Postmarketing management of drug use: toward rational public policy

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On Jan. 11 and 12, 1986, a conference on public health issues in the use of drugs was held in New Milton, England. The conference was organized by Professor Olli Miettinen and Dr. Walter Spitzer under the auspices of the Department of Epidemiology and Biostatistics, McGill University, Montreal. Professor William Inman, of the Drug Surveillance Research Unit, Southampton, England, hosted the meeting. Academics representing a spectrum of expertise relevant to public policy for drug management were invited by the organizers.* The conference was supported by equal contributions from seven drug companies (Boehringer Ingelheim Ltd., Ciba-Geigy Ltd., Hoffmann-La Roche Ltd., Merck Sharp & Dohme, Pfizer Inc. and Sandoz Inc.), who sent observers to the meeting.

During the conference, along with a small number of formal presentations (by Professors Inman, Lane and Melmon and Dr. Hutchinson), there was extensive discussion of issues involved in the rational management of drug use, and a loose consensus was achieved. After the conference a set of conclusions drafted by an editorial committee, the papers presented and the minutes of the discussions, in the form of resolutions, were circulated as a discussion document to the attendees for their comments and criticisms. After two revisions the document was circulated to a wider audience — 55 regulators and 43 others, including many academics interested in public policy on drugs.

Here we present the conference conclusions, a summary of the major comments and criticisms of the discussion document, and our suggestions and plans for further work.

Conference conclusions

The purpose of the conference was to consider the public health issues connected with the use of drugs after marketing. These issues are usually cast in terms of reduction of risk or prevention of harm: postmarketing surveillance is mainly concerned with the detection and quantification of adverse drug reactions, and the public agencies empowered with the oversight of drugs are, in the postmarket-
ing phase of their activities, mostly concerned with actions that restrict the range of medical options available to patients, some of whom may as a result of these restrictions receive suboptimal treat-
ment. Such actions include "Dear Doctor" letters (in the United Kingdom), boldfaced and boxed warnings (in the United States), and even outright banning of drugs.

As our deliberations proceeded we became convinced that this focus was simply too narrow. It is impossible to evaluate the harmful side effects of drugs in isolation from their beneficial effects, nor can the effect of one drug be considered without reference to what other treatments are available. Nor are restrictive actions necessarily the most efficacious means to improve drug use: various kinds of interventions, whose primary object is to promote rational clinical decision-making — for example, by educating or providing services to prescribers, dispensers or consumers — can in certain circumstances be far more productive of desirable change than any restrictive action.

Hence, we came to see that the proper context for thinking about drugs and the public health is sufficiently broad that it justifies a whole new concept that we decided to call the postmarketing management of drug use. We set for our task the consideration of the question What does the public interest require from the societal agencies that have a role to play in the postmarketing management of drug use?

To address this question we considered the four principal components of postmarketing manage-
ment: its goal, the information on which decisions should be based, the actions available to the societal agencies involved in postmarketing management, and the appropriate process for decision-
making. The main conclusions of the conference with regard to these four elements were as follows.

The goal

The goal of postmarketing management should be to improve the balance between the benefit and harm associated with the use of drugs in society.

Information base

To implement the goal of postmarketing manage-
ment, information must be collected on all drug effects, beneficial as well as harmful, on how good or bad these effects are, and on the overall pattern of drug use in society. Moreover, this information must be available to all the agencies who make postmarketing management decisions, in a form that allows its ready assimilation into the decision-
making process.

What information about drug effects should be collected during postmarketing surveillance? Ac-
cording to the goal, it is essential to determine whether the benefits accruing from particular drugs outweigh the harm they cause. Clearly, this requires information about beneficial as well as harmful effects. First, it is necessary to identify specific groups of patients that face particularly high risk for adverse effects or are particularly likely to derive benefit from the drug. Second, it is important to know for each relevant patient popu-
lation how likely each drug effect is to occur. Third, it is also necessary to determine how important to the patient's health the effect is, should it occur. For example, a 1% chance of rash has quite a different implication from a 1% chance of agranulocytosis, and a 1% chance of agranulocytosis is much less "acceptable" for a patient who takes an analgesic for a headache than for a patient taking an immunosuppressive drug following renal transplantation. Also, a 1% chance of aplastic anemia, which is likely to be irreversible, is less acceptable than a 1% chance of agranulocytosis, which can typically be reversed by dechallenge. Finally, we believe that it is helpful to combine these aspects of measurement into a common scale that will allow explicit trade-
offs between the beneficial and harmful effects of drug use. One such scale is described elsewhere by two of us (D.L. and T.H.), who also discuss in the article how the scale can be used in postmarketing management.

