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A Strategy for Regulatory Action When New Adverse Effects of a Licensed Product Emerge

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Abstract

Regulatory agencies grant product licences (marketing authorizations) for medicinal products in the light of evidence that the balance between benefit and harm in the population is favourable. Here we consider a framework for allowing regulatory agencies to make rational decisions when reviewing product licences in the light of new information about harms that change that balance. The regulator can revoke the product licence, restrict the product's availability or change the 'label' in different ways. We examine the features of the adverse effect that may be relevant in making the decision: namely, individual differences in susceptibility; the possibility of monitoring; and the availability of protective strategies. The balance of benefit and harm, and the time-course and dose relation of the adverse effect play important roles in the decision-making process. We set out how these factors can help determine the logical response to new information on the balance between benefit and harm, and provide a series of relevant examples. We believe that when regulatory agencies have to decide how to amend the product licence of a drug when new serious adverse effects cause concern, they would find it useful to adopt a framework of this kind, using different strategies for different cases. Our proposed framework could also be useful in risk management planning during drug development.

Background

Regulatory agencies (for example, the Medicines and Healthcare products Regulatory Agency [MHRA] in the UK, the European Medicines Agency [EMEA] and the US FDA), on the advice of expert bodies (such as the Commission on Human Medicines [CHM] in the UK and the Committee for Human Medicinal Products [CHMP] in Europe), grant product licences (marketing authorizations) for medicinal products in the light of evidence that the balance between benefit and harm in the population is favourable.[1,2] Here we consider a framework for allowing regulatory agencies to make rational decisions when reviewing product licences in the light of new information about harms that change that balance.

Such changes in the perception of the benefit-to-harm balance emphasize the tension between the desire to benefit the individual on the one

hand, and utilitarian regulatory decisions, which prioritize the good of the population. Although the benefit-to-harm balance may have become unfavourable on average in the population, it may still be favourable in some individuals. Furthermore, whatever the risk of harm, an individual may be prepared to take that risk in return for benefit. For example, patients with rheumatoid arthritis were willing to accept a 13–17% risk of death from a treatment in return for relief of pain or stiffness.[3]

Regulatory agencies have a limited number of available actions. These are to revoke the licence, to change the 'label' (i.e. to change the instructions in the summary of product characteristics about the use of the drug) or to restrict the availability of the drug (e.g. in the UK moving it from the general sales list to pharmacy-only or prescription-only availability or restricting its use to particular patients or prescribers).

The first of these options (i.e. revocation of a marketing authorization) denies benefit to those in whom the benefit-to-harm balance is favourable and deprives individuals of the opportunity to make decisions about the risks that they will take. But society often tolerates risky pursuits, such as hang gliding or cigarette smoking, provided the public good is not thereby jeopardized. There is therefore a case for maintaining the product licences for some medicines, despite important adverse effects, so that patients who are not susceptible to the adverse effects can benefit, and others can decide for themselves to risk the adverse effects in return for benefit.

The framework that we propose here to tackle this problem is based on the classification of adverse drug reactions by the DoTS method[4] (i.e. according to dose relation, time-course and susceptibility factors), the availability of monitoring and preventive strategies, and the benefit-to-harm balance. Our analysis yields a decision-making flowchart (shown in figure 1, with corresponding examples shown in figure 2).

The Framework

The framework is shown in figure 1. In developing this framework we have considered, in turn, susceptibility to the harm, monitoring strategies, preventive strategies, the balance between benefit and harm, and the dose relationship and time-course of the reaction.

Susceptibility to Adverse Drug Reactions

We define susceptibility as an individual's liability to have an adverse reaction when exposed to the drug in a given dosage regimen. Susceptibility is influenced by both intrinsic factors (genetic or acquired physiological factors, age, sex and concurrent disease) and extrinsic ones (such as diet

