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doi: 10.1111/j.1742-1241.2006.01257.x

EDITORIAL

International Journal of Clinical Practice

Drug safety: who is responsible?

One aspect of the ongoing debate on drug safety that has not received attention is the role of the practicing physician

Both the lay and medical press have been inundated with articles reporting the risk of drugs such as Vioxx, Celebrex and Natrecor. Industry has been accused of suppressing unfavourable data and misleading physicians and patients as to their true risks. Journals have been criticised for publication of incomplete safety data and not being rigorous in their review process. The Food and Drug Administration (FDA) has been accused of inadequate drug approval and surveillance policies. These highly publicised issues have elicited calls for reform of how clinical research studies are designed, funded and reported; calls for reorganisation of the FDA; and greater independence of clinical investigators from industry. Such discussions are appropriate and will hopefully lead to more timely and responsible information on drug safety.

It is true that in many instances physicians and their patients have been exposed to unnecessary risk because of the lack of reliable information provided by industry and the FDA. There are, however, also instances in which despite adequate information on safety physicians have misused or misapplied existing drugs resulting in adverse events. Randomised placebo-controlled clinical trials serve as the basis for evidence-based medicine. Their results are, however, often inappropriately or not applied to clinical practice. Life-saving therapies such as statins, angiotensin converting enzyme–inhibitors and beta adrenergic blocking agents are underused in patients shown to benefit from these strategies. On the other hand, clinicians when extrapolating the results of randomised trials to patient groups not directly studied in the clinical trial may not heed the important inclusion/exclusion criteria and monitoring parameters which contributed to the net risk/benefit of the intervention. Consider, for example the use of the aldosterone blocker spironolactone. The Randomised Aldactone Evaluation Study (RALES) (1) showed that patients with severe heart failure because of systolic left ventricular dysfunction (SLVD) when randomised to spironolactone at a mean dose of 26 mg/day had a significant reduction in total mortality. Patients were excluded from enrollment into RALES (1) if they had renal insufficiency or an increase in serum potassium and it was emphasised that serum creatinine may be an inadequate guide to renal function, especially in the elderly (2). Also of importance was the fact that in RALES (1) the patients' serum potassium was closely monitored and the dose of spironolactone adjusted accordingly. With these precautions the incidence of hyperkalemia in RALES (1) was <2% and not associated with any deaths.

The strategy of aldosterone blockade for patients with severe heart failure because of SLVD has been incorporated into both USA and European guidelines (3,4). These recommendations have however been accompanied by reports suggesting that when spironolactone is used in clinical practice it is associated with a high incidence of hyperkalemia often resulting in renal dysfunction, the need for dialysis and occasionally death (5–7,6). These reports have prompted the suggestion that the use of spironolactone be restricted to specialised multidisciplinary programmes of chronic-disease management (8) and have generated the concept in some physicians minds that the use of spironolactone in patients with severe heart failure because of SLVD is dangerous and best avoided.

In my opinion spironolactone *per se* is not 'dangerous' but rather how physicians have applied and monitored its use. Unfortunately, some physicians did not heed the recommendations in RALES (1) and administered spironolactone to patients with renal dysfunction, and/or an increase in serum potassium, often at doses greater than recommended in RALES. Most importantly, they did not monitor serum potassium or adjust the dose of spironolactone accordingly. For example in one report (7) of patients given spironolactone for heart failure there was a 15% incidence of hyperkalemia, yet in

approximately 1/3 of patients administered spironolactone, there was not a single measurement of serum potassium. Consider as an analogy the use of Coumadin to prevent stroke in patients with atrial fibrillation: one would consider it malpractice if a patient receiving Coumadin suffered a cerebral haemorrhage without a single measurement of their prothromin time. Coumadin, like spironolactone has known risks that are relatively infrequent and pale in comparison with its benefits when given to appropriate patients and properly monitored.

The explanation for the failure of some physicians to use spironolactone properly is complex but likely includes the fact that it is generic and therefore has been the focus of relatively little postgraduate physician or patient education from the pharmaceutical industry (9). The education of the physician is however not the responsibility of the pharmaceutical industry but of organised medicine, medical schools and government. The failure of physicians to properly use and monitor spironolactone is unfortunately not unique and not necessarily related to the fact that it is generic. For example, there is evidence that physicians did not heed warnings with regard to troglitazone with regard to monitoring hepatic function, resulting in unnecessary episodes of liver failure and death (10). Despite the known toxicity of amiodarone, some physicians do not monitor pulmonary, hepatic or thyroid function and do not give patients advice about avoiding exposure to the sun (11). Medication monitoring errors are a common cause of preventable adverse drug reactions (12) and physicians frequently prescribe drugs with 'black box' warnings in their labels without taking proper precautions or informing the patient as to the risks (13). Other explanations include increased pressure on physician's time, including administrative efforts related to third party care; decreased per patient reimbursement, and the resultant need to increase patient volume and throughput. The rapid pace of medical advances makes it difficult for the practicing physician to keep abreast of optimum current practice and details of drug administration and safety. Similarly, there is increased pressure on the time available to teach house staff and medical students about the drug dosing and safety. Bedside teaching rounds including detailed discussions about drug usage and safety have been curtailed in many institutions because of the limitations imposed on house staff availability (14).

