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What are the Real Lessons from Vioxx®?

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In major medical journals, as well as in the public media, it has been said that regulators have not managed the risk issues of rofecoxib (Vioxx®)[1] well. The Canadian Medical Association is even calling for a new body to be set up to monitor drug safety in that country. They are reported as saying that North America's regulatory agencies have "failed miserably".[1] In another article, the authors say: "our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified".[2] These are but two examples of the criticism of pharmacovigilance as it relates to rofecoxib and these reflect broader drug safety concerns.

In fact, pharmacovigilance detected the early signals of an increased risk of cardiovascular disorders with rofecoxib. At the annual meeting of the national centres participating in the WHO Programme for International Drug Monitoring in Tunis (October 2000) the Netherlands Monitoring Centre (Lareb) presented new evidence of cardiovascular disorders related to rofecoxib, with reporting of a high odds ratio for adverse cardiovascular effects, with some fatalities and occurring early in treatment. The affected patients were elderly and in addition, the dose of rofecoxib was often high. This prompted a response from many countries where myocardial infarction (MI) had been seen in association with rofecoxib use. So what happened after that, why did it happen and what can we do better?

1. Postmarketing Studies Confirmed the Early Signals

A review of the discussions in the WHO email conference system (Vigimed) and discussions at subsequent annual meetings of the WHO Programme in 2001 and 2002 reveals continuous monitoring of the selective cyclo-oxygenase (COX)-2 inhibitor situation, particularly of rofecoxib, by regulators. In several countries, regulatory authorities did warn both health professionals and the public about the latest developments reported in the literature on a regular basis via official newsletters and websites. Even in February 2000 there were recommendations to add information about cardiovascular events to the labelling of rofecoxib in the US[3] and elsewhere.

More information came from the VIGOR (Vioxx GI Outcomes Research) study,[4] which received wide publicity. The main criticism of this trial was that the comparator in VIGOR, naproxen, may have reduced the MI rate and many further studies, using a number of COX-2 selective drugs, were performed by the pharmaceutical industry with the MI rate in mind.

The Merck polyp trial, APPROVe (Adenomatous Polyp Prevention on VIOXX), is but one study that included a well designed safety evaluation and safety concerns led to the premature closure of this study at 34 months when the MI rate with rofecoxib at 18 months was found to be significantly higher than that in the control group. Two odd features of this study were the relatively low MI rate in the controls and the non-linear increase in MI in the rofecoxib group following long-term use (this could be inter-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

preted as a long-term effect, perhaps an effect on the arterial endothelium). This study led to the withdrawal of the drug by Merck and clearly could not have produced a result in <18 months.

For rofecoxib doses >25mg, there were stronger signs of an association with cardiovascular disorders before the withdrawal; in addition to the VIGOR trial, three observational studies had already been published that pointed to an increased risk of MI, the first in 2002.[5] Other studies have confirmed the dose relationship, which has not been fully reflected in the package inserts and summary of product characteristics (SPCs).

There is almost nothing in the current media debate on the overall effectiveness-to-risk balance of rofecoxib and even less on how it compares with other COX-2 selective drugs and other old or new analgesics, even though some of this information is available.

The main competitor to rofecoxib, celecoxib (Celebrex®), may not be any better than non-specific NSAIDs from a gastrointestinal (GI) tolerability point of view.[6] Differences in the safety profiles of rofecoxib and celecoxib have also been reported,[7,8] so there may be differences within the class both in terms of the GI tolerability and other risks.

There is little in the general or medical media to guide either health professionals or patients as to what would be the best likely alternative to rofecoxib. It is also worth noting that 80% of the prescribing of rofecoxib in one country did not fulfill the requirements stipulated in the SPC.[9]

Much other information on rofecoxib is available and only the main issues are outlined here, as the main purpose of this article is to consider whether another way forward in monitoring drug safety is desirable.

2. Insights and Challenges in Drug Safety

2.1 Decision Making

There is always a need to link evidence to decision in drug safety matters and decision to action. This is true for the overall status of the drug as well as in a data gathering sense. For example: the signal indicating that rofecoxib is associated with MI could be confounded by the age group or concomitant illnesses of patients treated, therefore, there was a need for a study to determine whether this was the case. But how important are these signals? What will the studies cost? As each study produces results, decisions must be made about what to do with rofecoxib, given its effectiveness and risk, both in terms of public health and in terms of information to help patients and prescribers. Apart from overall decisions about what to do with the drug at each step, consequent judgements are needed about communicating the decisions, how to communicate them and to whom.

