M. N. G. DUKES

SIDE EFFECTS OF DRUGS ANNUAL 8 1984

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A worldwide yearly survey of new data and trends

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1984

ELSEVIER, Amsterdam – New York – Oxford

ISBN 0 444 90339 9
Library of Congress ISSN 78-644057

Published by:
Elsevier Science Publishers B.V.
P.O. Box 1126
1000 BC Amsterdam

Sole distributors for the USA and Canada
Elsevier Science Publishing Co., Inc.
52 Vanderbilt Avenue
New York, NY 10017

Typeset by H Charlesworth & Co., Alphen a/d Rijn
Printed in the Netherlands by Casparie – Amsterdam

How to use this book

THE SCOPE OF THE 'ANNUAL'

Side Effects of Drugs Annual has been published in January of each year since 1977. It is designed to provide a critical and up-to-date account of new information relating to adverse drug reactions and interactions from the clinician's point of view. The Annual can be used independently or as a supplement to the standard encyclopedic work in this field, *Meyler's Side Effects of Drugs*, the ninth edition of which was published in March 1980, and the tenth edition of which will be published in June 1984.

SPECIAL REVIEWS

As new data appear, older findings may be discredited and existing concepts may require revision. Some fifty 'special reviews' deal critically with such topics, interpreting conflicting evidence and providing the reader with clear guidance. Special reviews are identified by the traditional prescription symbol and are printed in italic type. Older papers cited in these reviews are either listed by name or via cross references to previous Annuals or past editions of Meyler's Side Effects of Drugs, which can be found in most medical libraries.

SELECTION OF MATERIAL

In compiling the SED Annual particular attention is devoted to those publications which provide essentially new information or throw a new light on problems already recognized. In addition, some authoritative new reviews are listed. Publications which do not meet these criteria are omitted. Readers anxious to trace all references on a particular topic, including those which duplicate earlier work, are advised to consult *Adverse Reactions Titles*, a monthly bibliography of titles from approximately 3400 biomedical journals published throughout the world, compiled by the international Excerpta Medica abstracting service.

PERIOD COVERED

The present Annual reviews all reports presenting significant new information on adverse reactions to drugs from July 1st 1982 to June 30th 1983. Where possible more recent papers have been included. Subsequent Annuals will similarly cover the world literature appearing yearly between July 1st of one year and June 30th of the next.

CLASSIFICATION

Drugs are classified according to their main field of application or the properties for which they are most generally recognized. In borderline cases, however, some supplementary discussion has been included in other chapters relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component.

DRUG NAMES

Drug products are in general dealt with in the text under their most usual non-proprietary names; where these are not available, chemical names have been used; fixed combinations usually have no non-proprietary connotation and here trade names have been used as necessary.

SYSTEM OF REFERENCES

References in the text are coded as follows:

R: In the original paper, the point is *reviewed* in some detail with reference to other literature.

r: The original paper *refers* only briefly to the point, on the basis of evidence adduced by other writers.

C: The original paper presents detailed *original clinical evidence* on this point.

c: The original paper provides *clinical evidence*, but only briefly.

The code has not been applied to animal pharmacological papers.

The various Editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-8, SED-9, etc.; *SED Annuals 1–7* are cited as SEDA-1, SEDA-2, etc.

INDEXES

Index of Drugs: This index provides a complete listing of all references to a drug.

Index of Side Effects: This index is necessarily selective, since a particular side effect may be caused by very large numbers of compounds; the index is therefore mainly directed to those side effects which are acute or life-threatening or are discussed in special detail. Before assuming that a given drug does not have a particular side effect one should consult the relevant chapters.

The indexes have been compiled by Dr H. Kettner, Middelburg, The Netherlands.