The recent problems with drug safety have increased public and governmental scrutiny and led to recommendations for reforms by industry, journals and the FDA. While these efforts are important we also need to reform postgraduate, house staff and undergraduate medical education as well as to provide the practicing physician the time and tools to appropriately administer drugs so as to minimise their risks. Simplification of drug labelling, computer-based drug ordering systems, computer-based reference systems and academic detailing may alleviate some of the problems alluded to above but are unlikely to eliminate the need for better physician education and practice. New incentives need to be implemented to encourage proper drug use. No effective drug is free of risk. We need to be better informed as to their potential risks and when informed need to heed the recommendations. Drug safety is not only the responsibility of industry, journals and regulatory agencies, but also medical educators, and the practicing physician. Unless we all do a better job in correcting the problems outlined above many potentially lifesaving drugs will be discarded or under and overused resulting in unnecessary suffering and costs. In the hands of an informed physician and patient many 'dangerous drugs' if appropriately administered and monitored could be life and cost saving.

Disclosures

The author has stated that he has no interests which might be perceived as posing a conflict or bias.

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doi: 10.1111/j.1742-1241.2006.01125.x

EDITORIAL

International Journal of Clinical Practice

Drug-facilitated sexual assaults

Sexual assault includes rape – that is, vaginal, anal or oral intercourse which is physically forced or which occurs when consent was not capable of being given, including as a result of intoxication – and other types of physically forced sexual contact and verbally coerced sexual intercourse (1,2). In a groundbreaking 1987 American study, Koss et al. (3) found that sexual assault was surprisingly common; in a survey of around 6000 college students, a quarter of the men admitted to having carried out a sexual assault since the age of 14 years, while over half the women reported having experienced sexual assault since the age of 14 years. The human impact of these shocking figures was underlined by the 1992 publication of a brave and moving paper, entitled 'Rape and Responsibility' by Lynne Henderson (4), in which she started with the following introduction:

''I am a 'lucky' survivor of a rape committed by a stranger – 'lucky', because people believed in me, a jury convicted the man of raping me, and he is still in prison 10 years later. I know many women who have been raped who were not so fortunate, because they believed the rape was their fault, because no one else believed them, because they knew their rapist, or because they were married to him and it was not a crime. We share some things – the anger, the pain, the anguish, the fear – and not others; nevertheless, this is what I wished after I was raped and still wish: never again, not for any woman. Rape is evil''.

In the years since the publication of Henderson's paper, which gives an American perspective in respect of legislation, the issue of consensual sexual activity has become even more given to the phenomenon of drug-facilitated sexual assault using what are commonly described as 'date-rape drugs'. This is the subject of the detailed paper by Papadodima et al. (5) which appears in this month's issue of the *International Journal of Clinical Practice*. In their paper, which gives a Greek viewpoint in relation to legislation, Papadodima et al. mention the main substances that have been implicated in drug-facilitated sexual assaults, including alcohol, benzodiazepines, gamma-hydroxybutyric acid (GHB), ketamine, scopolamine, barbiturates, opiates, cannabis, muscle relaxants, antihistamines, chloral hydrate, amphetamines and cocaine.

To this list may be added ecstasy (E or 3,4-methylenedioxymethamphetamine; MDMA). It has been suggested that, in court, it may be that 'date rape' prosecutions may be more likely to rely on evidence from toxicologists, pathologists and police officers, who find MDMA and amphetamines in samples taken from victims of sexual assault, rather than on the testimony of psychiatrists and psychologists who may understand the effects on humans of these drugs and who may apparently dismiss claims that MDMA is a date-rape drug as a myth propagated by the media (6).

In any case, it does not appear to be a myth that another class of drugs, the benzodiazepines, may be used as date rape drugs. Benzodiazepines are a particular cause of concern, owing to their ability not only to induce relaxation but also to play tricks on the memory (7). Indeed, the association of the rapidly acting and essentially colourless and odourless hypnotic benzodiazepine flunitrazepam with date rape by being used to 'spike' drinks led the manufacturer Hoffmann-La-Roche to revise its formulation of Rohypnol so that it now dissolves less quickly and contains a blue dye designed to manifest itself if the drug is added to a drink.

Certain psychiatric disorders and personality traits may be associated with the perpetration of drug-facilitated sexual assault. Alcohol is likely to be the drug most commonly used in this way. In a recent American study of 356 male students comparing alcohol-involved perpetrators of sexual assault with both

