

RISMED 00164

Editorial (1)

Thirty years after thalidomide: still plenty to do

Karl H. Kimbel

Hamburg, Germany

Just thirty years ago, Lenz [1] in Germany and MacBride [2] in Australia raised the suspicion that thalidomide, an efficacious hypnotic agent which up to that time had been thought to be well tolerated, might not only induce severe neuropathies but also lead to malformations of the infant if taken during the early stages of the mother's pregnancy. The manufacturer of the drug tried with all the – more or less legal – means available to him to dispel the suspicion [3]. It took six years before the state attorney found the evidence sufficient to insist that the case be brought to trial. After three further years of court proceedings, the State Court of Aachen determined the case closed because of what it termed “lack of public interest and the small degree of guilt” on the part of the company and its employees. Obviously the manufacturer's willingness to pay 100 million DM in compensation to the more than 10,000 victims smoothed the court's way in coming to this decision. The judgement would not stand up to today's legal standards. But in its written commentary on the decision the court defined the duties of a pharmaceutical manufacturer farsightedly and precisely in such terms that they may still be regarded as valid today:

“... Even if a *serious suspicion* (author's italics) leads to the concern that a medicament also does harm to health, the user is still confronted with the need to take a decision on whether he is willing to risk injury to his person or not. This right of decision for the user has as a consequence a corresponding duty of disclosure.” [4].

This dictum was later upheld in a decision of the German Supreme Court, relating to injury caused by a steroid anaesthetic [5].

A manufacturer, all the same, can only “disclose” a new risk of a medicine if he knows of the injury and at least “seriously suspects” that there is a causal relationship to his product. It is evident that, for disclosure to be made at the earliest possible moment, one will have need *firstly* of an alert physician to report the first evidence, and *secondly* of experts who can decide whether or not the suspicion is serious. The latter will also help the manufacturer to arrive at a timely decision on whether or not action is justified. If the decision is wrong in either direction, that could have serious material consequences for the firm. In most countries, during the last three decades, more or less well qualified government bodies have in effect taken over the role of the “experts” in this matter, without

however, at the same time assuming liability for the humanitarian and material consequences of their decision. Thirty years after the thalidomide disaster, which produced a profound shock throughout the medical profession and much of the public, and led to urgent debate as to how future drug catastrophes might be avoided or at least mitigated, it seems timely to look again at what has in the meantime been achieved, to whose credit those achievements are, and what remains to be done in the future.

Despite the wide publicity which was accorded to the thalidomide trial all over the world, it was never challenged at the level of the Supreme Court. Nevertheless, the manufacturer's "duty of disclosure", spelled out by the trial court, found its way into the Medicines Acts of most developed countries. Paragraph 5 of the German Medicines Act, for example, stipulates that no medicine shall be marketed "which according to the present state of scientific knowledge and when used as prescribed is reasonably suspected of exerting noxious effects exceeding those regarded as acceptable by medical science" [6]. One must note that the concept of "serious suspicion" introduced by the court is here replaced by "reasonable suspicion", reflecting the fact that if one truly wishes to protect patients one cannot afford to wait until firm proof is available. The notion of the "acceptability" of some adverse effects is also eminently fair; clearly, there may be some life-saving medicines which cannot be withdrawn even if they have serious effects - a fact provided for in the law's reference to the standards set by medical science. Less satisfactory is the fact that there are no legislative rules governing the technicalities of disclosure (e.g. through a "Dear Doctor Letter" as used in the U.S.A. or the "Red Hand Letter" customary in Germany). The manufacturer has great deal of leeway, and he may find himself in a true dilemma. The means, the circumstances and even the wording of the disclosure may determine the fate of a medicine. There are plenty of situations in which the manufacturer will be less than motivated to comply with a duty of disclosure which is not clearly formulated.

From the nature of disclosure one must move on to the problem of gathering efficiently the evidence on which it may be founded. Even if the percentage of users experiencing a particular adverse effect is small, the sale of the drug in question to a million or more patients will mean that the absolute number of patients affected can be high, as evidenced by the fact that in Germany alone the number of thalidomide victims exceeded ten thousand. That has led the legislators of many developed countries to introduce means of limiting exposure to a new drug, and to insist on intensive monitoring for a reasonable period of time, though neither provision has in fact been widely employed and in some countries neither is even today to be found in the law. Only a very few countries insist on a special form of labelling for drugs introduced within the last 2-3 years, alerting the prescriber to the need to look for events which could point to an adverse reaction. New Zealand has done better than most, with its system of obligatory intensive monitoring for all drugs having "new" active ingredients [7].