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The seven pillars of foolishness

M.N.G. Dukes

The Editorial 'we', explicit or implied by anonymity, should by now have had its day. Editors, at least as vain as other mortals and probably more so, use and misuse it to impart to their pronouncements the majesty of plurality and the ponderousness of nameless authority. A medical editor may even find it a convenient way of suggesting to his colleagues and readers that he is speaking on their behalf. This, at all events, is not a pluralistic Essay; indeed, you may find it a very singular one. It is mine, and mine alone, and I shall not attempt to suggest that the views which I hold and the disgust which I feel at this moment are shared by anyone but myself. If you want facts about drugs, then set me aside and turn quickly over the next few pages so that you can feast upon the meat of the book without more ado. If, however you are interested in people, well or ill, please have a little patience.

Has it ever struck you that, for some of us who live in the world of drug therapy, a medicine so very easily becomes more important – certainly more central and more tangible – than the hundreds of thousands of people who take it? It has a name, protected by law and patent, whilst its users are but a grey, anonymous, heterogeneous mass. It is fathered by proud men in white coats, who conceived its origins upon laboratory blackboards. It is born in a retort. It is developed and nurtured like any infant to adulthood. It curtsies before the scientific world as might the most select of society *debutantes*, and then, somewhat incongruously, it is often promoted into fame in the medical marketplace in a manner of which a rock star might be envious. The mere patient has no say over the drug; he is ordered to take it by his physician, and if he does as he is bid the doctors pat him on the head and condescendingly call him compliant. If all goes well from the drug's point of view it has its long day of acclaim, bringing its industrial godfathers fame and fortune. If at any time its name and reputation are besmirched, grave advocates will be at hand to defend it. It may be a long time before the glory fades and other medicines take their place before the footlights. And even then, the old drug may be an unconscionable time a-dying.

I do not see any real alternative at present to this process; this is the way that technological society in the west chooses to advance and the way good business apparently must be done. If, in the interests of progress, mankind has to live with image-builders and the ever more subtle machinery of hidden persuasion, applied to a range of goods ranging from video-recorders and benzodiazepines to politicians, then there is not very much mankind can currently do about it. But somewhere limits must surely be set. One such limit must apply when one defines what can reasonably be regarded as progress, in the name of which this whole process is maintained. Not every new molecule which acquires a sales licence can claim to represent a step ahead; many a new drug is merely a step aside, some are quite distinctly a step backwards. How much sales talk can one tolerate for such fruits of pseudo-innovation? It has very often been argued that when a new drug appears in the medical marketplace

it is still too early to decide whether or not it represents a useful advance in therapy, and that many a new drug should be given a chance to prove itself in this respect over a period of years before the world passes judgment. So it may be, but did you ever see a drug introduced to physicians like that? 'Dear Doctor', the introductory letter might run, 'we do not really know whether our new product is any better, or safer, or more convenient to use than those which you already have, but we surely hope so. We would also like to earn back some of the money which we have spent on developing it, so that we can go on trying. Will you kindly give it a chance?' Oddly, if medical society had not grown so used to hyperbole, such an honest approach might prove to have some appeal to the prescriber. But nothing of this: the physician is beaten about the ears with the name of the new nostrum, with its supposed advantages, and with pictures which imply what words must not promise; all this goes on until he is so conditioned (compliant, perhaps) that he begins to prescribe it. If the truth be exactly as its founder fathers may have believed at the start, namely that the drug has nothing new to offer, this will in due time become evident; but that will happen only very slowly, for it will be a matter, not merely of confirming or rejecting a calm hypothesis, but of gradually eroding the inflated image of the drug which Madison Avenue advertising has built around it. And if the truth of the matter be that the drug is in fact risky the slowness with which that truth emerges in the face of many triumphal fanfares can mean unnecessary suffering.

Lest anyone think that this is another diatribe against the drug industry and its promotional techniques, let me at once take some other people to task. Where a flicker of a risk seems to be emerging it is not merely the marketing managers who will at first be loathe to admit it. What about the regulators in their ministerial offices? They have only just licensed the drug. If it is indeed problematical, what will parliament be saying about their licensing policies and their technical competence? Then there is the doctor. He has prescribed it and his first few patients appear happy. Is he very anxious to hear that he has been reckless or uncritical? Are his patients willing to have the new remedy, with the hope which it might bring, taken away from them? All these things can delay the admission, even where convincing evidence comes forward, that a hypothesis of risk is anything more than a hypothesis. Once a drug has got onto the market, the dice are heavily loaded in favor of its remaining there, with the reputation originally accorded to it, for a long time.

