Empowering Physicians and Patients Through Greater Knowledge of Drugs, For Safety's Sake

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Recently, a number of events occurred in the world of drug safety surveillance, also known as pharmacovigilance, which were mere blips on the radar screen of most readers of the daily newspapers. In September 2004, Merck Sharp & Dohme (MSD), the manufacturer of the selective COX-2 inhibitor rofecoxib (Vioxx), voluntarily withdrew the drug from world markets. This action produced considerable anxiety among some of our patients with chronic pain, who had been taking rofecoxib regularly. With few exceptions, most patients had learnt from their doctors and from the Internet that the newer anti-inflammatory pain-modifiers, including rofecoxib and celecoxib, were apparently safer in terms of gastric mucosal injury, perforation of peptic ulcers, and bleeding.[1-3] It is scant comfort to learn that other COX-2 inhibitors probably carry a similar pro-thrombotic risk.[4]

In 1998, the lipid modifying drug cerivastatin (Lipobay, Bayer) was marketed in Singapore. When Bayer ceased marketing, and recalled, Lipobay in 2001, the Centre for Drug Administration (CDA) of the Health Sciences Authority in Singapore, via its Pharmacovigilance Unit, issued a product safety alert. The alert letter pointed out the risk to elderly susceptible patients, in particular those also taking gemfibrizol, of drug-induced rhabdomyolysis – which may produce renal shutdown and death.[5] Yet there was only moderate anxiety among physicians and ordinary citizens. Anxiety was low because only a few patients had received cerivastatin at high dose – the CDA had stipulated that Bayer should write in the 'prescriber's information' section of package inserts that higher doses of the drug had caused myopathy and rhabdomyolysis in some patients during Phase 3 pre-market trials.

In turn, the few treated patients meant that cerivastatin appeared to have caused severe renal failure in only 2 to 3 elderly patients, according to spontaneous reports of adverse drug reactions (ADRs) to the CDA. But enough elderly people die naturally from renal failure that we cannot rely on spontaneous reports or mortality audits by physicians to detect a minor increase in renal deaths caused by any given drug. These methods regularly underestimate the true frequency of death and of morbidity. For cerivastatin, only 3 years elapsed, but for rofecoxib 6 years elapsed, between marketing and withdrawal. Why did the durations differ? This writer believes that one explanation derives from the nature of the unwanted side effects of the 2 drugs. With cerivastatin, most patients would experience unexpected muscle pain, and many might stop taking the drug, since dyslipidaemia itself produces no symptoms. In contrast, many patients taking a COX-2 inhibitor and enjoying relief from chronic or recurrent pain, would not be aware of any pro-thrombotic risk linked to the inhibitor. Some of these patients will have experienced myocardial infarction, unaware that the COX-2 inhibitor might have caused the event.

Some have argued that had the US Food and Drug Administration (FDA) seized upon the possible increase in coronary artery thrombosis linked to Vioxx, which information MSD had submitted in its marketing licence application in 1998, then it should have required MSD to carry out prospective randomised controlled trials (RCTs) designed to estimate the size of the pro-thrombotic risk in patients with different background risks of coronary thrombosis.[6] Information from such trials is especially important for drugs which will be taken by many people, and especially in those at high risk for cardiac and cerebrovascular events, who are normally excluded from pre-market drug trials.[7]

It is not as if clinical pharmacologists and epidemiologists have not been aware of the inadequacy of the spontaneous ADR reporting system that underpins post-marketing drug evaluation. Both the latter system and 'all-events reporting' are insensitive, non-specific, and slow methods of detecting infrequent drug effects, in particular drug-related increases in common disorders like stroke, myocardial infarction, and renal impairment. The large RCTs needed to detect such small increases unavoidably incur high monetary

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costs, which is why drug companies are reluctant to conduct such studies unless compelled by regulatory agencies to do so. But the FDA, whose budget is billions of US$, lacks the authority and political will to order manufacturers to make extensive safety checks. On balance the policy is probably pro-commerce. The pharmaceutical industry says it cannot afford to conduct large and costly trials to satisfy the consumers' need for safer drugs. Regulatory agencies lack the resources to conduct independent safety trials. What, then, is the best way out of this market forces-determined quagmire?

For ships passing one another in the night, neither the traffic controller nor the people on board the vessels worry more than they have to. It is only when slow-reacting organisations, like large vessels, encounter crashes that the general public are alarmed (for a time). We need to transform our professional institutions into nimble aircraft capable of avoidance movements in 3 dimensions, and our air traffic controllers into more aware, and more responsive entities. Wherever and whenever possible, we should prevent, as far as practisable, the subtle injuries caused by ill-prescribed medicines, i.e. drugs given to the wrong people, or to the right people for the wrong reasons.

The media tend to spotlight dramatic events, such as when the purported weight-reducing tablet 'Slim-10', imported from China, killed 1 Singaporean woman in 2002.[8] It takes some insight to recognise that even small and undramatic treatment errors, although smeared out over time, can also cost us dearly. If about 7 in 10 ADR-related hospital admissions are avoidable,[9] then should not physicians and administrators try harder to prevent them?

The human costs may ultimately exceed expectations: for example, the decreased birth rate of Singapore may, in time, strongly skew the country's productivity or wealth distribution for many years. Public appreciation is not fired up when a physician or health czar prevents a number of undramatic deaths or illnesses smeared over 5 or 10 years, or even when a wise policy saves $20 million over the same duration. Nevertheless, such considerations should not deter physicians from doggedly pursuing greater physician training and public education, for the sake of public safety.

We should aim systematically to hone doctors' prescribing and communication skills, and to minimise the needless injury resulting from patients inappropriately expecting prescription-only drugs for many self-resolving illnesses. Anything less is as unacceptable to patients as to rational physicians. Who will train doctors and educate the lay public? Not just clinical pharmacologists or clinical pharmacists, because there are never enough of them. Not just general physicians,[10] since they are almost an endangered species in Singapore. The entire organism that is the healthcare professional system, must buy into the prevention of drug-related illness. At every level and in every specialty, disease prevention must become the catchphrase. To administrators, prevention of health loss must become more important a goal than monetary loss.

The cynics will say, "If we cannot control the behaviour of human immunodeficiency virus (HIV) spreaders, how can we persuade our citizens from requesting drugs for every symptom?". The answer lies in giving knowledge and in transforming attitudes and beliefs, so that behaviour can change. Condom use and sexual abstinence should complement the anti-retroviral drug combinations, because the HIV can surely become resistant to the available anti-retroviral agents. Multiple strategies are mandatory because we have too much to lose. Similarly, physician training and public education about drug effects should complement rational prescribing. For now, there is no other way.

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