The thalidomide disaster led to an intensive search for reliable tests for teratogenicity as well as promoting the study of mechanisms underlying the chemical induction of malformations. The peculiarly horrifying nature of the

thalidomide effect provided a particularly strong impulse to this work. It is notable that although there have been other serious and unprecedented adverse effects since then (e.g. the induction of deafness and peritoneal fibrosis to a beta-blocker, to mention only one example) none has provided quite such a powerful stimulus to study the mechanisms involved or to propose methods for its early recognition. The reasons for the hepatotoxicity of certain antiphlogistics, and almost all anti-arrhythmic drugs remain unknown up to this day; so does the mechanism underlying the dry cough which plagues a fair proportion of patients taking ACE inhibitors; even the massive SMON disaster involving cloquinol in Japan was never explained. It is not unreasonable to postulate that, if medicines laws require the submission and disclosure of evidence on how a medicine works, they should also require study of the mechanisms of adverse reactions, even if (and perhaps particularly if) the drug in question has been removed from the market for this reason.

Educating physicians

To diagnose an adverse drug reaction and to differentiate it from the symptoms of the underlying disease is clearly one of the physician's most difficult tasks. It requires not only profound knowledge of the known forms of adverse reactions to all the drugs which he prescribes, but also the realization that *any* unwanted event may represent a hitherto unknown adverse drug effect rather than a direct complication of the underlying disorders or a purely incidental problem. The physician must be aware of all the methods available to him to confirm his diagnosis of the matter and – where possible – to elucidate the mechanism of an adverse reaction. He should in particular be able to determine whether some individual peculiarity of the patient caused or contributed to the event. This implies that he should be broadly conversant with the various immunological and pharmacokinetic methods which make it possible to recognize idiosyncratic or allergic reactions to an active ingredient or excipient, as well as with the abnormalities in the patient's transport and metabolic mechanisms which could be relevant to the compound concerned.

This ideal is very far from being achieved. The long delay between the first occurrence of an adverse event (not yet attributed to a particular medicine) and the first publication on the matter [8] points to the existence of a serious defect in the ability of the profession to recognize side effects – a deficiency which must be attributed to the way in which undergraduate, postgraduate and continuing medical education on the matter is handled. The situation is worst in countries where Clinical Pharmacology is underdeveloped, but it also seems to reflect the (more or less unconscious) suppression of “bad news” in the various education activities sponsored by the pharmaceutical industry.

Widespread psychological unpreparedness complements the intellectual failing. Increasing medico-legal pressures may cause the inexperienced physician much soul-searching when he finds himself faced with an adverse event which *might*

prove to be drug-induced. Suppose, he tells himself, it is not a problem inherent to the drug but one caused by his own error of dosage or his neglect of contraindications or interactions? By reporting it, will he not lay himself open to the risk of litigation? With such fears in the back of his mind, he will readily be discouraged. Arrogant replies to a reporting physician (from authorities or from companies) that his suspicion is “untenable” or cross-examination by a company’s sales representatives or lawyers may well deter him from ever reporting again. If, as seems to be the case, some government authorities are not prepared to accord the same degree of anonymity to the reporting physician as they normally do to his patient, both undergraduate and postgraduate education will unhappily have to prepare every physician to deal efficiently with the legal pitfalls of adverse reaction reporting, and not merely to diagnose an adverse reaction properly.

To what extent can the physician rely for his current knowledge on the data sheets issued, in one form or another, with every medicine? As we pointed out above, it is the manufacturer’s duty to disclose not only the beneficial but also the noxious effects of a medicine. In order to help him around the conflict with commercial interest which the duty may raise, the medicines legislation of many countries prescribes what a “balanced” information sheet should contain, and the regulatory authority is authorized to check the contents before the text is brought into use. If, however, one compares the content of a “Data Sheet” with the information likely to be supplied, for example, with a new video camera, one is likely to conclude that as a rule only a bare minimum of information is provided to the physician, particularly as far as adverse reactions are concerned. Hospital pharmacists, who have expressed their dissatisfaction, are normally given much more detailed information. Naturally the status quo has its defenders; companies tend to claim that physicians actually prefer an abbreviated product information sheet; even the Commission of the European Communities considers an abbreviated physician information sheet sufficient for its purpose [9]. It may be that the wealth of different preparations on the European market dictates such limitations; from the point of view of drug safety, however, one would argue that the information provided in this way should include not only all known or suspected adverse reactions but statements as to their known frequency and severity and the diagnostic criteria by which they can be recognized.

