The New Zealand Centre for Adverse Reactions Monitoring: a source of practice-based evidence

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ABSTRACT

The database of the New Zealand Centre for Adverse Reactions Monitoring (CARM) is an example of the practice-based evidence discussed in the June issue of the *Journal of Primary Health Care*. Databases of reported adverse drug reactions (ADRs) were established to generate hypotheses to be tested about previously unrecognised adverse reactions and interactions. Occasionally they are sufficient evidence in themselves. They can also identify prescribing practices that might increase the potential for ADRs to occur and provide feedback into guidelines in terms of the consequences of their use or non-use. Well-documented ADR reports can also highlight risk factors, thus providing a valuable contribution to risk benefit assessments in individual patients. Examples are discussed that support the use of ADRs as practice-based evidence in a non-hierarchical system in which case reports and case series, observational studies and randomised clinical trials contribute in a flexible relationship depending on the issue under investigation.

J PRIM HEALTH CARE 2013;5(2):170–173.

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The June 2012 issue of this journal included discussions around the value of evidence-based medicine in primary care and the case for complementary practice-based evidence. Barry Parsonson[1] suggested that it is time for a systematic evaluation of alternative methodologies to randomised controlled group trials (RCTs) for assessing clinical interventions. Methods that are applicable to small samples or to single individuals could then complement larger studies used to generate the evidence base for practical application. This practice-based evidence could also feed back into the evidence from clinical trials on the generality and applicability of the interventions in the 'real life' context.

In 1965 New Zealand became one of the first countries to collect and assess reports submitted by health professionals of suspected adverse reactions in individual patients to medicines and vaccines. This collection is the database of the Centre for Adverse Reactions Monitoring (CARM) based in the New Zealand Pharmacovigilance Centre.[2] When reports are assessed, lessons learned and actions taken, they become practice-based evidence in the way that Parsonson suggested. Distinctive features of the New Zealand database are the high proportion of reports from primary care, and, over several years, the highest reporting rate/population in international comparisons. Reports to each national pharmacovigilance centre can also be combined at an international level through the WHO Collaborating Centre for International Drug Monitoring.

The original intention when spontaneous reporting systems (SRS) for adverse drug reactions were established was earlier detection of unexpected adverse reactions after a drug was marketed. However, it became apparent that well-documented reports also provide very useful insight into prescribing practice that might allow adverse reactions to occur. Most relevant to the discussion about evidence-based medicine is that they can add to evidence from research, information about adverse outcomes that occurred when guidelines were not followed and when they were.

New information from ADR reports

In some instances, adverse reaction reports alone are sufficient evidence of serious harm. An example is lumiracoxib, a COX-2 inhibitor withdrawn from the market after the Australian Drug Reactions Unit received a small cluster of reports of hepatic failure in patients who had recently started this medicine. Since there were no obvious alternative explanations, the risk of serious harm with this medicine clearly outweighed potential benefits.[3] In contrast, reports of cardiovascular adverse effects attributed to COX-2 inhibitors, although of concern, were insufficient evidence for action because of the high prevalence of ischaemic heart disease and the absence of data in SRS databases on drug usage. However, they were a stimulus to further investigation. The hierarchical approach that considers RCTs as the gold standard for investigation had been applied but, although an increased risk of myocardial infarction with rofecoxib was demonstrated, this was not considered sufficient evidence as it was suggested that the most likely explanation was that naproxen, the comparator, was cardioprotective.[4] Eventually observational studies did establish the increased risk with various COX-2 inhibitors and other non-steroidal anti-inflammatory medicines.[5,6]

Guidelines and adverse reactions

Non-steroidal anti-inflammatory medicines are a common source of adverse reaction reports in the CARM database. Guidelines for their use have been published in several countries but are not easy to find. For example, in New Zealand they appear in the guideline for *Management of dyspepsia and heartburn*.[7] Details in reports of gastrointestinal haemorrhage indicate that some prescribers are not aware of recommendations to use gastroprotection in susceptible patients or to use moderate doses in the elderly or that co-prescription of aspirin might increase the risk.

Sometimes there is confusion when guidelines are applied. For example, some reports of cerebral haemorrhage in patients co-prescribed aspirin and warfarin indicated the use of two overlapping guidelines in elderly patients. Aspirin was started as prophylaxis for transient ischaemic attacks but warfarin was added rather than substituted when the patients developed atrial fibrillation.[8] Careful consideration of the applicability of a guideline is also needed, for example, even when combined anticoagulant and antiplatelet treatment is indicated (following acute coronary artery events or interventions); a patient's susceptibility to bleeding may change over the years and the prescription may need to be adjusted.

Statins, rhabdomyolysis, risk factors and practical wisdom

The history of HMG-CoA reductase inhibitor (statin) use and the development of rhabdomyolysis provides an illustration of how adverse reaction reports have provided practice-based evidence to increase safe use. Adverse reaction reports were essential for detecting this serious, painful and frequently fatal adverse effect since it was too rare to be properly evaluated in randomised clinical trials of efficacy. Given the nature of the case histories, it was concluded that this was a real but very rare adverse effect. With the introduction of cerivastatin a marked increase in reports of rhabdomyolysis was noted and a case-control study showed a small increase in risk with three statins but a markedly higher risk with cerivastatin and with co-prescribed statins and fibrates.[9] Cerivastatin was withdrawn from the market and warnings about recognising patients who showed early symptoms of rhabdomyolysis with other statins were issued.

