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The Application of Adverse Drug Reaction Data to Drug Choice Decisions Made by Pharmacy and Therapeutics Committees

An Australian Perspective

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Summary

Pharmacy and Therapeutics (P&T) committees undertake policy, regulatory and educational activities to promote rational use of medicines in their institutions with the aim of improving the quality of health and economic outcomes at these institutions. Formulary management is an important part of the P&T committees' activities and making drug choices is one of the committees' most difficult tasks.

The 3 types of information most commonly identified by P&T committees as necessary for making drug choices are effectiveness, safety and cost data; usually in this order of importance. There is some evidence, however, that safety data are not considered by all committees when they make decisions about adding a new drug to a formulary.

The role of adverse drug reaction (ADR) data in formulary decision-making (for registered drugs) occurs at several levels. First, ADR data obtained from pre-marketing studies of the drug are important and enable the committee to make an assessment of the risk of toxicity that should be anticipated for the drug. However, the limited nature of this information makes an absolute assessment impossible. Secondly, comparative safety information is necessary when deciding the place in therapy of a particular drug. Weighing up the comparative risks and benefits is a complex task which is a routine activity for most P&T committees whatever level of sophistication is applied. Thirdly, ADR data are an important ingredient of any economic assessment considered by a P&T committee. Calculation of the costs and consequences associated with the adverse effects of treatment demand careful assessment. Finally, aggregated adverse drug event reports which collate not only the consequences of adverse drug reactions but also medication incidents (medication errors) and which have been reported locally can be a useful quality assurance process for a P&T committee. This information will contribute to the identification of drugs for deletion from the formulary and less commonly in making decisions about additions to the formulary.

As formulary management forms only part of a P&T committee's work, so the

committee's interest in ADR is broader than the use of these data in making drug choices. The P&T committee may also be involved in promoting ADR reporting to either a central database or primary carers.

Although often of limited availability, ADR information has an important role in the formulary management process of P&T committees.

Pharmacy and Therapeutics (P&T) committees have a primary role in promoting appropriate use of drugs in the local setting as a part of good quality patient care. While the structures of such committees vary from representative or expert medical advisory committees to representative committees of a more multidisciplinary nature, the key functions of P&T committees are perhaps less variable. Several authors[1-5] have identified a range of strategies that P&T committees have used to achieve their 6 key objectives:

- formulary management
- promotion of prescribing standards
- evaluation of drug use
- provision of information on drug use
- promotion of adverse drug reaction (ADR) reporting
- supervision of drug expenditure.

These activities can be broadly categorised as policy, regulation and education functions, although several of the activities have elements which would appear under more than one heading. The best mix of activities is dependent on the problems confronting the P&T committee and the organisational structures in which the committee operates.

1. Drug Choices

Making drug choices is a core activity of most P&T committees, but it has also been identified as one of the most difficult activities, often requiring appraisal of large amounts of information and careful judgement.[2,4] The task can appear overwhelming with a ceaselessly expanding array of drugs available; many are only slight variations on a novel chemical entity, possibly filling important clinical niches but more often duplicating what is already available. Limited resources have increased the focus on value for drug expenditure which has led to the inclusion of economic, as well as clinical, considerations in the decision making process.

The drug formulary is the P&T committee's vehicle for identification of preferred drugs and treatment protocols to achieve effective and efficient care.[6] The drug formulary has an important role in ensuring quality prescribing, managing limited resources and acting as an educational tool for both students and practitioners.

The need for the duplicative review layer contributed by the formulary process following the national regulatory authority approval for marketing could be questioned. As Rucker and Schiff[7] argue, however, the national regulatory authority certifies that a drug is safe and efficacious for its labelled indication(s) only. Moreover, it provides little guidance on the comparative safety, efficacy and cost-effectiveness of competing products in particular patient groups. Early experience with new agents following approval is commonly obtained in the relatively controlled hospital environment. This is reflected in a 1995 survey in the US where 51.5% of products were reviewed by P&T committees prior to FDA approval.[8] In 1992, in western Germany, 247.5 million prescriptions were written for drugs of doubtful efficacy or safety and these prescriptions amounted to 31.1% of all prescriptions.[9] It appears that review of new drugs is likely to remain a central part of the formulary process for the foreseeable future.