It has been said often enough but I have to say it again: drug risks are inevitable. Much drug therapy as it exists today is still a lamentably crude means of influencing the workings of a machine as complex as the human body. It may one day be possible to make fine adjustments to physiological balances, and indeed there are a few instruments, such as the hormonal releasers, which render it possible to do so already; all too often however the only drugs available are pharmacotherapeutic blunderbusses which present a known or unknown degree of risk. That being so, one has to be extraordinarily careful about handling them socially and administratively in ways which may raise the measure of risk still further. Loading the dice in the way I have already described increases the risks; so for example does the use of fancy algorithms to test every shred of evidence of a drug's noxiousness before one is prepared to take it seriously. But the risks are raised to a wholly irresponsible degree if one puts the interests of the drug in the middle of the picture and those of the patient at the periphery. Yet that happens, and in some areas it is getting worse rather than better.

People still point to thalidomide as a monumental disaster, *the* monumental disaster, fortunately now a quarter of a century behind us; then they add blissfully that things like that do not happen nowadays. Unhappily they do. Not in exactly the same horrifying way, but in a multitude of others. During the last two years there has been a new epidemic of misery, and one cannot continue to pretend that all is well. The most unhappy aspect of it all has been that things have been made worse than they need have been; much of the misery could have been prevented entirely, much more cut short quickly, had society been awake, and honest, and interested.

Let me recall seven stories. They are seven aspects of the recent history of antirheumatic drug treatment, and since they have been well documented in these volumes and elsewhere I shall not repeat every detail; but I shall attempt to put all seven stories into some perspective. For they stand like seven pillars of foolishness, some taller than others, yet all monuments to human error, greed, vanity, self-interest, gullibility or shortsightedness. Thanks to such things, most of these stories are worse than they need have been.

Benoxaprofen

Benoxaprofen was (or is) an antirheumatic drug which was submitted to various drug regulatory agencies for licencing from about 1979 onwards. It was structurally related to many well-known antirheumatic drugs and most of its effects appeared very similar. There was, however, some qualitative shift as regards the relative importance of the two modes of action often described for these drugs; as compared with its predecessors, benoxaprofen seemed to have a little less effect on prostaglandin synthetase and a little more on leukocyte migration. The hypothesis was raised that this might result in a reduced incidence of those adverse effects – notably gastric bleeding – which seem to be linked to prostaglandin synthetase inhibition. The early clinical studies indeed suggested some practical benefit, but this is quite usual with most antirheumatic drugs of this type – the real gastric problems usually emerge later.

When the real problems emerged with benoxaprofen they were however more serious than with other drugs of its type. Not only was it causing the usual pattern of gastric irritation, but it was also apparently killing old people from hepatic disorders and it was inducing photosensitivity on a massive scale; it was also causing onycholysis in a frequency of anything up to fifteen percent. The brief and destructive career of benoxaprofen ended with its withdrawal in the summer of 1982 from the very few markets in which it had been accepted by regulatory agencies (1).

No party emerges very creditably from this story. The world's regulatory authorities found themselves from the start in disarray, handing down decisions on the original new drug application which ranged from complete rejection to open-armed acceptance. The company which marketed the drug, a highly respected and usually very sober organization, launched it with reckless, hysterical, preposterous advertising; whatever one may think of the words in which it was couched, visually it clearly conveyed the impression that one was dealing with a breakthrough of world-shattering importance. As a result, the drug was prescribed on a massive scale and when the troubles came they came in batallions. It seems probable that at least seventy elderly patients died and a great many more people suffered (2). Yet even then the foolishness was not over. Some regulatory agencies, conveniently forgetting the emphatic recommendation of the World Health Organization that drugs likely to be used in the elderly should be investigated in the elderly at an early stage, sought in retrospect to whitewash their acceptance of the drug despite the almost total lack of such geriatric trials. Company lawyers continued to deny cause and effect, no doubt in the hope of fending off liability proceedings. Even after the drug had been quietly abandoned, a vigorous defence of it was still being put up by gentlemen whose own adverse reaction monitoring systems had failed to detect the harm which was being done; in such cases, no doubt, one's own reputation weighs more heavily than anything else.