Careful assessment of reports of rhabdomyolysis in SRS databases were also valuable for identifying patient variables and co-prescriptions that increased susceptibility, thus contributing to prescriber education aimed at reducing the risk. Increasing age, medicines inhibiting CYP3A4 activity and thus inhibiting the metabolism of some statins, high statin doses, diabetes mellitus and acute renal failure frequently featured in reports.[10,11] Genetic susceptibilities to statin-induced myopathies were also identified.[12]

These observations were made in the context of increased reporting of rhabdomyolysis. For example, despite previous intensive monitoring, New Zealand only received its first report of rhabdomyolysis with simvastatin in 2002, with

continued reporting thereafter.[13] The reports often described elderly patients with multiple comorbidities, and higher doses of simvastatin, the most commonly prescribed statin at this time; also, co-prescription with diltiazem featured in several reports. This medicine is only a weak inhibitor of CYP3A4 and was not considered to interact sufficiently with statins to be a problem. However, there was increasing use of statins at higher doses in keeping with new guidelines for intensive lowering of LDL cholesterol for primary and secondary prevention of ischaemic cardiovascular events. A published case report[14] and a combination of NZ and Australian adverse reaction reports[10,11] suggested that diltiazem was contributing to inhibition of simvastatin metabolism as daily doses of simvastatin increased.

In the context of increasing reports of rhabdomyolysis, an analysis of clinical trials of high-dose versus moderate-dose statin therapy revealed that the rate of myopathy and rhabdomyolysis with 80 mg simvastatin daily was approximately four times greater than with 80 mg atorvastatin or lower doses of simvastatin.[15]

These developments indicate the need to continue monitoring throughout what is called the 'life cycle' of a medicine and for reporting serious adverse reactions, even if they are already known. In 2011, the US FDA advice limiting the use of simvastatin 80 mg daily was based on the accumulated evidence concerning the risk of rhabdomyolysis together with evidence of little extra benefit with this dose compared with lower doses.[16] Thus, practice-based evidence from adverse reactions reports and the research they have stimulated has led to advice that can minimise the risk of a very serious adverse reaction so that those most likely to benefit are prescribed these medicines and medicine interactions are avoided.

This is not the end of the story. Trisha Greenhalgh, in her article on evidence-based medicine, discussed Aristotle's concept of phronesis or practical wisdom.[17] In the context of this concept and statin use, we have observed in New Zealand reports that very elderly or very ill patients had been taking a statin for many years before they developed rhabdomyolysis and that it appeared to have been triggered by concomitant disease or medicine interactions as the patients became older or more unwell. Some of these patients had malignancies and had urgently required a macrolide antibiotic or imidazole antifungal agent while taking an interacting statin. This led us to suggest that careful consideration be given to the relevance of the five-year risk estimate of cardiovascular events to these patients and the need to consider on a case-by-case basis the need for a statin and at what point the risks of a very painful distressing event might outweigh potential benefit.

Assessing causality and report quality

It can be correctly argued that for each individual patient it is impossible to know all the variables that may have led to their adverse experience and their relative contributions. For example, would an individual patient have experienced haemorrhage with warfarin even if they were not taking aspirin? Did they also take an over-the-counter non-steroidal anti-inflammatory drug? Professor Arroll and colleagues[18] in the June 2012 issue of this journal discussed probabilistic reasoning in diagnosis and management of individual patients and this is what is also applied to assessment of individual and grouped adverse reaction reports. However, within the patient consultation, we tailor our questions, clinical examination and investigations to increase or decrease the likelihood of a particular diagnosis. This opportunity is afforded only to the clinician who sees the patient and not to those assessing adverse reaction reports. Adverse reaction reports that include the clinician's reasoning, as well as details about variables such as other medicines and comorbidities, make these reports extremely valuable as practice-based evidence.

Flexibility not hierarchy

In summary, the practice-based evidence derived from adverse drug reaction reports can, occasionally, be used alone to identify serious adverse reactions. More often they generate or strengthen hypotheses that need testing in formal studies. Nevertheless, formal studies do not necessarily discount hypotheses arising from adverse reaction reports if they are insufficiently powered or not designed to detect the adverse effect. It is now

ACKNOWLEDGEMENTS
The Centre for Adverse Reactions Monitoring in the New Zealand Pharmacovigilance Centre is funded by Medsafe, New Zealand Ministry of Health.

COMPETING INTERESTS
None declared.

apparent that adverse reaction reports also provide good insights into the environment in which medicines are used, the risk factors that might lead to serious adverse effects and the effect of advice and guidelines in practice.

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Doctor Colenso, I presume:
An account of missionary medical practice in New Zealand in the midnineteenth century

Illustrated by the work of the Rev. William Colenso FLS FRS in the Wairarapa and Hawke's Bay

Ian St George

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Ian St George's tribute to William Colenso's medical work was published to mark the bicentenary in 2011 of its subject's birth. Colenso is presented as a nineteenth century polymath, described by the author as a 'printer, missionary, explorer, politician, botanist, educationalist, liberation theologist—and importantly herein, healer and dispenser of medicines'. The extent of his medical involvement is highlighted by Colenso's claim in 1897 that at one time he had the 'most complete surgery in NZ'.

The text consists of lengthy extracts from Colenso's writing, both published and unpublished, and from secondary sources, with linking passages by the author. This is underpinned by extensive footnotes, contextualising the story. St George outlines Colenso's medical education, such as it was, and his practice while employed by the Church Missionary Society from 1834 to 1852. It also includes details of his own ill health, and his opposition to the consumption of tobacco and alcohol.

Colenso's entry in the *Dictionary of New Zealand Biography* makes no mention of Colenso's role as a healer. Ian St George's work is a welcome corrective to this omission.

Place of publication: Wellington
Date of publication: 2012
No. of pages: 59
ISBN 978-0-9876604-1-1

Copies are available for $10 from the Colenso Society, 32 Hawkestone St, Thorndon, Wellington 6011 (Email: istge@yahoo.co.nz)