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On Pharmaceutical Risk Minimization

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Abstract

Current regulatory guidelines related to pharmaceutical risk minimization put most emphasis on risk communication and control of the use of drugs. Little, if any, consideration is given to those aspects of an adverse drug reaction that ultimately determine whether the risk can be minimized. However, this limited scope is unfortunate and could prevent risk minimization activities from improving drug use safety. This article attempts to present an overview of possible elements of pharmaceutical risk minimization and to place these in a framework. The promotion of drug safety through risk communication and control of use should be advanced, with more attention to actionable and evidence-based guidance relating to the 'pretreatment evaluation', and in particular the 'on-treatment management' of the patient.

In recent years, the concept of pharmaceutical risk management has been introduced in order to promote the safe use of drugs. Although several guidelines have been published by regulatory bodies,[1-4] the definition and implications of pharmaceutical risk management are debated among various stakeholders.[5] To a large extent, the interpretation of pharmaceutical risk management seems to overlap with traditional pharmacovigilance as defined by the WHO.[6] However, the International Conference on Harmonisation (ICH) E2E Guideline on Pharmacovigilance Planning essentially passes over methods to reduce drug risks, such as risk communication.[7] With its focus on the detection and assessment of adverse effects, the E2E guideline recommends the preparation of a safety specification and a pharmacovigilance plan that might be submitted at the time of application for a marketing authorization. It recommends that the safety specification should be a summary of the important identified drug risks, important potential risks and important missing information. By outlining a strategy involving a set of pharmacovigilance methods, the pharmacovigilance plan will then specify how the concerns raised in the safety specification will be assessed. Recently, a broad definition of pharmaceutical risk management has been proposed which embraces risk identification and assessment, risk minimization and evaluation of risk minimization activities.[8]

Concepts such as risk assessment and evaluation of risk minimization activities appear to be fairly consistently understood, whereas the meaning of risk minimization seems more unclear. Although it has been declared that the aim of a risk minimization activity is to reduce the probability of an adverse reaction occurring or its severity should it occur,[4] current regulatory guidelines put most emphasis on

	Domain		
	Pre-treatment evaluation	On-treatment management	Guidance for use
Elements	Identification of susceptibility based on: • Age • Sex • Altered physiology • Exogenous factors: drugs, food, herbal preparations • Concurrent disease • Genetic traits • Culturally based beliefs	Strategies based on: • Route of administration • Prophylaxis • Treatment of adverse reaction • Monitoring scheme	Risk communication: • Information material intended for health care professionals and patients • Educational programmes • Reminder systems Control of use: • Legal status (conditions or restrictions imposed on prescription) • Control of dispensing • Control of distribution via wholesalers • Informed patient consent • Patient and physician registries
Performance measures	When diagnostic tests are available for evaluation of susceptibility factors for adverse reactions: • Sensitivity • Specificity • Predictive values	• Relative risks associated with prophylaxis or treatment • No specific performance measures for monitoring schemes • Systematic Information for Monitoring (SIM) score for monitoring recommendations	• Surveys of knowledge and awareness • Drug utilization studies • Laboratory data • Studies in registries of 'drug-relevant' outcomes
	Overall assessment: rate of adverse outcomes in relation to drug exposure		

Fig. 1. Elements of pharmaceutical risk minimization.

risk communication and control of use.[3,4] Little, if any, consideration is given to those aspects of an adverse drug reaction that ultimately determine whether the risk can be minimized. However, this limited scope is unfortunate and could prevent risk minimization activities from improving drug use safety. This article is an attempt to present an overview of possible elements of pharmaceutical risk minimization and to place these in a framework.

1. Elements of Pharmaceutical Risk Minimization

Once a new adverse drug reaction has been identified and assessed in terms of its nature and frequency, the information needs to be communicated to prescribers and patients. Apart from the provision of information on the nature of the reaction, an effective message should contain actionable and evidence-based guidance that could bring about real risk minimization. Elements of this guidance would likely include the evaluation of susceptibility factors observable before treatment, in addition to advice on useful monitoring or interventions that could be initiated at or after the start of treatment. Accordingly, as outlined in figure 1, key elements of a risk minimization plan could roughly be assigned to one of three domains: 'pre-treatment evaluation', 'on-treatment management' and 'guidance for use'. Within each domain, various measures can be applied in order to assess the performance of individual elements.

1.1 Pretreatment Evaluation

Elements in this group are related to various assessments of the patient that offer an opportunity for risk minimization before the start of therapy.