1.1 Formulary Decision Making Processes

Summers and Szeinbach[10] use value analysis to describe the decision making process of P&T committees. They argue that the value placed on possible outcomes will differ depending on the committee members perceptions of patients, providers, society and contextual variables. They iden-

tify the 2 outcomes that are important to most P&T committees as the effect of the drug on drug treatment quality or therapeutic performance and its impact on hospital costs. While this model of decision making is commonly applicable, other models are also observable in P&T committee deliberations. For example, expert opinion[11] may be overly influential in the decision making processes of some committees or 'tradeoff contrast' may occur where an alternative will appear intrinsically more valuable depending on what it is being compared to.

Whatever the decision making process, 3 principal types of information are routinely cited as necessary to P&T committee decisions: evidence of efficacy, safety and cost. Other important information may include patient acceptance and therapeutic need or demand.[5,12] This information is generally obtained from medical or pharmacy journals, the pharmaceutical industry, professional meetings and the national regulatory body (via the approved product information).[8] It is not unusual, however, for the sponsor (prescriber requesting the drug be added to the formulary) to be the local expert in the therapeutic area under discussion and many committees will include consideration of this expertise in their deliberations.

2. The Role of Adverse Drug Reaction (ADR) Data in Formulary Decisions

ADR data play an important role in decision making regarding formulary additions and deletions. The type of data ranges from that collected in randomised, blinded and controlled clinical trials to post-marketing surveillance and reports of local experience.

2.1 Safety Data

When a new drug is considered for addition to a formulary, the P&T Committee will generally consider the adverse event data reported in clinical trials. Schumacher[12] suggests that the formulary committee assesses the relative weighting for safety data as 2.0 compared with effectiveness (2.5), patient acceptance (1.5) and cost (1.0). Interestingly, this is consistent with the work of Denig et al.[13] which assessed the relative importance of various categories of information to the drug choices made by individual hospital physicians. The average of individual weightings from their results were efficacy 2.3, own experience 2.0, adverse effects 1.9 and cost 1.0. However, variations were observed between different therapeutic classes.

Surprisingly, a survey of P&T committees in Australia[5] found that only 71% of survey respondents considered adverse effects when making decisions on proposed formulary additions (fig. 1). Rural or district hospitals (<200 beds) and private hospitals were less likely to use adverse effect data than referral or teaching hospitals. In the case of private hospitals this probably reflected adoption of the national formulary (Pharmaceutical Benefits Scheme Schedule) since items on this list are reimbursed by the Australian Government. Public hospitals are not eligible for this reimbursement and are more likely to develop local hospital formularies. The small rural hospitals had limited access to personnel and resources for decision making by a P&T committee and only 50% used adverse effect data when deciding to list a new drug on the formulary.

There are some major limitations of the safety data provided to a P&T committee. First, at the time a new drug is first considered for formulary addition, usually soon after or before marketing, relatively little is known about its safety: on average about 1500 patients will have been exposed to the drug and often the exposure will have been for periods much shorter than intended in routine clinical practice.[14] Some of these data will be derived from randomised, blinded, controlled trials, but a proportion will come from nonrandomised or open label studies. Secondly, the patients exposed to a drug in clinical trials may not be representative of those prescribed the drug in the community. Finally, it is uncommon to have comparative safety data for the new product and the drug it is most likely to replace. This is an important consideration since, in the absence of definitive knowledge,

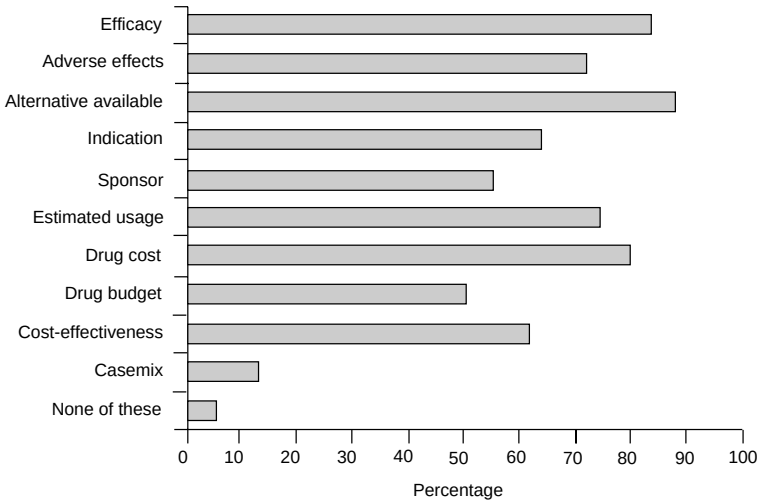

Fig. 1. Percentage of survey respondents[5] reporting use of particular information types when making formulary decisions (n = 303 public and private hospitals represented by 287 Pharmacy & Therapeutics committees).