Benoxaprofen was a compound which seemed to bear promise of better things to come, and it is sad that it has gone; but the patients who were killed by benoxaprofen, many of them unnecessarily, are dead as well; no amount of whitewash and denial will bring them back to us.

Zomepirac

Like the benoxaprofen drama, that involving zomepirac was limited largely to one country – in this instance the United States. Zomepirac is basically a traditional antiinflammatory analgesic agent. It is extremely closely related to tolmetin which has

been sold in some countries for many years as an antirheumatic drug. Tolmetin is a perfectly usable compound, though a little too prone to cause anaphylactoid reactions, and had zomepirac been presented as its twin sister it would no doubt have been used in the same way and treated with the same respect. But the image builders took over; zomepirac was selectively investigated as an analgesic; with its other properties relegated to the small print it took its bow in the advertising columns as heaven's own gift to pain sufferers. This time, the advertising men appear to have had not only the doctors but even the stock market and the regulators in their pockets; when zomepirac turned out to induce anaphylaxis on a scale commensurate with the scale of its promotion, astonishment and dismay were expressed on all sides. The drug was withdrawn in March 1983, and the accusations as to who was responsible for it all are still flying; but at least eight people are dead (2), and to judge from scattered news items rather more. Given a little more caution by everyone involved – need any of them have died at all?

Osmosin

Osmosin was laid to rest by its founder fathers in January 1984 (3); its victims had been laid to rest the previous year. Developed at a time when the patents on indometacin were running out, Osmosin provided it with an elegant but costly kinetic face-lift. Its osmotic tablets released the drug slowly through a semipermeable membrane as they travelled down the gastrointestinal tract, thereby prolonging the duration of activity and perhaps promising to reduce gastric irritation. Even at the time when it was developed, there were murmurings to the effect that in this way gastric problems might merely be shifted to a lower level. As things turned out, this is apparently what happened; the Osmosin tablets seem either to have adhered to the intestinal mucosa, became lodged in diverticula or peppered the gut with potassium which, astonishingly, was used as an excipient. When perforations resulted, the anti-inflammatory effect may well have masked the consequences until it was too late; certainly people who had tolerated plain indometacin well for a long time died when they were needlessly switched to Osmosin. In the drug's own obituary, the company claimed that extensive studies had failed to demonstrate any special risk (3); so they may have done, but that presumably only reflects the inadequacy of the studies. There is a splendid company there in Rahway which has done fine things for medicine and will do fine things again; it should not have its monuments in the churchyards.

Two butazones

The double story of phenylbutazone and oxyphenbutazone is quite a different one. These drugs have been with us for a generation. They arrived at a time when in the field of antirheumatic treatment there was little to choose from, and they found their place. They caused their problems, but the nature of these became known very early; the 1960 edition of Meyler's *Side Effects of Drugs* recorded a series of cases of agranulocytosis as well as a range of other complications and their incidence. Twenty years later, the 'butazones' as they were loosely called, were almost hidden among the throng of newer nonsteroidal antirheumatic agents which now jostled one another in the market place. Nevertheless they had retained something of their early reputation for the treatment of ankylosing spondylitis, though it is not clear whether they really deserved it. Things might have gone on as they were for another generation, with both products falling gently into obscurity, had not, in the summer of 1983, an internal memorandum from Messrs Ciba-Geigy dropped into the hands of Dr Sidney Wolfe of America's Public Citizen action group (4). The memorandum estimated that there had been 1182 deaths due to these drugs worldwide and it not unreasonably raised the question within the company whether it was not time to stop promoting them. Public Citizen called for an immediate ban on both drugs as an 'imminent hazard to public health'. Dr Ole Hansson of Sweden, who appears to be deeply convinced that Ciba-Geigy is incorrigibly wicked in its ways, took up the cry in the Scan-

dinavian newspapers; on December 14th Norway banned both products and throughout the world regulatory agencies sat down to consider whether or not they should follow suit; some seemed very likely at least to make gestures of concern.