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Hence, a careful evaluation of a new adverse drug reaction should always include an evaluation of possible susceptibility factors. Many of these factors are related to common variables and could be helpful in guiding decisions on whether or not to treat, adjust the dose, or initiate some other useful measure.[9,10] Age is easily determined, and both children and elderly patients may be at an increased risk of adverse drug reactions. As to the latter group, apart from age *per se*, increased susceptibility may be a consequence of reduced organ function, concomitant diseases or polypharmacy. The sex of the patient may be important, and the female sex has in some instances been identified as a susceptibility factor for adverse reactions.[11] Attention to age and sex is essential, since the young, the elderly and women tend to be under-represented in premarketing clinical trials, which are part of risk assessment activities. Altered physiology, such as impaired renal or liver function, may reduce the elimination of some drugs and consequently increase the risk of adverse reactions. Various exogenous factors such as other drugs, food or herbal preparations can occasionally affect the pharmacokinetics or pharmacodynamics of a drug and thereby lead to adverse reactions. The inhibition of cytochrome P450 3A4 by grapefruit juice or clarithromycin and the induction of P-glycoprotein by St John's wort are examples of important interactions.[10] Concurrent diseases sometimes increase the risk of adverse drug reactions. Allergies to sulfonamides, particularly sulfamethoxazole (often used in combination with trimethoprim as cotrimoxazole), are more frequent in AIDS patients, but the reason for this increased risk is not fully understood.[12] Lastly, although it is in its early stage, pharmacogenetics holds the promise of providing new markers of risk.[13] The best example of a genetic polymorphism that has had a clinical impact is that observed with the gene encoding thiopurine *S*-methyltransferase (TPMP), an enzyme of importance for the metabolism of azathioprine and mercaptopurine.[10] Some degree of deficiency is present in approximately 10–15% of all individuals, and if these subjects are given standard doses of thiopurines, there is an increased risk of haematotoxicity. However, the reaction can be prevented by the identification of susceptible patients before treatment and the administration of lower doses to those at risk. Finally, it seems reasonable to assume that culturally based beliefs in some situations may influence the outcome of a drug treatment.[14] However, it needs to be emphasized that in real life it is not feasible to obtain accurate risk estimates for all possible susceptibility factors for each new adverse drug reaction. In order to describe the performance of a diagnostic test used in a pretreatment evaluation of potentially susceptible subjects, traditional measures such as sensitivity, specificity and predictive values, could be useful.

1.2 On-Treatment Management

Once a treatment decision has been made, a number of procedures initiated at or after start of treatment can reduce the risk of an adverse drug reaction. In some situations, the route of administration may be important to the adverse effect profile. For example, the development of devices for the inhalation of glucocorticoids and β_2-adrenergic receptor agonists has reduced the extent of systemic side effects associated with these drugs. Moreover, instead of intravenous administration of alemtuzumab (a humanized anti-CD52 monoclonal antibody) in patients with B cell chronic lymphocytic leukaemia, administration by the subcutaneous route offers an opportunity to reduce the risk of influenza-like symptoms.[15] Alternatively, the severity of symptoms associated with intravenous administration can be reduced by prophylactic treatment with glucocorticoids. The same class of drugs, in addition to serotonin 5-HT_3 receptor antagonists, dopamine D_2 receptor antagonists and benzodiazepines, is also useful for prophylaxis of chemotherapy-induced nausea

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and vomiting.[16] In some cases, adverse drug reactions can be successfully treated; for example, in patients treated with alemtuzumab, neutropenia responds promptly to colony-stimulating factor therapy, and reactivation of cytomegalovirus can be resolved with ganciclovir treatment.[15]

Monitoring can be defined as a process of checking a system that changes with time, in order to guide changes to the system that will maintain it or improve it.[17] In the conception of a risk minimization plan, the potential for useful monitoring for an adverse drug reaction should always be explored. In that assessment, a number of factors must be considered. Implementation of a monitoring scheme will be facilitated when the measured variable is linear with time after initiation of treatment, when changes evolve slowly and are both sensitive and specific for potential harm. Other aspects that need to be taken into account are the severity of the reaction, the efficacy of the possible action (e.g. reversibility after treatment discontinuation) and costs.[17] For example, whereas monitoring for adverse reactions caused by an inhaled glucocorticoid is fairly uncomplicated, the challenges are far more complex when a patient is treated with ciclosporin to prevent graft rejection. In the early phase of the drafting of a monitoring scheme, data are needed on the time-varying nature of the adverse drug effect to optimize the selection of time-points for measurements.[18]

