MEDICAL PRACTICE

Contemporary Themes

Study of information submitted by drug companies to licensing authorities

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Summary and conclusions

Reports of clinical trials included in applications submitted by drug companies to licensing authorities in Finland and Sweden in four different years were studied. Many reports were submitted, but most of the trials were uncontrolled and of poor quality. Many of the reports were unpublished, and thus, as the submissions are secret, were not available to doctors. These unpublished reports were in most respects as valuable as the published reports. Most of the reports included some information about adverse effects; the information was often deficient, but skilled analysis might increase its value.

This study provides support for those who want to see public disclosure of the reports of trials submitted in licensing applications.

Introduction

In Sweden (population eight million with 14 000 practising doctors) 878 clinical trials of unlicensed and licensed drugs with new indications were carried out in 1977. A similar number of trials may be conducted in other countries, yet the benefits, proper indications, and side effects of drugs are often poorly determined. This paradox may be explained by the large number of drugs, selective publishing of results, and the poor quality of many of the trials.

Most countries now require considerable data supporting the efficacy and safety of a drug before they will allow it to be marketed,[1] but this information is confidential and not available to doctors. As part of a research project on the control of psychotropic drugs during 1950-77 in Scandinavia I had permission to study the information submitted to the Finnish and Swedish drug licensing authorities. My report has three aims: firstly, to describe the quantity of clinical trials included in the applications; secondly, to indicate the number of unpublished trials included in the applications and to compare their value with that of published trials; and, thirdly, to discuss whether this information might be used to study the adverse effects of drugs.

Methods

The system of drug licensing in Scandinavia has been described[2]; the Finnish system was not described separately but is essentially the same as the systems in the other Scandinavian countries. The licensing system, which requires a drug to be efficacious as well as safe, existed in Finland and Sweden for the whole study period (1965-75).

I studied applications for the licensing of psychotropic drugs in Finland and Sweden for 1965, 1970, 1974, and 1975. I also studied a random sample of non-psychotropic drugs in Finland. Initially for 1970, 1974, and 1975 I randomly selected the same numbers of non-psychotropic and psychotropic drugs, but after I had excluded some drugs (drugs for external use, intravenous fluids, and new preparations of drugs already licensed) the number of non-psychotropic drugs was smaller. For 1965 I deliberately chose fewer non-psychotropic drugs to reduce the amount of work.

Psychotropic drugs included: (1) hypnotics, sedatives, minor tranquillisers, and intravenous anaesthetics; (2) antipsychotics; (3) antidepressants and psychostimulants; (4) anorectics; (5) narcotics; (6) antihistamines with profound sedative effect; (7) reserpine and its derivatives; (8) centrally acting muscle relaxants; and (9) antiepileptics. All applications to license drugs (either alone or combined in a preparation) were included in the analysis, except those that were merely for a change of form or strength (depot preparations with

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dosage intervals of over one week were regarded as new drugs and included in the analysis) and those that resulted from a change of manufacturer.

All reports of clinical trials on the efficacy of the drugs that were submitted before the final decision on licensing were included in the analysis. For Sweden, however, reports of clinical trials of synonym preparations—that is, drugs including the same active substance(s) as drugs already registered (five preparations)—were excluded, as were short summaries of 111 controlled trials because of lack of time and some reports because they could not be found. Trials were defined as controlled when as well as a group receiving the new drug another group receiving other treatment or no treatment was studied. Trials in which patients received first one treatment and then another were defined as controlled. Trials with only vague comparisons with previous treatments were defined as uncontrolled. For uncontrolled trials I collected information about only the type of report, the number of patients treated, and how adverse effects were presented. A report was defined as published if it had appeared in or been accepted for a journal or book, or was a report of a meeting. A controlled trial was defined as good if the technical design was likely to give clear information on the efficacy of a drug: this was determined by considering several criteria. If the method of allocating patients and controls was biased or not given then the trial was defined as poor. If more than 20% of the subjects dropped out of a trial or if the report did not indicate the critical features of design it was defined as poor.