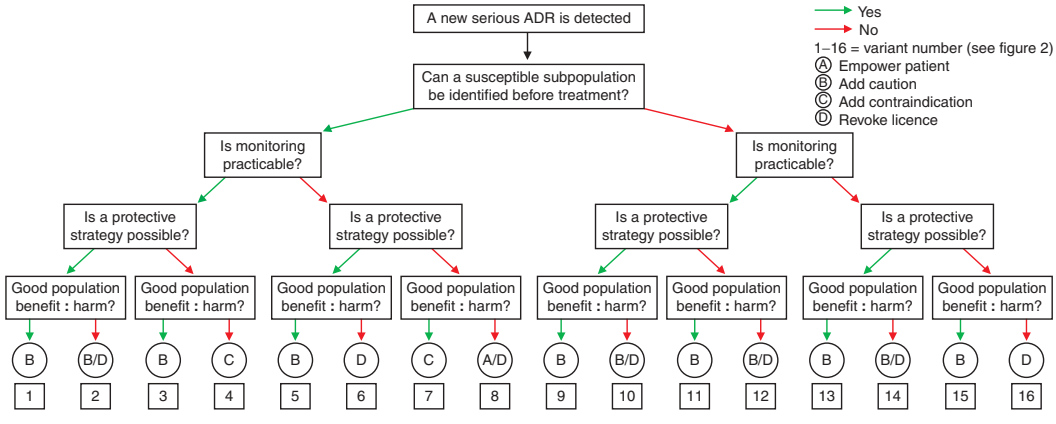

Fig. 1. A regulatory strategy based on individual susceptibility, the distinguishability of a subgroup, the availability of a monitoring strategy, the availability of a protective strategy, and the population benefit-to-harm balance. **ADR** = adverse drug reaction.

Variant (see fig. 1)	Drug	Adverse effect	Susceptible subgroup distinguish-able	Monitoring strategy available	Protective strategy available[1]	Good population benefit : harm balance	Action
1	ACE inhibitors	First-dose hypotension	Patients taking diuretics	Blood pressure	Admit for observation; in bed for first dose	Yes	Add caution about monitoring[2] and protection[1]
2	Bromfenac	Liver damage	Treatment for more than 10 days	Liver function tests	Restrict duration of therapy		Add caution about monitoring[2] and protection[1] or revoke licence
3	Mercaptopurine	Marrow suppression	TPMT deficiency	Blood count		Yes	Add caution about monitoring[2]
4	Methyldopa	Haemolytic anaemia	Coombs'-positive patients	Blood count			Add contraindication in susceptible patients
5	Isotretinoin	Teratogenicity	Women of child-bearing potential (surrogate for fetus)		Avoid pregnancy	Yes	Add caution about protection[1,2]
6	Thalidomide (for sedation)	Teratogenicity	Women of child-bearing potential (surrogate for fetus)		Avoid pregnancy		Add caution about protection[1,2] or revoke licence
7	Abacavir	Hypersensitivity skin reactions	HLA B*5701			Yes	Add contraindication in susceptible patients
8	Alosetron	Ischaemic colitis	Men > women				Empower patient or revoke licence
9	Warfarin	Bleeding		INR	Dosage adjustment	Yes	Add caution about monitoring and protection[1]
10	Etomidate	Reduced steroidogenesis		Serum cortisol, etc.	Corticosteroid replacement or prophylaxis		Add caution about monitoring and protection[1] or revoke licence
11	Clozapine	Neutropenia		White cell count		Yes	Add caution about monitoring
12	Cisapride	Torsade de pointes		Electrocar-diography			Add caution about monitoring or revoke licence
13	Cyclophosphamide	Cystitis and bladder cancer			Mesna	Yes	Add caution about protection[1]
14	Azapropazone	Gastrointestinal bleeding			Acid suppression		Add caution about protection[1] or revoke licence
15	Sulfonamides	Stevens-Johnson syndrome				Yes	Add caution (use only when benefit : harm balance exceptionally good)
16	Dextropropoxy-phene/paracetamol (co-proxamol)	Respiratory depression					Revoke licence

Fig. 2. Variant regulatory strategies based on individual susceptibility, the distinguishability of a subgroup, the availability of a monitoring strategy, the availability of a protective strategy, and the population benefit-to-harm balance (variant numbers and colours correspond to those in figure 1). **1** Includes precautionary, preventive and mitigating strategies. **2** Especially, although not necessarily, in susceptible individuals. **INR** = International Normalized Ratio; **TPMT** = thiopurine methyltransferase.

and co-prescribed drugs).[4] The probability of an adverse drug reaction can be uni-modally or multi-modally distributed in the population, depending on the nature of the susceptibility.

Monitoring Strategies

Monitoring in a chronic or recurrent condition has been defined as periodic measurement that guides the management of that condition.[5] When we consider adverse effects, which may be either acute or chronic, we define monitoring as systematic assessment aimed at detecting and sometimes quantifying the adverse effect.[6] Effective monitoring strategies can be used to improve the balance between benefit and harm.[7] An obvious example is the use of the International Normalized Ratio (INR) in monitoring therapy with oral anticoagulants.

Protective Strategies

Any harm from a drug can be avoided by not using it. However, here we consider circumstances in which there are strategies for reducing the risk of an adverse effect when the drug *is* used and the extent to which such strategies can be used to reduce the risk of adverse effects and thus avoid revocation of the product licence.

