

Editorial

Drug–drug interactions and adverse drug reactions: the bollards and flashing lights syndrome

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INTRODUCTION

Drive along any highway and the chances are that you will come across lengths of bollards and flashing lights. The aim is to warn of danger ahead. Quite often though, no such danger exists. There are neither roadworks nor accidents or spills. Such false alerts are disconcerting and lead to complacency when the same signals re-appear. Important dangers are missed and a multitude of insignificant ones clutter the horizon. So it is with drug interactions and adverse effects. There are now a number of studies describing prescribers switching off, software-generated, onscreen drug interaction alerts when writing prescriptions (1, 2). In a recent study (1), a fifth of the general practitioners responding to a survey admitted to overriding drug–interaction alerts without properly checking them. One of the main reasons given for this apparently reckless behaviour was the perception that the alerts were frequently irrelevant. Nine out of ten respondents agreed that it should be more difficult to override alerts for potentially lethal drug combinations. The inference is clear. Drug interaction warnings are not specific enough to help prescribers in their high-pressure environments to prescribe safely. Urgent action is required.

The problem is not restricted to computerized drug–interaction alert systems built into prescribing software. The core of the problem lies elsewhere: the information given in the Product Labels (FDA terminology), Data Sheets or the Summary of Product Characteristics (SPC). These documents aim to include all the important information to prescribers but have, with respect to the adverse

effects and drug interactions, evolved to become legal documents. Rare and common interactions are grouped together as are the important and less serious ones. Discrimination is minimal. Companies aim to cover themselves against not warning of possible adverse effects or drug–drug interactions but make access to the relevant data difficult by not releasing ‘internal’ reports. Consequently, risk factors, for drug–drug interactions or adverse effects, such as co-morbidity or dietary factors, which may render normally unimportant interactions potentially lethal, are rarely listed. With rapid advances in pharmacogenetics, much relevant information, which may contribute to making warnings about drug–drug interactions and adverse effects more specific, is now emerging (3–5). This information needs to be assessed for its clinical relevance.

Recent surveys indicate that drug interactions are an important contributor to the depressing statistics on iatrogenic morbidity (6). Although the honest admissions made by prescribers in Magnus, Ridgers and Avery’s survey (1) should be lauded, they should also be of great concern to drug manufacturers, prescribers, educators, drug regulators, formulary compilers, patients and health care providers alike.

WHAT IS NEEDED?

Aronson (7) recently called for clearer presentation of warnings to (i) identify which drug is affected by an interaction and which causes it, (ii) give more systematic categorization of drugs, (iii) define terms such as ‘prolonged’ and ‘regular’ in relation to drug use and (iv) define the seriousness of the interactions and hence when they should be avoided. Such expert advice is of course very much welcome. However, one major difficulty is that, the data to provide the necessary specific advice is often not

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available and formularies, guidelines and prescribing support software are forced to hide behind imprecision. Drug–drug interactions are reduced to class effects and specific interactions involving, say ketoconazole, are generalized to the imidazole antifungal drug class. Other warnings are generalized using terms such as ‘avoid inhibitors of CYP3A4’, which even experts would be hard pressed to translate into an ordered number of specific drugs or dietary components. The data for ranking the different members of any class of drugs, in terms of intensity of interaction effect, is not readily accessible in a user-friendly format. Warnings in prescribing guides such as the British National Formulary, which usually mirror those in the manufacturers’ drug SPCs, often take these generic forms.

The literature details numerous reports of what were seemingly minor interactions developing into major ones when several mechanisms act in synergy. A recent case report (8) describes severe opiate toxicity from ingestion of small doses of codeine which would usually be safe, as a result of (i) a CYP2D6 genotype leading to ultrarapid metabolism of codeine to morphine, (ii) concurrent use of CYP3A4 inhibitors, which reduced clearance of codeine so that more is available for activation to morphine and (iii) impaired renal function. Similarly, a second report (9) in this issue of the Journal describes rhabdomyolysis from cerivastatin, probably due to CYP2C8 impairment.

Compilers of formularies and drug regulators do not have the resources to undertake the thorough assessments that are necessary to make sense of this exploding volume of drug information. The help of the wider scientific community is necessary. To enable this, the industry must release adverse reaction and drug–drug interaction data held in their ‘internal’ reports, often submitted as part of their applications for marketing authorizations in an expeditious manner. An important lesson to be drawn, from recent high-profile post-marketing drug withdrawals such as of rofecoxib and cerivastatin, is that the current state of affairs helps no one.

Despite considerable effort aimed at designing-out adverse reaction and drug–drug interaction propensity from new drugs (10), success has been meagre. Predictive models based on *in vitro* and *in vivo* parameter estimates have low sensitivity and generally, poor predictive power. For the

foreseeable future, continued vigilance will be necessary if the high level of iatrogenic morbidity reported in recent studies (11–14) is to be reduced. Organizing the presentation of adverse drug reactions, and drug–drug interactions, more systematically so that prescribing guides can be made more specific and reliable is required. Organizations such as the Cochrane collaboration have made an important contribution to the systematic assessment of randomized controlled trial data. However, systematic reviews have been less useful in profiling the adverse effects of drugs (15). How to present adverse reaction and drug–drug interaction data in a balanced manner in relation to efficacy remains a challenge, given that such adverse effect data are usually from observational studies, and from which precise estimates of frequency cannot be obtained. Although risks can theoretically be estimated, whether a treatment is safe enough is ultimately judgmental. Consumer lobbyists therefore need to try and take the shrill out of their warnings too.

To prevent prescribers from over-riding drug alerts, rule-based prescribing systems are in use (16, 17). Their general usefulness will be determined by the reliability of the data on which the rules are based. An important task is to present risk estimation as reliably and comprehensively as possible. As the case-examples cited indicate, comorbidity and pharmacogenetic data need to be included where important. Sadly, as a whole, we, the community generating, interpreting, integrating, and reporting on, adverse reaction data, have not been sufficiently up to the task. Neither have the drug industry nor the drug regulators. We need to do better and put up bollards and flashing lights only when necessary. Otherwise, even conscientious prescribers will become reckless and more patients will be harmed.

CONFLICTS OF INTEREST

The author has served as a member of the UK Committee on Safety of Medicines and acted as a consultant to the pharmaceutical industry.

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