From what I have already said it will be clear that my main concern is with patients dying or suffering needless injury; but in the way in which society is now suddenly reacting to Dr Wolfe and Dr Hansson there is something very wrong as well (5). Most of the evidence of the harm which these drugs can do was available two decades ago, largely quantified. If it is true that, because of the arrival of somewhat safer products, one should reevaluate and perhaps discard these old stalwarts, then that could have happened any time from 1970 onwards, certainly by 1975, on the basis of a careful comparison of the benefit-to-risk ratio of all the compounds available. Alas, regulatory agencies do not usually do these things; they are too busy approving new drugs to take a hard look at old ones; when they do so, it all too often happens because people like Dr Wolfe and Dr Hansson have raised the hue and cry. I have a shrewd suspicion that aspirin has killed a multiple of those who are said to be victims of the butazones, and that several other drugs are rather worse than these two; but I have to suspend judgement because I do not have the comparative data available. Unhappily, neither does anyone else; the medical world too has been much too busy testing new antirheumatic drugs to learn much more about the comparative merits of those it already has. Is there not something amiss with our priorities?

Pyrithioxine

Pyrithioxine hydrochloride is what my friend Dr Leo Offerhaus calls a chameleon. It is a vitamin B6 derivative and reputed to be an anabolic for the brain, very good for contusion, behavioral disorders in children and senile dementia (6). Even for these purposes it is sold under thirty of the most musical names with which a drug was ever blessed, including Cerebrotrofina, Musa, Gladius, Scintidin, Tonomentis and Life. Small wonder that when it suddenly surfaced in France, chameleon-like, as an antirheumatic agent physicians had no idea what it was and compliantly prescribed it. When it began to cause rashes and stomatitis did one in a thousand physicians know of its structural link – the dithio group – to penicillamine, with which some of these rheumatic patients must have been treated earlier? Had they known, they might have prescribed it more critically. Some elderly rheumatic patients were indeed already receiving the same compound under another connotation for their ailing medical state. But do you know what the physician who asked about the chemical nature of this new antirheumatic drug was told? He was solemnly informed that it was 3,3′-dithiodimethylenebis(5-hydroxy-6-methyl-4-pyridylmethanol)dihydrochloride monohydrate. Mercy be with us – will doctors never insist on having generic names and some intelligible indication of what they are really dealing with before they write a prescription?

Oxametacin

Space is at a premium, and I must be brief. Oxametacin, by all accounts, is a miracle, for the clinical papers which I have seen conclude that it is the equivalent of indometacin without its side effects (7). I am nevertheless also assured that it has been discussed around certain regulatory tables and gave rise there to some amusement. Privately, all I can conclude is that the published material is not all of a standard which I would like to see, that the drug is metabolized in part as indometacin, and that the patients without side effects did not receive an effective dose. If better work proves the contrary, I shall be delighted to be corrected; so far, I am forced to believe that this is not the way to help rheumatic patients to avoid adverse reactions. This gem, should you require it, is to be found in the pharmacies of Italy; you will be hard put to it to find it in most other places.