Statistical differences between mean values were determined by the two-sample t test, and between proportions by the method of Armitage.[3]

Results

QUANTITY OF CLINICAL TRIALS

Table I shows the number of reports of clinical trials included in the applications. More trials were included in applications made in 1974 and 1975 than in earlier years; and there were more trials in Sweden than Finland and more for psychotropic than non-psychotropic drugs. When only applications for new single drugs were analysed the mean number of trials included with each application was higher. Between 9% and 19% of the trials were considered to be good. The greatest number of trials included in an application was 112—for a minor tranquilliser submitted in Sweden in 1965; the same application also contained the most controlled trials (44).

Table II shows the numbers of patients estimated to have been used in the trials. Between 25% and 43% of the patients were used in controlled trials, and between 5% and 19% in good trials. The mean number of patients used was higher in uncontrolled than controlled trials; and the mean number used in trials included with one application varied from a few hundred to several hundreds, although most trials were small and rarely used more than 100 patients.

In Sweden and Finland the licensing authorities do not require all reports of clinical trials carried out with the drug to be submitted. I do not know how the manufacturer decides which trials shall be included, but, for example, one application submitted in Sweden in 1965 listed several hundred published trials and yet had only 82 reports attached. For the 13 drugs submitted in both Finland and Sweden only 74 (41%) of the 181 controlled and 88 (28%) of the 314 uncontrolled trials were included in both applications, the rest being included in only one.

COMPARISONS OF PUBLISHED AND UNPUBLISHED TRIALS

Reports of many trials, both controlled and uncontrolled, were not published. In Finland the proportion of controlled trials that were not published increased with time: for psychotropic drugs 15% of the trials were unpublished in 1965, 17% in 1970, and 41% in 1974 and 1975. The trend was different in Sweden (table III).

Table IV compares published and unpublished trials in 1974 and 1975 (the pattern was similar in other years). Unpublished trials of psychotropic drugs included control groups about as often as published trials, and gave information on adverse effects more often than published trials. There was no significant difference between the numbers of good trials published and unpublished. Forty-seven per cent of the patients used in controlled trials of psychotropic drugs in Finland and 39% of those in Sweden were reported on in unpublished reports.

Unpublished reports more often contained information on how patients were selected and which patients were excluded than published reports. Unpublished reports of trials of psychotropic drugs also more often specified when and why patients were excluded during the study. This was not so, however, for unpublished reports of trials of non-psychotropic drugs.

TABLE I—*Number and types of clinical trials included in applications to licensing authorities*

	Psychotropic drugs				Non-psychotropic drugs, 1974 and 1975, Finland
	1974 and 1975		All years*		
	Finland	Sweden	Finland	Sweden	
All drugs:					
No of applications	29	9	100	32	21
Mean No of trials/application	18·0	26·4	8·7	23·1	8·9
Percentage of controlled trials	45	45	39	30	43
Percentage of good trials	15	19	11	9	11
New single drugs†:					
No of applications	11	7	26	19	8
Mean No of trials/application	33·7	33·5	22·9	31·5	18·6

*Years studied were 1965, 1970, 1974, and 1975.
†Drugs containing only one active substance.

TABLE II—*Estimated* numbers of patients used in different types of clinical trials included in applications to licensing authorities*

	Psychotropic drugs				Non-psychotropic drugs, 1974 and 1975, Finland
	1974 and 1975		All years†		
	Finland	Sweden	Finland	Sweden	
Total No of patients	40 807	14 551	71 641	53 147	10 218
No (%) of patients in controlled trials	17 139 (42)	6257 (43)	23 642 (33)	14 881 (28)	2555 (25)
No (%) of patients in "good" trials	7753 (19)	2619 (18)	9313 (13)	3720 (7)	511 (5)
Mean No of patients/trial in:					
Controlled trials‡	73	58	70	65	37
Uncontrolled trials	83	64	91	75	66
Percentage of trials containing more than 100 patients:					
Controlled trials	4	9	5	10	5
Uncontrolled trials	19	13	23	16	9
Mean No of patients/application	1407	1617	716	1661	487

*When reports of trials contained no information about the numbers of patients studied the mean number of patients studied in the other trials was used to estimate total numbers.
†Years studied were 1965, 1970, 1974, and 1975.
‡Included patients in both control and study groups.