To determine whether a particular management option targeted at a particular drug (such as the banning option) is justified, it is not sufficient just to determine the effects of that drug alone. Rather, it is necessary to take into account what alternative treatment options would be used if the management option were chosen and then to estimate the effects of these options on the health of the relevant population of patients. Thus, over-
all patterns of drug utilization have to be moni-
tored to determine what changes in drug use would result from any contemplated management act.

Available actions

The range of possible postmarketing manage-
ment actions should include measures to promote rational decision-making, such as educating pres-
cribers, dispensers and consumers about proper drug use. Action should also be taken to provide services that facilitate such use. These should function in addition to currently standard restrict-
tive measures like warnings and banning.

The public interest is best served when pres-
cribers and patients have available a broad range of effective therapeutic agents, together with the information that makes it possible to determine in each clinical situation which of these is best to use. Thus, rather than concentrating on measures that restrict the range of available therapeutic options, the agencies concerned with postmarketing manage-
ment should instead carry out programs that
promote the use of available agents in the most effective possible ways and discourage their use when they are contraindicated for particular patient populations. For example, information aimed at patients can be disseminated in the form of package inserts, newspaper articles and so forth stressing the importance of compliance and the avoidance of particular foods or other drugs that may interact with a problem drug or describing early warning signs of an impending adverse effect. Or information can be circulated to physicians about norms for the appropriate use of specific drugs, including patient selection, use, duration or other aspects of the therapeutic mix.

Banning drugs can act against the interest of particular classes of patients, because it does not distinguish between a drug's effects in different clinical situations, used in different ways or used for different kinds of patients.

Process

Postmarketing management decisions should always be preceded by the scientific assessment of their likely health effects, and this assessment should take place in an environment as free from political pressure as possible. The actual decision-making process should be consistent, explicit and coherent.

The process whereby postmarketing decisions are arrived at should not be arbitrary. In particular, it should satisfy certain established criteria. These criteria should be consistent; that is, they should not change from one problem to another. For example, new drugs should not be treated differently from old drugs. In addition, the criteria should be explicit; that is, the successive stages of analysis and argument that must be carried out before a decision is made, and the steps involved in integrating these stages into a final decision, should be made explicit. Decisions should be publicly justified in terms of what resulted from these successive stages. Finally, the criteria should be coherent; that is, the stages of the decision-making process should fit together to form a consistent, rational whole.

Comments and criticisms

The comments received in response to the circulated discussion document were both thoughtfull and challenging. While many respondents expressed agreement and enthusiasm for the main themes developed in the conference conclusions, there were some critical reservations, particularly from the representatives of national regulatory and monitoring authorities.

First, many respondents were troubled by the lack of concreteness of the conclusions. It is all very well, they argued, to insist that risks be balanced against benefits among specific groups of users of a drug when compared with alternative therapeutic options, but how are such comparisons and balances to be carried out? And what exactly is the role of quantitation in the procedure? How and to what extent can scientific considerations and political imperatives be meshed into a single process?

Second, some respondents felt that the organization of the conference and its conclusions were unbalanced. No active members of national regulatory or monitoring agencies participated in the proceedings (though several past members of such bodies were included in the academic panel), whereas representatives of industry funded and scheduled the meeting and participated in its deliberations. On the other hand, the burden of implementing the conference conclusions seemed to fall on the regulatory authorities, but nothing was said of the responsibility of industry for its actions in making drugs available, educating prescribers about their proper use, gathering information about their benefits and risks, and even deciding whether to withdraw them from the market.

Finally, several respondents criticized the conclusions for their lack of geographic breadth. Regulators from other developed countries felt that the conclusions were particularly relevant to the United States and the United Kingdom and that the relevant legal, institutional and practical arrangements in their countries had not been taken into account; others pointed out that the special needs of underdeveloped nations with respect to drug availability, information and management were entirely ignored.

Where do we go from here?

We feel that for further progress in this field an explicit set of procedures for implementing the conference conclusions must be developed, then the procedures must be presented for comment and criticism to a group representative of all interested parties.

Subject to the availability of funding from industry or elsewhere we at McGill hope to complete these tasks within the next 2 years and thus extend and make more concrete the dialogue that has begun between the various parties involved in the complex area of postmarketing management of drug use. We feel that decision theory can provide a useful structure within which this dialogue can occur and, thus, will in the long run lead to more coherent public policy for postmarketing drug management.

Reference

1. Lane DA, Hutchinson TA: The notion of "acceptable" risk: the role of utility in drug management. J Chronic Dis (in press)