The Benefit-to-Harm Balance

The benefit from a drug varies according to its efficacy at a given dose and the nature and severity of the condition it is used to treat; the harm depends on the risk and extent of adverse effects and one's ability to prevent them or to detect them and mitigate their consequences. A highly effective drug, used to treat a serious condition, with a low risk of minor or trivial easily detected adverse effects, has a highly favourable benefit-to-harm balance. The availability of an alternative drug that is as effective and safe, or more so, will also affect the decision to use one or the other. In our framework we consider, as the regulator must, the balance between benefit and harm in the whole population that is going to be exposed to the drug, rather than in a subset of that population or in the individual.

Time-Course

The risk of some adverse reactions is the same throughout treatment (time-independent reactions). However, for many reactions the risk is higher at specific times (time-dependent reactions). There are six categories of time-dependent reactions: immediate (or rapid), first-dose, early, intermediate, late and delayed.[4,8] The time-course of a reaction is one determinant of the practicability of a rational monitoring strategy and allows it to be planned.[7,9]

Dose Relationship

The relationship between the dose-response curve for a beneficial effect and the dose-response curve for adverse reactions can have one of three different patterns:

Pattern 1: Adverse reactions are toxic reactions when they occur only at doses that are higher than those that produce beneficial effects.

Pattern 2: Adverse reactions are hypersusceptibility reactions when they occur at doses that are lower than those that produce beneficial effects.

Pattern 3: Adverse reactions are collateral reactions when the doses that produce beneficial effects and those that produce adverse effects are in the same range.

Knowing the dose-response pattern of an adverse reaction gives information about whether a change in dosage would affect the risk of the reaction.

Analysis and Discussion

The framework (figure 1) arises from a series of questions that follow a logical order:

1. Can a susceptible subpopulation be distinguished as such before treatment?
2. Is a monitoring strategy practicable? If so, the implementation of such a strategy will depend on the time-course of the reaction.
3. Is a protective strategy possible? If so, the implementation of such a strategy will depend on the time-course of the reaction and the pattern of its dose responsiveness.
4. To what extent does the benefit outweigh the harm in the population?

Can a Susceptible Subpopulation Be Distinguished as Such before Treatment?

For some reactions there is universal susceptibility (e.g. cardiac arrhythmias from intravenous adrenaline [epinephrine], red man syndrome from vancomycin). In such cases a population strategy is required. Such a strategy might be in the form of a warning, or advice to monitor, or a preventive manoeuvre.

If not all individuals are susceptible, one should consider whether those who are sufficiently susceptible can be distinguished as such in advance. In such cases, one's strategy would be directed at those individuals. For example, patients who are immunosuppressed are more likely to develop an acute infection with a live vaccine. First-dose hypotension due to an ACE inhibitor is more likely to occur if a patient has heart failure, and particularly in those who are taking a diuretic. In these cases the extent to which an individual is susceptible will vary from one individual to another; however, it should be possible to identify a threshold at which susceptible individuals would be distinguishable from those who are not sufficiently susceptible for a strategy to be worth while.

Is a Monitoring Strategy Practicable?

A suitable monitoring strategy will depend on the time-course of the reaction, whether it is directed at the whole population or at a subgroup with identifiable susceptibility. For example, patients who take clozapine are most susceptible to the adverse effect of neutropenia during the first 24 weeks of therapy,[10] which is when monitoring should be intense. On the other hand, neutropenia due to carbimazole occurs unpredictably and suddenly, and so it is not useful to monitor the white cell count.[11]

Is a Protective Strategy Possible?

Whether a monitoring strategy is or is not available, a protective strategy may be possible. Protective strategies encompass (i) those that are precautionary (i.e. prevent the circumstances in which the adverse effect would occur); (ii) those that prevent or at least reduce the risk of the harm; and (iii) those that mitigate the harm when it occurs. Preventing pregnancy while a patient is taking thalidomide is precautionary; giving mesna with cyclophosphamide reduces the risk of haemorrhagic cystitis; advice to withdraw carbimazole when a sore throat occurs mitigates the harm from neutropenia. These strategies can be incorporated into policy statements, such as the inclusion of cautions and contraindications.

In planning a protective strategy it may be important to take into account the time-course and dose responsiveness of the adverse effect.

Differing Time-Courses

Folinic acid rescue in patients taking high-dose methotrexate needs to be given as a short course at a precise time, soon enough to prevent marrow aplasia due to methotrexate, which occurs rapidly, but not so soon as to prevent the beneficial effect. In contrast, osteoporosis due to glucocorticoids is a late adverse effect, and protection by a bisphosphonate requires long-term implementation.