judgements about safety are made based on a calculation of risk.[14]

When effectiveness is equivalent, P&T committees tend to take one of two courses when dealing with limited safety information. If the contrast in safety between the new drug and its comparator is equivocal, the committee is likely to err on the side of the drug they know and have experience of. More commonly, however, the marketing claims will be for an improved safety profile. If the marketing claims are substantiated by data (and this is not always the case) the committee will weigh up the probability that the improved safety profile will remain a 'real' phenomenon or reflection of the truth against the probability that it is an artefact of more limited exposure to the new drug. The quality of the studies from which the safety data are taken and the number of patients involved in these studies will be important inputs to the committee's deliberations.

2.2 Acceptable Clinical Risk

A more difficult task for a P&T committee involves weighing up the comparative risks and benefits of a new therapy for which there is evidence of better efficacy but for which safety data are equivocal or suggestive of reduced safety compared with the alternative. In many institutions, such a decision will be based on the empiric judgement of the committee members, and their subjective preference for efficacy and safety in the specific situation will be of prime importance in determining the outcome. More objective methods of weighing clinical efficacy and risk are available, including decision analysis or multiattribute-utility analysis, but descriptions of use of these methods by P&T committees are rare.[15,16]

Decision analysis has been recommended as a means for P&T committees to take into account certain events such as drug costs and uncertain events such as toxicity in their decision making. It is a quantitative method that incorporates both probabilistic data and value judgements into analysis of the problem. The decision analyst structures the chronological sequence of intermediate decisions and chance events and their most important possible consequences, usually with the aid of a decision tree.[15] While this is an attractive method for inclusion of risk and benefit data into rational decision making, it is rarely used by P&T commit-

tees in Australia although greater use may occur in other countries.

A P&T committee's assessment of what is an acceptable risk is determined by the data, the committee members' individual views and the argument provided by the sponsor for the formulary addition. It is less usual for a P&T committee to consider what risk may be acceptable to a particular patient group when making a decision. The applicant and often the advocate for formulary addition is usually a medical practitioner who may also take a patient advocacy role or, alternatively, some committees have attempted to address this by including consumer or general practitioner representation on the committee.[5]

2.3 Economic Consequences

As P&T committees are reviewing more economic data it is important to understand the impact that ADRs can have on an economic analysis. The costs and consequences specified in the analysis should include the cost of treating adverse effects and the consequences of ADRs, particularly the impact on mortality or quality of life.

If a new product is purported to cause fewer ADRs, it is important to ascertain the significance of the consequences in absolute, rather than simply relative, terms. For example, if the new drug causes headache in 50% fewer patients, it is important to know whether the comparator causes headache in 1% or 20% of people. Additionally, a sensitivity analysis at the 95% confidence intervals of the risk reduction should form part of the economic analysis to illustrate the statistical significance of the risk reduction. This will provide a best and worst case scenario.

Costs should be realistically calculated; opportunity or potential costs are often difficult for a P&T committee to appreciate if they cannot be realised by the institution. A complete analysis of costs would also include the anxiety or pain and suffering associated with the adverse effects of the drug for patients and their families.

2.4 Post-Marketing Surveillance and Error Reports

Most P&T committees have access to ADR reports from their institutions;[2,5] our Australian survey found that 67% of committees received regular ADR reports and 71% received medication incident (medication error) reports. As these frequently rely on spontaneous or voluntary reporting, they primarily provide sentinel information. The reports may stimulate the P&T committee to further investigate or monitor the safety of a drug but are inadequate alone to cause a change in formulary listing. ADR data from a larger population such as may be collected by a national ADR reporting mechanism is likely to yield results which would be valuable to P&T committees, especially when reviewing a number of drugs belonging to the same class or considering deletion of a drug from the formulary.