The time elapsing between the recognition of a new adverse reaction and its inclusion in the data sheet or package insert is still unacceptably long. Serious reactions are commonly brought to the practitioner’s attention through a “Dear Doctor Letter” or its equivalent, but those which are less severe (though often no less important to the sufferer!) will have to wait until the next national data sheet compendium appears. In such a volume, the changes which have been introduced are not underlined or otherwise marked, so that unless the physician is prepared to compare entire volumes page by page he will not know what has been added, modified or deleted. The patient’s lot is even worse; his package insert may be up to five years old and fail to make reference even to adverse effects known for the greater part of that period. It is incredible that, in the age of electronic communication, vital information for the physician and the patient is still conveyed – except

in a few laudable experimental situations – through these medieval channels of communication. Even the Commission of the European Communities adheres to the principle of the package insert and the United Kingdom and the U.S.A. are currently preparing to introduce these relics of the past.

It is now universally accepted that it is ultimately up to the patient to decide whether he wishes to take the risks known to attach to a particular medicine. The information which he receives is often merely an unstructured compilation of all the adverse reactions listed in the literature, partly defined in medical terms of which he has no understanding. How can he decide without consulting his physician again? Even the latter may not be able to tell him anything about the prevalence of particular reactions because he has been given no information. Little wonder that the patient does not want to take an unknown risk and sets the medicine aside; the sad figures which we have on patient compliance make it clear that this is a real problem. Consequent failure to take a necessary medicine may expose him to risks greater than those which might have been created by his taking the drug. The fact that so many tons of medicines are thrown away – or go undispensed – should convince legislators that failure to ensure proper presentation of adequate information may be injurious to health in more than one way.

Identification, verification and the consultant's role

Even a physician well trained in the recognition of adverse drug reactions may not always be able to investigate all the aspects of an unwanted event so as to arrive at a comprehensive diagnosis and to ascertain (or discount) a causal relationship. This limitation of the individual's means is not unusual even where other medical problems are concerned; that is the reason why consultants are called in, where those problems relate to diagnosis or to treatment. But who is one to call into consultation where an adverse reaction is suspected? There is no doubt that it should be a suitably qualified physician, preferably a clinical pharmacologist. He should not only have access to all the pertinent literature, but also to drug consumption data and to whatever is known as to the frequency of side effects and the circumstances under which they are prone to occur. He should further have all the necessary diagnostic tools to hand, for example, the ability to determine blood levels. Finally, he should be in close touch with experts from all the clinical disciplines to seek advice, wherever necessary, on those specialized matters on which his own knowledge falls short. For the verification of the event he must necessarily work in close association with all experts in the field of drug safety, and he should have access to all adverse reaction registries as well as to public and industrial data on morbidity and drug use.

The place of such a consultant could be at a hospital (a point to which I shall return below), at a municipal or governmental drug information centre, or on the scientific staff of a Medical Association. Even regulatory agencies and the pharmaceutical industry could benefit from the presence of one or more such consultants on drug safety on their staff; a few do so already. The independent consultant not

linked to a particular party however provides the real clue to the situation of drug safety, and here the problem arises of ensuring that he finds his place and his future. Since such a consultant can hardly be expected to live from the fees received for his advice in individual cases he will have to be supported, e.g. by the authorities responsible for drug safety or, even better, by an independent drug safety foundation supported by the pharmaceutical industry. If this position creates an opportunity and a duty for him to set up and conduct studies to improve drug safety (e.g. epidemiological investigations requiring the collaboration of many physicians) his position will be further strengthened.