TABLE III—*Publishing status of controlled trials included in applications to licensing authorities. (Figures are numbers (%) of trials)*

	Psychotropic drugs				Non-psychotropic drugs, 1974 and 1975, Finland
	1974 and 1975		All years*		
	Finland	Sweden	Finland	Sweden	
No of trials	234	108	341	225	69
Published in journal	115 (49)	59 (55)	177 (52)	88 (39)	30 (43)
Published elsewhere	9 (4)	2 (2)	24 (7)	16 (7)	
Not published	96 (41)	42 (39)	116 (34)	99 (44)	24 (35)
Only summary available	14 (6)	4 (4)	24 (7)	23 (10)	15 (22)

*Years studied were 1965, 1970, 1974, and 1975.

TABLE IV—*Comparison of published and unpublished reports of clinical trials (excluding those for which only summaries were given) included in applications to licensing authorities in 1974 and 1975*

	Psychotropic drugs				Non-psychotropic drugs, Finland	
	Finland		Sweden			
	Published	Unpublished	Published	Unpublished	Published	Unpublished
% of trials that were controlled	47	52	48	45	47*	26*
% of controlled trials that were "good"	35	37	48	36	23	46
% of controlled trials giving information on adverse effects	56*	77*	73	83	43*	83*
Mean No of patients in controlled trials†	69	81	60	56	45*	23*
Mean No of patients in uncontrolled trials	97	70	59	78	78	58

*Difference significant at 5% level.
†Includes patients in both control and study groups.

TABLE V—*Numbers (%) of controlled trials for which information on adverse effects was available in reports included in applications to licensing authorities*

	Psychotropic drugs				Non-psychotropic drugs, 1974 and 1975, Finland
	1974 and 1975		All years*		
	Finland	Sweden	Finland	Sweden	
No of trials	234	108	341	225	69
Adverse effects not mentioned	37 (16)	9 (8)	58 (17)	29 (13)	14 (20)
No adverse effects found	7 (3)	1 (1)	14 (4)	9 (4)	7 (10)
Indefinite statement only	33 (14)	10 (9)	51 (15)	20 (9)	9 (13)
Number of adverse effects given	94 (40)	59 (55)	143 (42)	122 (54)	30 (44
Number of adverse effects related to size of group at risk	56 (24)	25 (23)	68 (20)	38 (17)	9 (13)
No information	7 (3)	4 (4)		5 (2)	

*Years studied were 1965, 1970, 1974, and 1975.

Unpublished trials were often carried out in a standard manner: the drug company produced a study design and offered it to several doctors who then gathered data. The drug-company workers prepared the report, and sometimes both they and the doctors appeared as authors; but if the report was published usually only the doctors appeared as authors.

INFORMATION ON ADVERSE EFFECTS

Table V shows that most reports of controlled trials contained some information on the adverse effects of the drugs. Most reports of uncontrolled trials also contained such information. Normally, just a list of the number of adverse effects or the number of patients affected was given, and in fewer than a quarter of the trials was the number of adverse effects related to the number of patients at risk.

Many reports did not specify how the adverse effects were defined or determined. For example, I studied how often the reports included results of laboratory tests on blood and of liver and kidney function, which might show adverse effects. In controlled trials of psychotropic drugs at least one test was carried out in 15% of trials in Finland in 1965, and in 37% in 1974 and 1975 (in Sweden the proportions were 8% in 1965 and 65% in 1974 and 1975).

Often the adverse effects were not mentioned in the conclusions of reports when the actual value of the drug was being assessed. This stems in part from the failure to relate the number of adverse effects to the number of patients at risk.

Most of the trials were designed to study the short-term efficacy of the drug and therefore were not suitable for studying adverse effects: few patients were used, the duration of treatment was short, and there was no follow-up. Pooling information from different studies might have provided valuable information, and this was sometimes done—more often in 1974 and 1975 than earlier years, and more often in Sweden than Finland. The pooling was almost invariably done by the manufacturer.