None of the judgements are straightforward, particularly when there is little information available. It is very easy to see what to do with a safety signal *after* information is available; it is very difficult to decide which signals to follow up in order to get that additional information. This difficult ruling is largely left to the regulators and their advisors, who decide on behalf of the public. Yet there is no real knowledge about what risks patients in particular and the public in general are prepared to take, given a certain benefit (this is even more difficult when one considers competing treatments). Quality-of-life tools are continuously being developed and there are some very imaginative approaches to understanding risk perception and tolerance. These should be pursued much more actively in order to find a set of baseline acceptable risks for different situations. Patient groups, in particular, must play a role in decisions; an esoteric professional group making such resolutions in secret is not tenable.

Acceptable benefit-to-risk balance is an individual judgement for each patient and every effort should be made to obtain enough information on the issues of effectiveness versus risk to properly enable those singular judgements by doctors and their patients.

At both a public health level and for individual patient decisions there is a clear need to be able to compare effectiveness and risk profiles of drugs in a more meaningful way.

2.1.1 Comparisons in Safety

There are older and newer pain medications on the market that are much less well investigated than rofecoxib. Many have more problematic effective-

ness-to-risk profiles than rofecoxib. One is the analgesic dextroproxyphene/paracetamol (acetaminophen) [co-proxamol], which has only recently been restricted in the UK, despite concern over its safety for many years (for example, see Edwards[10]). Also, a new finding in one drug *might* apply to other related drugs where information is lacking, as a class effect. This is now a matter of debate with the selective COX-2 inhibitors and other NSAIDs. Withdrawing one drug on the basis of a highly publicised, single adverse effect without considering the effectiveness-to-risk balance of competing products and also considering this balance in different indications may lead to the substitution of another drug with the same problem or worse. In the EU, complex comparisons of rofecoxib with other selective COX-2 inhibitors have been underway since 2002, but have not been publicised.

The WHO has led the way for such drug comparisons with its Model Lists of Essential Drugs. Comparisons between drugs for different indications by experts result in clear guidance that can be appraised critically by all concerned. It does not mean that drugs not on the Model List are either ineffective or unsafe, but that they must be considered carefully against the gold standard of the Model List.

2.1.2 Concern to Evidence

New concerns about drugs are generated by spontaneous reports all the time: about 300 serious associations between new drugs and adverse drug reaction (ADR) combinations come up for consideration every quarter in the WHO database. It is instructive to consider the way these concerns are managed. In my view, an excessive amount of time is spent making sure that every 'serious, unlabelled' report is sent by industry within the arbitrary time of 15 days.[11] The '15-day rule' has no evidence basis. Undue delay in getting and analysing reports would be deleterious, but there is a great need to understand the more difficult challenges of getting and analysing the additional useful evidence that is then needed to fully evaluate the individual case after the first report has been filed. There is a view that large multipurpose patient care databases may be used for safety signal detection, but there will still be questions about data quality and the tools used to find the signals. For example, data mining has been used on the IMS Health Disease Analyser database by the WHO Foundation Collaborating Centre for Drug Monitoring and this has revealed interesting signals, but each of them requires further elaboration as do concerns spontaneously reported by health professionals and others. One advantage of the use of healthcare databases is that the signals might be better quantified; however, they lack the individual diagnostic aspect of a spontaneous report, as well as the human aspect of there being enough concern to lead to an active decision to report the issue.

A further delay usually occurs over when to initiate further studies, performing the studies and analysing the results. The consequence is frequently that regulatory responses occur years after the first signal is made known. Little is done to measure the impact of regulatory activity and the consequences of delays.

In the rofecoxib situation, as in many others, it has largely been academia that has designed and conducted further studies to address safety concerns. Many are done in collaboration with the pharmaceutical industry, which is naturally reticent to fund studies. Only some studies are agreed internationally between regulators. Almost all are undertaken without health professionals and the public knowing that a safety concern is being investigated. As with the APPROVe study, the studies may take years to produce a finding and, as with the VIGOR study, the results may produce more controversy.

Regulatory agencies are taking more initiative with regards to conducting the studies they need, but as they have few resources they tend to depend on others. The pharmaceutical industry plays a key role in deciding when and how safety studies are done.