Whereas standard measures of relative risk (e.g. odds ratio or rate ratio) can be used to describe the effects of various prophylaxes and treatments, no established metrics are in widespread use for the description of the performance of specific monitoring schemes. However, the Systematic Information for Monitoring (SIM) score has been proposed as a measure of the quality of the monitoring recommendations provided in the prescribing information.[19]

1.3 Guidance for Use

'Guidance for use' constitutes a third domain that includes activities that are related to risk communication or control of use. With regards to risk communication, the challenge is to effectively convey information that influences the behaviours of prescribers and patients. The professional label (e.g. Summary of Product Characteristics) remains the main vehicle for the transfer of information to health care providers, and the Patient Information Leaflet is the corresponding document intended for patients. Efforts aimed at advancing the clarity and impact of these sources of information is a priority for regulatory agencies.[20] The optimal format of the information is subject to debate, and various improvements have been proposed.[21,22] In addition, educational activities or the use of computerized prescribing with reminder systems, can be useful in enforcing the message.[23]

Apart from risk communication, interventions aimed at controlling use can reduce the risk of exposing susceptible patients or ensure that only patients with expected benefits are treated. Examples of approaches aimed at controlling use include change of legal status, mandatory registration of patient or physician, and demanding informed patient consent.[4] In addition, interventions aimed at the distribution from pharmacies or wholesalers offer additional possibilities to control use of the drugs.

In accordance with their focus, current guidelines on risk minimization provide advice on relevant performance measures.[3,4] Surveys of knowledge and awareness can be used to assess whether information has been effectively provided to prescribers and patients. In the assessment of an intervention, drug utilization studies are useful for the monitoring of patterns of exposure and co-prescribing.[24] Furthermore, laboratory databases can provide data on compliance with recommended monitoring, and valuable information can be retrieved from registries

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relevant to adverse drug reactions (e.g. registers for blood dyscrasias or birth defects). The ultimate endpoint for an overall assessment of a risk minimization plan is some measure that directly relates the rate of an adverse reaction to the extent of drug exposure.[25]

2. Discussion

The current understanding of risk minimization is obviously influenced by recently published guidelines from the US FDA and the European Medicines Agency (EMEA).[3,4] Both identify risk communication and control of use as the most important risk minimization tools. As an example, the risk minimization plans (RiskMAPs)[1] proposed by the FDA are anticipated to involve one or more tools that can be assigned to the following categories: (i) education and outreach; (ii) reminder systems; and (iii) performance-linked access. The latter risk minimization tool is a system that links product access to required laboratory testing or other documentation. In contrast, although the FDA guidance is slightly more comprehensive, both guidances offer only limited and sketchy advice in relation to other facets of risk minimization.

However, in itself, even a clear and regulatory compliant communication of the nature, severity or frequency of an adverse drug reaction does not necessarily promote drug safety. If the message does not contain any actionable and evidence-based advice related to the 'pretreatment evaluation' or 'on-treatment management' of the patient, the effect may be limited. In this context, an interesting example is provided by recent efforts to minimize the risk of progressive multifocal leukoencephalopathy (PML) during treatment with natalizumab. PML is an often-fatal demyelinating CNS disorder caused by infection of oligodendrocytes with the JC polyomavirus. Currently, it is impossible to identify patients at risk of developing PML during natalizumab therapy, and there is no evidence that stopping the therapy will affect the clinical course of the disease.[26] Also, there is no evidence that any of the proposed treatments is effective. Hence, in spite of skilful communication, the nature of the PML infection suggests that there are at present very limited opportunities for true risk minimization, and ensuring that only the target patient population is exposed seems to be the best way to achieve a positive benefit-risk balance. Lastly, even if forcefully communicated, lack of adherence to prescribing information has been noted in situations in which the advice was vague and without clear supporting evidence.[20] In particular, improved and evidence-based monitoring strategies have been called for.[17]

The limited scope of pharmaceutical risk minimization, as currently perceived, is unfortunate and could hinder progress. A wider framework, as the one proposed in the present article, could assist in providing shape, structure, clarity of purpose and direction for a range of elements central to risk minimization.[27] In conclusion, the promotion of drug safety through risk communication and control of use should be advanced with more attention to actionable and evidence-based guidance relating to the 'pretreatment evaluation' and, in particular, the 'on-treatment management' of the patient.

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1 Following new US legislation, this plan may in future be referred to as a 'Risk Evaluation and Mitigation Strategy' (REMS).

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