Seven stories and many morals

The chain of stories could continue; the particular nastinesses or oddities associated with indoprofen, ibufenac, aclofenac, mefenamic acid, acemetacin, fenclofenac and glafenine are much in the same vein. For the present purpose, these seven tales must suffice. Not all of them had a tragic ending, but all of them illustrate some of the absurdities in the way in which the community has behaved and continues to behave when it deals with drug safety. Even from the purely scientific and epidemiological point of view it is difficult enough to come by reliable information on adverse reactions, and to spot it sufficiently early to prevent much injury being caused. Yet, even as the facts begin to emerge, any attempt to interpret and objectify them may be bedevilled by the machinations of people who have their own interests to defend and their own axes to grind. It is entirely proper that the truth about side effects and benefit-risk ratios should emerge from a weighing of a mass of conflicting evidence, but the process is immeasurably complicated and delayed where costly reputations and much money are at stake. Doctors, companies, regulatory agencies, politicians, consumers and nowadays even stockbrokers (yes, *stockbrokers*!) all throw up their own particular smokescreens when suspicions of major adverse reactions are discussed; all that one can do, and must do, is to set aside most of the commentary and interpretation that is cast around on such a vexed issue, go back to the patients who are at the centre of the problem and verify the facts. For let me say it once again; it is only the patient who matters. For him or her a serious side effect is of course not a side effect at all; it is a very central effect indeed, perhaps one of life and death.

These problems can arise in every field of drug therapy, but it is today tragically easy to identify them in the field of antirheumatic treatment. For two decades most nations have in good faith accepted the argument that every nonsteroidal antiinflammatory drug which shows promise must be given a chance, since it may contribute something to therapeutic progress. As a result, the financially profitable field of antirheumatic drug therapy has in many countries become a fairground, the noise in which is utterly confusing to pharmacologists, physicians and patients alike (8). No one particular segment of the community is really to blame; society has created a situation in which everyone is under pressure to behave in a particular way; if I had a good new antirheumatic drug to sell I too would be obliged to sell it with trumpets and bells, however distasteful I might find it, since otherwise no-one would notice. It is clear that too much injury is being caused by drugs in this field; the proportion of drugs which come, kill and go is too high, and amid all the clamour it is now impossible for the doctor to decide which risks are worth taking in his patient's interest.

Should one not, to begin with, look very carefully at the comparative merits of all the antirheumatic drugs currently known, sponsoring impartial research where necessary to find the data needed to prune the market and update the textbooks? If no-one else will do it, the drug regulatory agencies of the world, which are very slowly closing their ranks, might share out the task, if possible in collaboration with the pharmaceutical industry. It has to be done. As recently as January 1984 one could find statements in the medical literature to the effect that aspirin, after three generations, was still the drug of choice in rheumatoid arthritis (9). That may not always be true, but the fact that in 1984 it can still be said with some authority and backed by substantial evidence surely makes one wonder whether society has been using its resources optimally to find better and safer antirheumatic medicines. The fact alone that the number of nonsteroidal antiinflammatory drugs licensed for sale in various European countries varies sevenfold (10) reflects the uncertainty as to how the situation should now be handled.

Again, I think the medical profession should be taking a hard look at the way in which new antirheumatic drugs are currently sold to it, and the consequences which that has for everyone. More restrained promotion could be more informative and a great deal less wasteful. If only a fraction of the money currently being spent, at the community's expense, on breathless four-colour advertisements and double teams of detailmen were to be diverted into basic research in the better industrial laboratories

society might be on the way to developing the truly new and truly safer antirheumatic drugs which patients need. Whether one believes that industry can regulate itself into a more balanced situation, or whether one expects governments to impose a solution will depend on one's own private philosophies, but I know it must happen if there are not going to be a series of other pillars of foolishness lining our way through the 'eighties'. Accidents will still happen, patients will still be injured and killed by the unforeseen and unforeseeable, but people will hopefully no longer die merely because society has been as hesitant to admit the risks as is currently the case.

There is an unhappy turn of phrase currently going around medical meetings which refers to patients as 'the people out there...' Perhaps that is merely symptomatic of the wrongheadedness which besets the world of drug experts. The patients are indeed out there, and the drugs are in here with us, being coddled in the warmth. It may be the destiny of the clinical pharmacologists to bring drug policies and policy makers back where they belong, at the bedside and in the consulting room, with the patient – every patient – at the heart of things, whilst the chemists, the stockbrokers, the image makers and the detailmen wait, cap in hand, at the door for judgement to be pronounced.

Copenhagen, January 1984

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