The risk of adverse reactions in anaesthesia

Adverse drug reactions are regarded as a serious problem in anaesthesia, as indeed they are in therapeutics in general. An international symposium, entitled The Perception, Measurement and Management of Therapeutic Risk, provided a forum for many experts in this field to bring the problem into perspective. The symposium was presented by the Trust for Education and Research in Therapeutics, in conjunction with the Drug Safety Research Trust, Southampton [1]. The majority of delegates were from the pharmaceutical industry, and most of the discussion regarded long-term oral therapy, but many points are of particular relevance to drug related adverse events in anaesthesia.

Risk Watch: the Odds of Life, by John Urquhart and Klaus Heilmann [2], is one of the definitive texts concerning the risks of modern day living, including exposure to medical practice and disease. Both these authors contributed to the seminar.

Professor Heilmann described the factors that are often emphasized or disregarded when assessing the degree of risk associated with therapeutic intervention. It is human nature to panic in the face of sudden unfamiliar disasters, but to accept, without concern, less dramatic events. An occasional severe reaction to a drug leads to far more concern than that generated by the enormous daily death toll on our roads. If three fully loaded 747 jumbo jets crashed every day, few people would continue to travel by air. However, this number of deaths (540 000 per year) is approximately equal to the number of premature deaths in the U.S.A. caused or accelerated by smoking.

Reporting of drug related events by the media often influences the perception of risk. However, it is important to remember that the function of the media is not only to inform but also to entertain. This leads inevitably to varying degrees of sensationalism and “victim orientated reporting.” This term refers to a style of reporting seen too often in the general and medical press. Let us take an example in anaesthesia by considering the following head-line concerning a new neuromuscular blocking agent: “Three patients die on exposure to Relaxium.” This type of reporting does not tell us how many patients were exposed to this drug on this occasion, what other influences were acting on the patients at the time, the total number of patients ever exposed to the drug, or the benefits other patients may have gained from Relaxium. It seems that it is the view of many medical practitioners, most of the general public and all of the media reporters, that drugs should be perfect. Unfortunately, this is not yet the case. But has this attitude been responsible for the premature removal from the market of useful drugs?

At a time when medical specialties are becoming increasingly complex, dependence is placed to a large extent on the opinions of experts. In the case of adverse reactions to drugs, it is extremely common to find strongly differing expert opinions. Statements are often equivocal and conflicting. How can members of the public, both general and medical, have confidence in doctors and the pharmaceutical industry in these circumstances?

Professor Heilmann also made a plea to those responsible for the withdrawal of a drug to take full account of the consequences of their absence. The removal of any drug may result in a less effective and more dangerous replacement, but this problem may not concern the company withdrawing the drug, often in response to a campaign waged against it. How important, in arriving at this decision, is the company’s desire to save its other products?

How do these factors contribute to the decision to withdraw an anaesthetic agent? It has been suggested that victim-orientated reporting, panic, conflicting expert opinions, fear of drug companies and no consideration of the consequences to patients of removal of the drug, all played a part
in the removal of Althesin [3]. How many of these factors influence the debate on halothane toxicity and will they eventually be responsible for its withdrawal?

Dr Urquhart, the co-author of Risk Watch: The Odds of Life, stressed the importance of accurate measurement and reporting of risk levels. The risk of an adverse event is often quoted as, for example, 5 per 100000. This is equivalent to 1 per 20000, which gives instantly a clearer picture of the likelihood of harm. Dr Urquhart called for all risks to be quoted in this way and defined the population at risk, in this example the 20000, as a "unicohort". The unicohort, therefore, is the number of people at risk of a particular hazard divided by the total number of individuals who become victim to the hazard per unit time. The degree of risk is related inversely to the size of the unicohort.

An example of the usefulness of this concept is provided by the number of deaths occurring in scheduled airline flights in the U.S.A. In 1960, 499 passengers died, compared with 655 in 1977 [2]. It would seem, at first glance, that flight safety had not improved in those 17 years. However, this is an example of victim-orientated reporting and further analysis of the data reveals a different picture. The number of passengers exposed to the risk of death in these 2 years was 62 million in 1960 and 240 million in 1977. This gives unicohorts of 0.124 and 0.366 million, respectively. The unicohort immediately shows that the chances of death in flight were three times greater in 1960 than in 1977. A similar approach has been used for some time by the Adverse Drug Reactions Group of the Committee on Safety of Medicines.

Professor William Inman, Director of the Drug Safety Research Unit, discussed post-marketing surveillance. He called for the abandonment of "promotional" surveillance. This process, undertaken by the pharmaceutical company, is expensive, poorly controlled and often selective, as high risk patients are usually omitted. Therefore, the data obtained are of low credibility and often inaccessible to those outside the company. Furthermore, this method of audit may damage the efficiency of the more established monitoring systems.

Dr Geoffrey Venning gave a view of the problem, based on his considerable experience in the pharmaceutical industry. He suggested that most experts focused their attention on idiosyncratic drug reactions (type B). Dose-dependent reactions (type A) were often ignored. Type A reactions caused more deaths than type B, and as evidence for this he presented his review of the adverse drug reaction literature published in 1983 [4]. Only five of the 61 deaths reported were type B reactions, and of the 56 deaths resulting from type A reactions, 38 were probably or possibly avoidable. He suggested that the dose chosen for a new drug in phase II of its development had not been shown always to be the most appropriate, based on safety and efficacy data. He conceded, however, that volatile anaesthetic agents were an exception, as a result of the intensive monitoring performed by anaesthetists. Dr Venning's evidence invites the following question: how many reactions to anaesthetic agents reported as idiosyncratic are, in fact, type A reactions caused by inappropriate dosage?

Professor William Asscher, Chairman of the Committee on Safety of Medicines, described the established methods of detecting adverse drug reactions. Clinical trials detect adverse reactions only if they are relatively common (1 in 100). The yellow card reporting system may detect reactions as rare as 1 in 10000. No discussion was held on the role of yellow cards in anaesthesia, but this question has been reviewed previously [5].

It is our view that anaesthetists have a special duty to report on adverse drug events because of their close personal involvement in drug administration. Also, because of the nature of anaesthesia and intensive therapy, anaesthetists may be tempted to use drugs in ways which lie outside the product licence. A doctor incurs a considerable degree of professional responsibility in this case and is wise to record in the notes the reasons for using the drug outside its product licence. Patients should be monitored carefully during this time and observations should be noted.

This seminar, therefore, emphasized several points of relevance to anaesthesia when considering adverse drug reactions. The risk of a reaction must be defined clearly and reported in a clear and unsensational manner. Before removing a drug from the market, the consequences of its removal must be considered fully and other influences such as market forces should be ignored. Finally, the most important consideration when making decisions regarding availability
of a drug should be the welfare of our patients. Responsible adverse drug reaction reporting should assist this aim.

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REFERENCES