

Reviews of books and studies

Florence AT, Salole EG. (Eds.): Formulation Factors in Adverse Reactions. Topics in Pharmacy, Vol 1. John Wright, London, 1990, 124 pp.

The first recognized major incident of an adverse drug reaction was due to an excipient, viz. a toxic solvent in a sulfanilamide elixir causing a large number of fatalities in the U.S.A. back in 1937. Since the thalidomide disaster around 1960, extensive world-wide efforts to control adverse drug reactions have been directed mainly towards the active ingredients in the rapidly growing family of medicaments, and rightfully so. Ill effects due to formulation factors, however, still do occur, probably not very frequently, but in large variety, as is evident from articles and reviews in the medical and pharmaceutical literature. It is the merit of this book to provide a competent presentation of all important aspects of this problem, illustrated by examples from practical life, whilst not pretending to comprise a comprehensive and fully detailed review. The presentation was drawn up by six different authors, but inequalities and overlapping are largely avoided. Every article is rounded off by a conclusion suggesting how to avoid the type of adverse reactions just described.

A survey of the different types of adverse reactions to excipients is given by P.F. D'Arcy. After a short list of commonly used excipients the review deals with problems caused by colouring agents (especially tartrazine), preservatives, sweeteners and flavours (the story of cyclamate and saccharin), components of topical formulations like bases and solvents and emulsifiers and surfactants, and alcohols. A suggestion is presented as to which excipients should be required to be declared on the label, and the need is stressed for building up data bases covering all components of pharmaceutical dosage forms.

A thorough survey of drug allergy is presented by H. Bundgaard. The underlying immunochemical mechanisms are explained in detail, and various examples are presented of allergic reactions to the active substances as well as to their metabolites and impurities and degradation products. It is noted that the frequent reactions to acetylsalicylic acid are in all likelihood due to impurities in the preparations and not to the drug itself, and that similar conditions may be responsible for reactions to phenindione, phenylbutazone and the corticosteroids as well. The complex mechanisms underlying allergic reactions to the penicillins are dealt with in particular detail. The intriguing question as to the possibly allergic nature of organotoxic damage is not touched upon. Suggestions are presented about how to avoid or reduce allergic reactions in drug therapy.

Adverse reactions to parenteral products are dealt with by M.C. Allwood. The presentation covers the effects of different excipients and of particulates in the solution, as well as its possible reaction with various plastic materials, and the effect of surfactants in changing fluid drop size when the infusion rate is guided only by the number of drops per unit time. No mention is made of the local tissue necrosis that may result, particularly after intramuscular injections of certain solutions.

K.S. Channer explains the problems connected with drug passage through the oesophagus. Factors enhancing delayed transit with risk of irritation and subsequent stricture formation or ulceration and haemorrhage are described in detail. The recommendation is

that drugs should be swallowed while standing up, with at least a cupful of water so that the total dose has to be swallowed in several portions; more toxic drug substances should preferably be formulated as film-coated oval tablets or hard gelatine capsules.

Finally the editors A.T. Florence and E.G. Salole provide a survey of the significance of the physical properties of different types of drugs. The presentation covers ophthalmic medications (which may produce local as well as systemic adverse reactions), oral dosage forms (the importance of tackiness and adhesiveness and disintegration, and how to measure it is discussed, but no mention is made of the particle size which may cause absorption problems, as for example in the digoxin affair of 1972–73), parenteral therapy (including implants) and aerosols (oropharyngeal candidiasis after corticosteroid aerosols, paradoxical bronchoconstriction, etc.).

The book is the first volume in a series aiming at “senior undergraduate and postgraduate students in pharmacy, medicine, nursing and allied health sciences, and practitioners in these fields”, and a promising beginning it is. Surveys of this high professional standard must be welcomed by everybody interested or professionally engaged in this widespread area.

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Richard P. Hoffmann: Drug Death – A Danger of Hospitalization; An Exposé of Life-threatening Adverse Drug Reactions and Medication Errors in Hospitals. Charles C. Thomas, Springfield, Illinois, 1989, 131 pp.