Medication incidents are reported to P&T committees because of the concern that these will result in adverse drug events, i.e. some injury will be incurred by the patient. Bates et al.,[17] using an intensive surveillance methodology, found that of 530 medication incidents which occurred at a rate of 5.3 incidents/100 medication orders, an adverse drug event occurred in only 0.9% of cases. This is consistent with more recent work which used Australian National Diagnosis Related Group (AN-DRG) codes to flag adverse events; 0.95% of separations had an adverse drug event recorded.[18] Consideration of medication incident reports is likely to have important implications for formulary drug choice in only a limited number of situations. If a drug with a relatively narrow therapeutic margin, requiring frequent monitoring, is often the subject of medication incidents there may be concerns about the potential for patient harm if educational and policy initiatives cannot remedy the problem. An alternative solution in this situation would be to select a different drug with a better therapeutic index for inclusion on the formulary. Certainly the argument of lower medication incident risk would be an important consideration in a relatively small number of formulary decisions.

3. Other Concerns with ADRs

The work of the P&T committee extends beyond making drug choices and ADRs are of concern in some of these other functions.

3.1 Promotion of ADR Reporting

Many P&T committees are concerned with the promotion of ADR reporting in their facility. There are 3 main purposes for promoting ADR reporting and publication or feedback of information about specific reactions within the hospital setting. The first is to raise awareness about the potential for ADRs; to raise the index of suspicion among staff so that patient care will not be compromised by continuation of undetected adverse drug reactions.[2]

The second, equally important, purpose is to pick up significant new reactions. Referral hospitals are often at the fore-front of use of new drugs and during the introductory period can play an important role in detecting new reactions. In Australia, the national Adverse Drug Reaction Advisory Committee (ADRAC) report that approximately 30% of all its ADR reports originate from hospitals, 30% from general practice and another 30% from the pharmaceutical industry. About 10% of reports come from a variety of other sources. Hospitals, therefore, are important contributors to knowledge about drug safety once the drug is in the marketplace.

Third, the ADR reporting programme can act as a focus for education of both undergraduates and practitioners about identification and management of ADRs.

3.2 Promotion of Systems for Communication about ADR

The second and more general concern the P&T committee has is to promote systems of communication when an ADR has occurred in a hospital patient. The P&T committee has a role in developing or promoting policy for communication of an ADR report for a particular patient to the patient's primary healthcare provider. The mechanism of communication may be simply the discharge summary but it is important that the implementation of the chosen mechanism is regularly reviewed, preferably by the P&T committee. This is an important quality of care issue for patients that relates to drug use in the hospital and falls within the P&T committee's objectives.

In addition to communication with the primary healthcare provider, it is important that documentation of the ADR which occurred during one admission is apparent in the medical notes at the time of subsequent admissions. If the ADR report is buried in a large file, the risk of unintended rechallenge is increased. The P&T committee can provide appropriate policies and recommend implementation of strategies to deal with this issue.

3.3 Role in Determining the Effectiveness of the Pharmacy and Therapeutics Committee

The incidence of adverse drug events in hospitals has been of concern to P&T committees particularly as it relates to patient outcomes. If the goal of P&T committees is to optimise the quality of patient care or outcomes with respect to drug therapy, preventable adverse drug events can provide an indicator of the committee's success in achieving this.

The Joint Commission on Accreditation of Healthcare Organisations in the US include in their standards for P&T committees' policies and procedures provision of policies to ensure safety of overall medication use with specific reference to systematic and intensive assessment of adverse drug reactions.

Likewise, in work recently undertaken within our own group to develop indicators for P&T committees, 4 of 17 indicators related in some way to policies or procedures for documenting, reporting or following up ADRs.[19] There was general agreement in our broad consultation with healthcare providers, administrators and consumers that ADRs should be a prime concern for P&T committees.

4. Conclusion

ADR data are an important source of information to aid a P&T committee when making decisions about formulary additions and deletions. While information on effectiveness is a primary consideration, safety information is of close secondary importance. The ADR data available to P&T Committees at the time of making a drug choice are often quite limited, necessitating ongoing monitoring of adverse events throughout the life of the drug. As the role of P&T committees extends beyond formulary decisions so does their use of ADR data.

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