The WHO Programme for International Drug Monitoring publishes early concerns about drug safety to all members of the programme. Surveys on what is done about such early concerns have been performed in different countries and the responses are variable.[12,13] The WHO has made requests to national centres to communicate to all members of the WHO Programme for International Drug Monitoring about safety issues they are investigating. An internet discussion channel, Vigimed, was set up to facilitate this, but the input from developed countries about their on-going work on drug safety signals has been limited. Pressure from the pharmaceu-

tical industry to keep safety discussions confidential has been cited as a reason for this. Work may, therefore, be duplicated in different countries unnecessarily but, more importantly, countries are often faced with a series of crises when regulatory decisions become public and they may not even have known that there was a problem under investigation. For example, when the third generation oral contraceptives were found to be associated with a higher risk of venous thromboembolism, developing countries that were actually involved in the seminal study were excluded from the discussion of the results.

2.1.3 Evidence and Decision

On receiving a first signal, the decision to take action should be based upon the level of certainty of the signal and its seriousness. In the rofecoxib situation, a limited warning was quickly given, which was a reasonable approach given the high background prevalence of cardiovascular disease in the treated population. The kind of regulatory decision should obviously be based on what is reliably known at the time, although some use of the 'precautionary principle' can reasonably be invoked in selected situations where there is great potential for harm. In most instances the decision will involve providing better information to guide health professionals in the avoidance of harm from a drug.

Repeated confirmation of a dose-response relationship with MI in the rofecoxib case both substantiated the causative relationship and gave a reason to suggest limitation of the dose administered. The final finding, before the withdrawal of rofecoxib, of a relationship of MI with long-term use (already disputed and at variance with the early signal from spontaneous reports) could also have led to a warning against such use. Why did this not happen, rather than withdrawal?

Many withdrawals of drugs over 'safety' problems are not necessarily warranted from a public health perspective. They may be strategic, for example: the company has another drug for the same indication that they wish to launch and the withdrawal of an old drug, out of patent, can remove some or all of the generic competition for the indication at the same time; a company may decide that a potential fall in sales following a warning renders the drug cost-ineffective; or it may be that the company does not wish to pay out for claims against them, which may sometimes be unjustified in a public health sense, although reasonable in the strict liability of law.

The APPROVe study was sponsored by Merck. The independent ethics committee advised the discontinuation of the study because of the MI risk; the number of possibly affected people was quite large, so it is easy to see why Merck pre-emptively discontinued the drug to avoid possible heavier litigation costs.

Almost all drug regulatory activity is part of a dialogue between the regulators and the pharmaceutical industry. Safety issues are usually, but not always, raised by regulators. On request, large volumes of information are provided by the pharmaceutical industry to regulators for the latter to analyse. Suggested changes to the ADRs mentioned in the SPCs and warnings are generally more easily accepted by the pharmaceutical industry than restrictions or withdrawals. This may have been so with rofecoxib. A question arose, given that early warnings on MI were in place, as to whether it was unnecessary to add the dose restriction. As the 2001 US FDA Advisory Committee Document[3] states, "Rofecoxib (Vioxx®) 50 mg/day is the dose recommended for the treatment of acute pain and twice the highest recommended dose for osteoarthritis (OA)". Physicians should not have been prescribing doses >25mg for more than very short periods.

Given that some general warning about rofecoxib was already extant and that broader, more complex comparisons needed to be performed, withdrawal of the drug was not necessarily the best action in terms of public health; however, more communication of the unfolding situation would have been helpful.

In drug safety, the evidence always changes over time. Usually one obtains improving evidence of the nature and extent of the risk, but the judgement over what to do and when is all too often a value judgement with little consistency between instances. A publication in the academic or public media often triggers action for one drug risk, when others go relatively unnoticed for years (as with dextropropoxyphene/paracetamol).[10]

2.2 Communication of Decisions and Information

The media are a major source of diversion from the broad consideration of drug safety issues as described previously, to a very narrow focus on a newsworthy topic of their choice. Dealing with the consequences of this publicity takes a huge amount of professional time.

This is partly due to the failure of regulators and the industry to inform the public about what they are doing in the way of pharmacovigilance.