Adverse events, including adverse drug reactions and hazards of medication, have become an increasing problem in disease management and if the problem which they present is to be solved in the shorter or longer term, they must be debated in the open. In doing that it is equally important neither to frighten the public nor to discredit drug therapy in general. The balance between safety and efficacy must accordingly be considered here, just as in any other situation in which drugs are involved. It is in that context that this grim and provocative book should be judged. Its main, and noble, aim is to combat medicinal attacks on human integrity, health or even life. It concentrates on the situation of hospital patients. The book is essentially an irate professional's righteous wrath at a system that allows faulty and dangerous medication. In producing it, Dr Richard Hoffmann, an experienced hospital pharmacist, is legitimately taking up a real challenge; hospitals, doctors, regulatory authors and others need to be confronted with the otherwise hidden examples of suspected or obvious misconduct in drug treatment. Exactly that is the most impressive feature of this exposé of drug dangers in the U.S.A. hospital world; the real picture is, however, much more multi-faceted and complex. The author does not of course imply that health professionals or hospitals conspire against the innocent and defenseless patient, but his book may leave that impression in the minds of the innocent and defenseless reader. The safety/efficacy concept is not properly considered at this level.

This is not a misleading book, it is simply not well balanced. Although it is more a publicity-seeking venture than a piece of scientific documentation, it points to relevant

problems of hospital medication. Books like this may be categorized together with some media features that wallow in hospital horrors, but perhaps this is not entirely reprehensible because penetration to the public is rarely the strength of scientific publications. If one accepts that philosophy, this book is of a certain value.

Much of the information provided is anecdotal and based on case reports, some of them gloomy stories, some of them not quite clear-cut, clinically speaking. Statistics on adverse reactions and related problems are also presented, although not infrequently in a slightly seductive manner. In order to obtain a fair balance the influence of various risk factors on the occurrence and consequences of ADRs must, of course, be thoroughly discussed. This important point is covered primarily by a brief (five pages) and superficial chapter, with a mere eight (!) lines being devoted to the impact of the patient's condition, clinically the most significant factor. In contrast, ample space is given to ADR underreporting, the background for hospital errors in medication, and legal perspectives, all interesting (and quite well-treated) topics, but somewhat out of proportion with the remaining purviews of this book.

There are literally scores of recent publications on AE/ADR and negligence in hospitalized patients and in non-hospitalized patients, too. Many of them are referred to in Dr. Hoffmann's book. He does not claim that his own publication, like those cited, is a scientific enterprise, but it may appear so to the lay reader, who on the other hand will be well informed of complicated medical details and of the hospital bureaucracy, not easily obtained otherwise. Some of the recent heavy-weights (e.g. [1-5]) in this field appeared, however, after he published his book, but the factual information provided by Dr. Hoffmann is largely correct, even if compared with the most recent observations. It is frightening to note that 10% of hospitalized American patients experience more than trivial drug problems and that 0.1% of the patients die from ADRs. Medication errors in hospitals may score as high as 20%. But to extrapolate these figures to society as a whole may not be correct, though it is surely scaring.

As previously mentioned the book discusses the paramount problem of ADR underreporting quite extensively. However, the list of references is, in this chapter, limited to 48. In contrast, a 1988 list of selected references on ADR reporting [6] includes 250 articles. The "system" tries, all in all, to improve.

The pressing and painful question is what to do about the overall ADR problem. This book provides us with only few and partial answers; yet its mere existence is in a sense a kind of response because more debate and more information is essential. However, to prevent medication calamities in a constructive way, more professional action and more untraditional thinking are needed. Research into causes, distribution of practical guidelines, establishment of system analysis and control, creation of quality assurance programmes, and development of e.g. computerized error catching systems must all be initiated, in addition to education and information. Accusations and provocations may help to reach public attention, but are surely not enough. Furthermore, the sporadically biased attitude of Dr. Hoffmann sometimes overshadows the many welcome features of this book. His honest efforts will, one hopes, be helpful all the same.

What is basically required goes beyond the scope of this book and can be substantiated by quoting the conclusion of one of the most recent and significant scientific investigations in this field [5]: "Adverse events result from the interaction of the patient, the patient's disease, and a complicated, highly technical system of medical care provided not only by a diverse group of doctors, other care givers, and support personnel, but also by a medical-industrial system that supplies drugs and equipment. Reducing the risk of adverse events requires an examination of all these factors as well as of their relation with each other". Dr.

Hoffmann's experience with hospitals exemplifies a certain and important part of this problem, but the way it is done is open to criticism. His intentions are, nevertheless, commendable and his book deserves to be read – with a little more than a grain of salt.

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