Should the consultant not be professionally associated with a medical institution it will be indispensable for him to be in constant touch with an Institute of Clinical Pharmacology and with a wide range of specialists who are confronted daily with adverse reactions in ambulant patients, and he should have the opportunity to examine such patients himself. He should further maintain regular contacts with the regulatory authority and regional pharmacovigilance centres as well as with colleagues and institutions abroad (for example, the WHO Collaborating Centre for International Drug Monitoring). Taking this complex of tasks as a whole one can conclude that the consultant in this field must be a physician himself, capable of enjoying the full trust of medical colleagues and capable himself of recognizing, identifying and verifying adverse drug reactions. The medical part of his task is vital; just as one should never attempt to diagnose a disease over the telephone or from a patient's files, so one should never form a final view of an adverse reaction without oneself having seen it.

Institutionalization of medicines safety centres

Patients experiencing the most important of all safety problems – those relating to severe and even potentially life-threatening reactions occurring in ambulatory patients or at home – almost invariably end up in hospital; that is likely to be the case irrespective of whether the primary health care physician has recognized the actual cause of the problem or not. In addition, the intensive drug therapy which is common (often for good reasons) in hospital means that a relatively high proportion of in-patients will develop adverse reactions requiring diagnosis and treatment. For such reasons, large municipal hospitals with a high patient turnover seem especially suitable places for the investigation of medicinal risks. In a university hospital, the scientific aspects of patient care will ordinarily enjoy a high priority in the work programme, and the safety of medicines will comprise part of that programme. In a municipal hospital, where there is no general scientific programme, a special department to deal with the safety of medicines is called for. The nucleus of such a department must be formed by one or more Clinical Pharmacologists, but ideally they will be motivated to work so closely with the entire medical staff and with the hospital pharmacist that the department will effectively have its ramifications throughout the hospital; if it does, it may well in turn form the basis for a regional centre, serving the practitioners and specialists in

the area. Nor should one forget the educational value of developing such activities within a hospital. It can contribute to the process of continuous medical education, not only by attracting practicing physicians to lectures and seminars but also by enrolling them as effective outside consultants for its work on drug safety.

Since the costs of establishing a regional medicines safety centre are unlikely to be justifiable in the initial phases in terms of a reduction in drug expenditure or an increase in hospital income, it may be advisable to envisage a joint centre, dealing with both the safety of medicines and with drug information. This will also help to compensate for the negative connotation which the study of adverse drug reactions still carries, and it will encourage collaboration with the clinical staff by providing them with an important additional service. Clearly, the advice given by the centre's staff will only be accepted at the bedside if it is recognized as coming from a competent source and if it does not interfere with the responsibilities of the physician who is treating the patient. The possibility that advice and information might be seen as interfering with the practicing physician's independence of decision and action could explain why some physicians prefer such advice from a pharmacist, since the latter makes no claim to clinical competence. The role of the pharmacist is however inevitably limited by the fact that he cannot provide assistance in the actual therapeutic decision, nor in the identification of adverse drug reactions where the interpretation of the essential evidence is likely to demand a full medical education.

In some countries, e.g. France [10], the regional centres concerned with the safety of medicines ("pharmacovigilance") are units within university departments of pharmacology. This is an excellent situation provided the Chairman of the department has strong interests in clinical pharmacology and has good relationships with all physicians in the clinic and the field; in that case he may contribute experimentally to the elucidation of the mechanism of adverse reactions. Just as is the case with anaesthetics, however, pharmacovigilance is a discipline which must be on duty around the clock and wherever it is needed most; it cannot cease to operate when a university department of pharmacology closes down for the day.

Dissemination of information on adverse drug reactions

As a rule, medical information is, as pointed out above, passed to and through the medical profession almost exclusively by means of the printed word; only very recently have electronic tools cautiously begun to play a small role. All the same, the urgency of the problems to be dealt with where adverse reactions are concerned has long been recognized as demanding something better than the usual sedate pace of medical communication. When the American Medical Association established a registry for drug-induced blood dyscrasias in 1954 [10] – long before the thalidomide disaster – it was clear that the usual slow processes of scientific communication would not suffice where one's aim was to identify problems of medicinal safety at the earliest possible point in time. Its spontaneous reporting system therefore bypassed the usual process of submission to journals and the

leisurely pace of peer review. The German Medical Association followed suit in 1958 [11] and many other countries, in the face of increasing public awareness of the problems, thereafter established their own spontaneous adverse reaction reporting systems. In the early 1960's, the World Health Assembly called for the setting up of "an international system of monitoring adverse reactions to drugs, using information derived from national centres" [12]; such a centre became operative in Geneva in 1970, and was transferred to Uppsala in 1978.