Regulatory agencies are very much involved in what information is given with a drug product, but it is the pharmaceutical company that takes the legal responsibility and may, therefore, face hugely expensive claims for damages. Consideration of possible litigation is the main consideration in the wording of drug information. It is not surprising that great pressure is put on regulators by the pharmaceutical industry (sometimes at a personal level) to have the drug information worded as they want it. Society needs to deal with the problem of acceptable risk and how or whether or not those who are harmed should be compensated. The current situation of high levels of compensation after litigation leads to defensive wording in drug product information, which may lead to both over-warning and omission of useful information.

Much useful information is available from pharmacovigilance data that are dispersed throughout research papers in the literature. Ways must be found to provide this information in a way that is useful to a prescriber. For example, there is little information on when to look for a particular ADR; does it only occur early in treatment or must one consider such an ADR throughout the total duration of use of the drug? The way to diagnose and manage particular ADRs needs to be mentioned in the drug information unless such procedures are truly a part of standard medical practice.

It is already known that warnings and letters to health professionals have little effect,[14] so it would seem that much more emphasis should be placed on better communication practices. This means new strategies and not just blaming health professionals for not heeding occasional and inconspicuous warnings: it means providing useful information that can be accessed at an appropriate place and time. This includes knowing about evolving risk situations that are under investigation.

WHO has been involved in two major initiatives concerning communication[15,16] and the widely-quoted Erice Declaration (1997) contains the following:

- Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged and information provided in ways that meet both general and individual needs.
- Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and healthcare providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.
- All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal, must be recognised and overcome.
- Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.
- A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with and that information and solutions are effectively communicated.

3. Moving Forward

There has been a very strong reaction in the media over the withdrawal of rofecoxib and calls for

major modifications to pharmacovigilance systems have been made.

Spontaneous reports signalled the risk associated with rofecoxib and the nature of this risk, very early. Thus, suggestions to replace spontaneous reporting by other systems are illogical and are not supported by the evidence provided by the rofecoxib situation at all. Moreover, spontaneous reporting, if viewed correctly, is a way for health professionals and the public to air their concerns about drug therapy. This is a valuable process that needs more promotion, as well as renewed interest in the reports themselves. It is a very stupid vendor that ignores client concerns. Spontaneous reporting should not be considered as just a problematic, bureaucratic process, but as part of a two-way communication about problems that concern people and that require resolution; this is not usually achieved by removing the drug from the market. Moreover, it is wrong to consider spontaneous reports as a form of epidemiology. Each report is the result of a diagnostic process that concludes that *in an individual patient,* a drug might play a causal part in an ADR. Note that we have traditionally asked for suspicions, not certainties, to be reported in pharmacovigilance. This is done to increase the sensitivity of a process that is often criticised for under-reporting. If drugs and clinical events are to be related using other methods, such as data mining of healthcare databases, issues of selectivity and specificity will still be debated.

It is what happens after the first signal of an ADR has been found that should be the major focus of our concern. There is no easy way to determine which signals to further investigate and how to do this. Some guidelines have been promulgated for this process, but the sheer variety of potential important health outcomes linked to each signal really makes a general approach impossible, other than to suggest that if an ADR is serious, has been responsible for several reports and is related to a widely used new drug, it is probably worth taking investigations further. One factor that is frequently mentioned is that the quality of information gained from spontaneous reports is too poor for evaluation. This demeans the ability of the reporter to recognise a possible ADR, by assuming that it is the same kind of activity as filling in a form. In other words, a badly completed form means that the reporter's ability to diagnose an ADR, possibly caused by a drug, is also poor. This is illogical, particularly given the workload health professionals carry, which is well recognised as a strong factor in under-reporting.

Some people propose that large patient care databases will solve the problems of signal detection as well as analysis. Although it is certainly possible that such databases include more complete data, one still needs some way of finding the early signals of ADRs. One option is to data mine longitudinal healthcare data sets. The WHO Foundation Collaborating Centre for Drug Monitoring has been successfully working on such a project, but it will take years of work to maximise the efficiency of such an approach and compare its performance with that of spontaneous reporting.

One could spend a good deal of time and effort debating better systems and data, but the real problem lies not with these areas, but in the joint issues of decision making, resources and priorities. It is always assumed that it is wrong to raise concerns about drugs, on the grounds that this may scare patients and also because the drug may be unjustly blamed. This is to assume that the drug has priority and that both health professionals and the public are unable to understand the issues. There may be some truth in the latter, but this could be overcome by much better communication and information as well as time being made available during consultation with doctors and other health professionals to deal with these important issues; both lack of communication and time during consultations being a matter of inadequate resources.