Discussion

This study shows that applications for licences for new drugs submitted to Finnish and Swedish authorities contain the results of many clinical trials, and yet many of the reports of these trials are unpublished. The secrecy of these data included in applications has been much debated in the United States. A Department of Health review panel[4] has produced a list of drawbacks to the secret system: it deprives the Food and Drug Administration (FDA; the licensing authority in the United States) of outside criticism, detracts from the scientific environment at the FDA, forces pharmaceutical companies wastefully to duplicate work, and interferes with the free exchange of scientific knowledge. An American public-interest group, the Environmental Defence Fund,[5] has listed further advantages that might result from disclosing the test data: the testing procedure might be improved; the FDA would have to explain and defend its decisions; and the influence of drug companies on the FDA might be reduced. The secrecy was apparently created to protect the interests of the drug companies, to encourage more research, to ensure that honest information was submitted to the FDA, and to protect the FDA from criticism. The review panel recommended that the data should not be kept secret, and new laws have been proposed to this effect.

The results of this study support disclosure by showing that a considerable amount of valuable, unpublished data is on the files of the Finnish and Swedish licensing authorities. The quality of this unpublished material seems to be as good as that of the published data. The results also suggest that not all of the data available on some drugs are included in applications submitted in Sweden and Finland; therefore, in countries

where the licensing authorities require more complete documentation even more information may be undisclosed.

Much of the information on adverse effects was of poor quality, for two reasons: the reports did not say how the adverse effects were defined and determined; and the incidence of adverse effects was often not calculated, nor was it related to the efficacy of the drug. Nevertheless, most reports contained some information on adverse effects, and possibly a skilled epidemiologist might be able to make good use of this. The unpublished reports contained more information on adverse effects than the published reports.

The results of this study also raise questions about the waste of clinical and research resources used in the sizable proportion of trials whose design made it unlikely that they would supply valuable information about the efficacy of the drug. This waste is deplorable when there is such a need for careful evaluation not only of new drugs but also of drugs already in use.

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General Practice Observed

Family trends in psychotropic and antibiotic prescribing in general practice

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Summary and conclusions

A ten-year retrospective study of the consultations of 50 families with a city general practice was used to test the hypothesis that mothers who receive an excess of psychotropic drugs have children who receive an excess of antibiotics for episodes of acute respiratory illness. The children of the 10 mothers classed as high psychotropic users were seen twice as often with acute respiratory illness and received twice as many antibiotics as the children of the mothers who had received no psychotropic medication. The association between high psychotropic and high antibiotic use was not linked in time, and indeed the time of highest antibiotic use coincided with the time when the mother received fewest psychotropic prescriptions.

It is suggested that at many of these consultations the mother rather than the child should have been treated as the patient.

The prescribing of drugs in general practice is rightly regarded as a fundamentally important field for research work. Apart from the commonly discussed issues that include, for example, cost, quantity, and the risks of side effects and of interactions, many less tangible issues merit study. In particular the frequency with which general practice consultations result in a prescription (about two out of three consultations[1-3]), the high expectations of patients (both real and assumed[4]) that they will receive drugs, and the high (but variable) degree with which different doctors respond to these expectations are all factors which suggest that important influences in prescribing other than those of the presenting illness remain to be identified.

The most commonly prescribed group of drugs are the psychotropic drugs—one-sixth of all prescriptions[5]—and much has been written on their use.[6 7] When repeat prescriptions are excluded antibiotics become the drugs most commonly prescribed. It is widely accepted that—rightly or wrongly—antibiotics are often prescribed for reasons other than to reverse apparently relevant pathology, and published work has discussed some of these.[8 9] We examine a further hypothesis relating to the use of both psychotropic drugs and antibiotics—namely, that children who receive an excess of antibiotics for episodes of acute respiratory illness belong to mothers who receive an excess of psychotropic drugs. The work was mounted in the belief that demonstration of such a trend would reaffirm the importance of non-physical determinants of prescribing for physical illness in general practice, and show the degree to which psychological or social aspects of illness within one patient (or within his family or his environment) can overlap with the physical symptoms and signs to affect the making of diagnoses and decisions on management.

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