WHO's involvement did not end there. Particularly with the Organization's "Adverse Reaction Terminology", developed when the International Classification of Diseases proved inappropriate for this purpose, the foundation was laid for the collection and evaluation of reports on suspected adverse drug reactions from most of the world's developed countries. To date, information on more than 500,000 suspected adverse effects has been entered into the system. All the same, there is still a long way to go. Twenty years after the establishment of the WHO system, an independent group of experts still had to conclude that "serious unanticipated adverse effects, resulting in regulatory action, have thus far not been identified through inspection of the international data base." [13].

This disappointing conclusion, shocking though it may be, does not come entirely unexpectedly. The enthusiasm initially engendered by the seemingly limitless possibilities available to store, evaluate and search vast masses of data, prospects which had been opened both by the use of the computer and by the willingness of numerous physicians around the world to co-operate in the venture, clearly led to the neglect of some basic prerequisites. The data entered into the system were in the great majority of cases not verified by physicians having direct access to the patients concerned. The terminology was initially compiled in haste, incorporating innumerable (not always compatible) proposals from national centres, and it was insufficiently scrutinized for consistency and clarity of definition; nor was the question of compatibility of terms in different languages adequately solved. Coding at national centres was often undertaken by non-medical personnel or by physicians who were insufficiently conversant with the exact significance of terms. All these facets require correction. The development of medicines safety centres which are truly capable of investigating each suspected reaction with the help of the treating physician, and which are able to transmit all important data promptly and accurately to the WHO Centre in Uppsala seems an essential step if better use is to be made of this potentially invaluable institution.

Containment of risk

When a drug is found to be noxious, drug regulatory authorities have one royal road to a solution, i.e. withdrawal of the offending product from the market. It is a drastic step, but relatively simple and therefore temptingly attractive to the regulator. Anything more subtle, such as the limitation of the list of indications, strengthening of the contraindications or the publication of warnings will involve tiresome argument and a broad expert consensus which will have to stand up in

court if it is challenged. This is perhaps one reason why so many preparations which have some value have disappeared from the market. Sometimes the manufacturers concerned have given up the battle themselves, considering the costs of re-orienting their drug to the narrower indication which an authority is still willing to accept but which will inevitably mean lesser earnings [14]. If withdrawal is sometimes to be deplored, so at the other extreme is the inactivity which agencies sometime exhibit in situations where something needs to be done. Between those two all-or-none extremes there lies in fact a wide opportunity for containment of risk. One way of approaching that process is to define strictly the indications in which the benefit still outweighs the risk. Another is to define the type of patient in whom, independent of dose, the risk is especially pronounced, e.g. because of idiosyncrasy or allergy. Similarly, one can contain risk by taking account in the dosage scheme of limitations imposed by a patient's metabolic or excretory capacity – e.g. in the elderly.

Relative measures such as these unavoidably demand thought, goodwill and effort; the manufacturer must be willing to explain the limitations of safe use in his labelling, and the average physician to explore them in his patients. Once again the ideal is not attained, and most of the parties are at fault. Recent promotional claims for a “self-adjusting” drug or a product with “autofocus” are seductive, improperly suggesting to the physician that there is no need for him to make the effort. This is unfortunate and misleading, but so long as clinicians and even clinical pharmacologists do not support regulatory agencies by establishing sound criteria for the titration of medicinal dosage in the individual patient we shall have an increasing display of these so-called wide spectrum medicines which in fact induce the physician to take improper and unnecessary risks. The groups most at risk are, as is so often the case, children and the elderly, who account for a substantial market yet tend to be treated by the regulatory world as if they do not exist.

Manufacturers not uncommonly do at their own initiative and without prompting from regulatory agencies perform supplementary studies on marketed drugs. These however are more likely to be concerned with the demonstration of a supplementary benefit than with the further elucidation of a possible risk. One rarely hears of a manufacturer offering for sale a simple test to detect possible hypersensitivity to his product, or making available free blood level determinations to trace those metabolic abnormalities which may render the use of his product risky. The most neglected area of risk containment, however, relates to a company's failure to use the data sheet and package insert to instruct the user or prescriber of a drug on how to recognize an impending adverse reaction, how to avoid such problems, and in what situations further consultation is likely to be advisable.

