of drug-related harms – part I: a systematic review. Drug Saf 2010 Nov 1; 33 (11): 985-94
4. Aronson JK, Ferner RE. Preventability of drug-related harms – part II: proposed criteria, based on frameworks that classify adverse drug reactions. Drug Saf 2010 Nov 1; 33 (11): 995-1002

Correspondence: Professor *I. Ralph Edwards*, Uppsala Monitoring Centre, Box 1051, Uppsala SE 751 40, Sweden.
E-mail: ralph.edwards@who-umc.org