Different Types of Dose Responsiveness

Protective strategies for hypersusceptibility reactions include desensitization in patients with penicillin hypersensitivity and the coadministration of histamine H_1 and H_2 receptor antagonists, adrenaline and hydrocortisone to prevent hypersensitivity reactions to equine rabies immunoglobulin.[12] For toxic reactions, one would limit the dose of the drug, and in some cases (e.g. ciclosporin) plasma, serum, or whole blood concentration measurement may help.

What is the Balance between Benefit and Harm in the Population?

Although the prescriber should try to estimate the balance between benefit and harm in the individual, the regulator can only estimate it from systematic data obtained from the relevant population. The balance between benefit and harm from any treatment depends on the intrinsic probabilities of the benefits and the harms, and on the availability of strategies to minimize harm

and maximize benefit, such as monitoring, as discussed above. The decision should also be affected by the availability of alternative drugs with different efficacy or safety.

It is outside our scope to discuss how the balance of benefit-to-harm of a drug in the population should be assessed. Others have gone into this in detail.[13-16] However, the cases of clozapine and cisapride are instructive. Clozapine ameliorates schizophrenia and causes fewer extrapyramidal effects than classical antipsychotic drugs. When it was first introduced it was the only drug available for treating negative symptoms. The observation of severe neutropenia made the benefit-to-harm balance unfavourable, and clozapine was withdrawn for a time. However, since it was then shown that severe neutropenia could be avoided by monitoring, the balance between benefit and harm became favourable. Since then the advent of other equally effective and safer antipsychotic drugs has again reduced the favourability. Incidentally, this demonstrates that the balance between benefit and harm can change with time as new developments occur.

In contrast, cisapride was one of several remedies used to treat gastro-oesophageal reflux and symptoms of impaired gastric motility, relatively benign conditions; it was not exceptionally beneficial and it caused a serious adverse effect, prolongation of the QT interval with the risk of polymorphous ventricular tachycardia (torsade de pointes). Even though monitoring for this is possible, the balance between benefit and harm is unfavourable and the manufacturers eventually withdrew the drug from the market in some parts of the world.

Implementation

It is outside our scope to investigate the practicality of implementing the strategy that we have proposed. However, we note three points.

Regional Variations

Assessment of the balance between benefit and harm may be different in different regions. For example, in wealthy countries chloramphenicol is hardly used, since other more expensive antimicrobial drugs are safer, although they may sometimes be less effective. In contrast, chloramphenicol is widely used in developing countries, where cost is an important consideration and the very small risk of the serious adverse effect of aplastic anaemia is accepted. Since susceptibility to this adverse effect cannot be identified, whether to allow the drug to be used is a value judgement based on non-pharmacological considerations. Cost, and particularly cost effectiveness, is a major factor that leads to differences in decisions about licensing by different regulatory agencies. Other regional differences could be minimized by the use of a uniform strategy, such as the one that we are proposing.

Adequacy of Data

For appropriate regulatory decisions to be reached, adequate data are required. This is as true after marketing as before. Any postmarketing risk management strategy should include a requirement for submission to the regulatory authority and its expert committees of adequate data on which to base a decision.

Different Perceptions of the Balance of Benefit and Harm

Patients, doctors and regulators will inevitably have different perceptions of the balance of benefit and harm of an intervention and the extent to which a risk of harm is acceptable in return for perceived benefit.[17] On the whole, patients will be more willing to accept the risks of harms if they perceive benefits, than their doctors or regulators will be to expose them to those harms. This is well illustrated by the case of alosetron, whose product licence the FDA revoked when reports of ischaemic colitis appeared, but reinstated after protests from patients.

Conclusions

Regulators who need to make decisions about risk management of adverse drug reactions should ask four dominant questions: whether there is an identifiable group or subgroup of

susceptible individuals; whether monitoring can help to reduce the risk of an adverse effect; whether there is a protective strategy; and what the balance between benefit and harm is. The flowchart in figure 1 shows how analysis of these factors leads to different recommendations. Figure 2 shows how this approach applies to different historical examples; in each case the strategy would have predicted what was actually done. The next step is to test this strategy prospectively. It also remains to be investigated whether such a strategy could be used in risk management planning during drug development.

In recent years, legislation and guidelines have been introduced in the EU and the US to require pharmaceutical companies to institute risk management plans and to develop tools by means of which, for example, the effectiveness of changes to product labels, prescriber education programmes or safety monitoring must be measured.[18-22] Our proposals complement these requirements.

We also believe that when regulatory agencies have to decide whether to amend the licence of a drug whose adverse effects have caused concern, they would find it useful to adopt a framework of this kind, which guides the selection of different strategies for different cases.

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