Decisions on drug availability are made by regulators and the pharmaceutical industry, both of which make assumptions about the public good. Almost all media and consumer pressure, as well as ethics, suggests that individual patients should be empowered as far as possible to make their own decisions about treatment, preferably in a dialogue with a knowledgeable health professional. There are very few, if any, modern drugs in which the overall risk really is greater than the effectiveness. This means that if a drug is taken off the market there are going to be many more patients who are taking the drug without any ill effects and who may be disadvantaged to a greater or lesser extent. What is needed is to put patients' needs at the forefront of

care and to make sure they get good information from health professionals who have adequate training and time. In other words, let us concentrate much more on how patients are treated and how one drug compares with another for treatment of the same indication and less on whether a drug is on the market or not.

In the case of rofecoxib, this would mean that we would get more information on its real association with a lower prevalence of GI bleeding than non-selective NSAIDs and the size and nature of the risk of cardiovascular problems. Are the cardiovascular problems shared by all NSAIDs or perhaps only the more COX-2 selective drugs, including the older NSAIDs, some of which are relatively selective for the COX-2 receptor?

Most regulatory agencies have few resources for investigation of the risks associated with drug treatment and, therefore, must ask the pharmaceutical industry to agree to investigate their own products; this leads to delays in action. There is almost certain to be a divergence of opinion between regulators and the pharmaceutical industry as to what early safety signals require further investigation, but surely patients should have a major input into the decision, as they are taking the risk. Patients should be asked what risks they are prepared to take for what benefits, perhaps even as part of the registration of a new product. Techniques for assessing a person's views on the benefit and risk trade-offs they are prepared to make are well known to quality of life investigators. There is also a great need for research into effectiveness-risk evaluation and particularly as it applies to comparisons between drugs. What passes for a so-called 'benefit-risk' decision about drugs is laughable, as the rofecoxib example shows. In the general and medical media debate there is almost nothing about what doctors should prescribe or what patients should do or take as an alternative to rofecoxib or, indeed, possibly as an alternative to COX-2 inhibitors as a whole. Are patients going to be at greater overall risk by reverting to treatment with older NSAIDs? Wouldn't we like to know?

One is really forced to the conclusion that safety process decisions by regulatory agencies are very superficial in that they offer neither detailed comparisons of drugs, nor more than basic information on risk and effectiveness and those by the pharmaceutical industry are driven by commercial concerns. This is not a criticism of the professionals involved, it is an indictment of regulatory systems that do not allow resources for the comparison of drugs with regards to effectiveness and risk. Such systems are seen in most countries. The endpoint of regulatory activity is safety information of very limited quality (what does 'elevations of liver enzymes have been seen in clinical trials' mean for the prescribing doctor and potential patient? How many patients have had enzyme level elevations? What levels were seen? Was the drug stopped? How long until resolution?). Much more useful information must be made available for practicing health professionals *when and where they need it*, not in some obscure place. When a drug is registered, there is often expert appraisal of the evidence presented at registration by an external consultant; why can these not serve a much broader function? Why is it that computer patient management systems are not mandated to include information, checks and balances that will aid the prescriber at the time of prescribing? With empowerment by good knowledge of the effectiveness-risk balances of drugs, patients and doctors would be able to choose the better drugs and the ones with less favourable overall effectiveness-risk balances would become relegated to use in special need situations or simply cease to be cost effective.

4. Summary

The Vioxx® situation was not a failure of regulation itself, neither was it an issue of data collection, nor of the quality of studies performed. It was and is a complex decision-making/communication challenge in which some improvements are possible. Making wise drug safety decisions is not easy and is made worse by:

- a lack of clear goals of acceptable benefit and risk for those who are affected; i.e. the patients;
- decisions being driven by legal and bureaucratic concerns rather than the need to provide timely and well thought out communication;
- regulatory structures being overly cumbersome already, overwhelmed by data from the pharmaceutical industry, not transparent and such that

they do not include procedures for assessing impact of their actions;
- the need for regulatory agencies to consult the pharmaceutical industry before decisions are made and information given, rather than consulting patients;
- the pharmaceutical industry taking all the punishment (and therefore being defensive), when decisions are shared with regulators;
- regulators lacking resources to perform studies quickly;
- safety departments in the pharmaceutical industry being over-ruled due to marketing issues and concerns over litigation;
- the pharmaceutical industry being one that is strongly driven by market forces, leading to small safety budgets.

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