Where do we go from here?

If we are seriously determined to make pharmacotherapy safer, then even when we are dealing with medicines which are relatively specific in their action we must drastically reduce the number of adverse drug reactions which even today still go

unrecognized or unreported. We need not only to enlarge and emphasize the place occupied by the safety of medicines in medical school training and continuing education but also to offer the physician free access to comprehensive and objective textual information, as well as to independent consultants who can help him to identify adverse drug reactions. Obviously this will only be feasible if medical school curricula are adjusted accordingly and post-graduate medical education is freed from commercial influences.

The physician should feel that he has some encouragement to publish adverse experience with new and time-proven medicines, assisted if he so needs by the regional drug safety centre or a university department of clinical pharmacology. If he is not inclined to publish, he should be made aware of the need to report his case to one of these institutions so that it is entered into the national documentation of suspected adverse effects. He should be encouraged to participate in epidemiological studies to determine the relative risk of particular adverse reactions, thereby improving the estimation of benefit/risk ratios.

As to the national authority charged with the collection and evaluation of data on adverse drug reactions, it should realize that the reports in their possession are hot scientific and medical material which can be of the greatest value. Such an authority should make its data available to the medical profession and compare it regularly with findings and suspicions from other countries; it should ensure that the data are interpreted by a group of competent experts. The national authority should encourage and promote epidemiological studies on the occurrence and course of adverse reactions to complement its own supply of data and pointers. Drug utilization data, so necessary if information on adverse drug effects is to be interpreted so as to determine its relevance for population subgroups (e.g. defined by age and sex) should be available to the authority and to all who need them.

This is surely not the first time that these suggestions advanced in these pages are made; some were made three decades ago, and the reason to advance them once more here is that on some fronts, despite a great deal of writing and talking, regrettably little progress has been recorded. All credit to the achievers, but not enough has been done to solve problems which are in essence largely soluble. University departments, regulatory agencies and other organizations concerned with improving pharmacotherapy are, with only a few exceptions, even today understaffed and underfunded. Has the time not come to shift a part of the taxpayers' load in improving drug safety to those who, alongside the patient, will benefit most from it, i.e. the pharmaceutical industry? Where in the world has any other business seen its product liability burden in effect assumed by the public purse?

Karl H. Kimbel MD
Deputy Editor for Drugs

References

- 1 Lenz W. Kindliche Missbildungen nach Medikamenten während der Gravidität. Dtsch Med Wochenschr 1961;86:2555–2556.

- 2 McBride WG. Thalidomide and congenital abnormalities. *Lancet* 1961;ii:1358.
- 3 Wenzel W. Transcript of the Contergan[®] trial, Berlin 1972.
- 4 Landgericht Aachen, Beschluss v. 18.12.1970-4 KMs 1/68 "Contergan".
- 5 Supreme Court decision on "Estil[®]" *N Jur Wochenschr* 1972;25:2217; *Pharm Ind* 1972;34:742.
- 6 German Drug Law (Arzneimittelgesetz) of Aug 24, 1976 § 5 (2); *BGBI I* p. 2445, 1976.
- 7 Coulter DM, Edwards IR, McQueen EG. In: Inman, WHW, *Monitoring for Drug Safety*, p. 119-133. MTP Press Ltd, 1986.
- 8 Edwards IR, Lindquist, M, Meeting on adverse drug reaction reporting in Europe, IBC Technical Services, London, Sept. 1992.
- 9 Council of the European Communities, Directive 89/341/EEC, March 3, 1989.
- 10 Association française des Centres de Pharmacovigilance, Paris.
- 11 Smiley RK, Cartwright GE, Wintrobe MM. Fatal aplastic anemia following chloramphenicol administration. *JAMA* 1952;149:914.
- 12 Annual Report 1958, Drug Commission of the German Medical Profession, Cologne 1958.
- 13 Anon. International Drug Monitoring: the role of the national centres, World Health Organization, *Techn Rep Ser No 498* (1972).
- 14 Formal agreement between WHO and the Government of Sweden (1978).
- 15 Status Report of an independent group of experts recommended in 1988 by the Executive Board Committee on Drug Policies of the World Health Organization, Geneva 1990.