Hospital Topics

Drug-induced Blood Dyscrasias in Sweden

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Summary

Cases of drug-induced aplastic anaemia, haemolytic anaemia, thrombocytopenia, and agranulocytosis reported to the Swedish Adverse Drug Reaction Committee during the five-year period 1966-70 have been analysed and compared with cases of the same cytopenias from "all" causes. Oral diuretics were a dominant cause of drug-induced thrombocytopenia, methyldopa of haemolytic anaemia, and oxyphenbutazone of aplastic anaemia. Computer systems should help such studies, particularly in showing a changing pattern of complications and causes.

Introduction

Drug-induced blood abnormalities are becoming a serious problem throughout the world. Circumstances make it difficult—in many countries virtually impossible—to estimate the frequency of such complications in a given community. In Sweden several factors favour studies on drug-induced conditions. Firstly, an Adverse Drug Reaction Committee has been in existence since late 1965; secondly, since 1964 the diagnoses of all patients discharged from hospitals in the Uppsala region have been recorded using data processing equipment;[1] thirdly, the sales of all drugs to a sample of patients in one part of the Uppsala region have been recorded since early 1968;[2] and, finally, figures are available for the total sale of individual drugs in Sweden. Thus it is possible to find not only all patients with a given diagnosis but also cases of drug-induced disorders and to relate these to a well defined population and, to some extent, also to the sale and consumption of drugs.

We present here an analysis of four studies of drug-induced aplastic anaemia, haemolytic anaemia, agranulocytosis, and thrombocytopenia carried out during a five-year period. These studies have been reported in detail elsewhere.[3-9]

Methods

ALL BLOOD DYSCRASIAS

Data on all patients discharged from hospital diagnosed as suffering from any of the four blood dyscrasias—those in which no drug cause was suspected as well as those known to be drug-induced—were collected over the five years 1964-8 in the Uppsala health care region. The identity number of the patient (in Sweden each citizen has a personal "birth number"), the diagnosis (in I.C.D. code), the hospital, and the department of the hospital from which the patient was discharged were ascertained from the computer data bank. Complete medical records of each patient were then obtained by courtesy of the head physician of each hospital department. In this paper data from this source are referred to as "all blood dyscrasias" and are compared with data on drug-induced blood dyscrasias.

As all our studies were retrospective and based on medical records it was not possible to apply the diagnostic criteria too rigidly. For every patient, however, the diagnosis at discharge was critically reviewed. This resulted in the rejection of several cases—for example, those that had erroneously been given the specific diagnosis and all equivocal ones. Thus for all patients included the diagnosis had satisfied L.E.B. (an experienced internist and clinical haematologist). Some of the criteria used were: *thrombocytopenia*—platelet count below 100,000/mm^3 regardless of clinical symptoms; *acquired haemolytic anaemia*—overt anaemia with multiple signs of increased haemoglobin breakdown (high bilirubin, high serum iron, low haptoglobin, etc.) with or without positive Coombs test result; *aplastic anaemia*—pancytopenia without reference to the relative cellularity of the bone marrow (mean values on admission: haemoglobin 7·0 g/100 ml, W.B.C. 2,400/mm^3, platelets 55,000/mm^3); and *agranulocytosis*—no fixed border value, the peripheral blood values on admission varying from 0 to 180 cells/mm.^{3} Bone marrow samples had been taken in most cases, but since they had been evaluated by many different persons the written reports were of varying quality. Thus though the bone marrow findings contributed to the diagnosis in many instances it was not possible to draw any general conclusions about them.

DRUG-INDUCED BLOOD DYSCRASIAS

Data on all patients in the whole of Sweden for whom full medical records were available and who had been referred to the Swedish Adverse Drug Reaction Committee during the years 1966-70 inclusive as suffering from drug-induced blood dyscrasias were examined. These data were reported previously[3-9] and the selection of patients has been described.

The causal relationship between a drug and a reported reaction is evaluated by a working party (three medical officers) of the Swedish Adverse Drug Reaction Committee, and in doubtful or severe cases also by the Committee itself (11 members). Patients regarded as having *drug-induced disease* were classified according to the following: (*a*) causal relationship *probable* (provocation test result positive, adverse reaction disappeared when medication stopped, adverse reaction resembled other cases reported to the Committee or found in the literature), and (*b*) causal relationship *not excluded* (criteria under (*a*) not fulfilled, possibility of several drugs used concomitantly, provocation test not possible, etc.).

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INDIVIDUAL DRUG CONSUMPTION

Since early in 1968 all drug purchases made by a section of the population of the City of Östersund, Uppsala, have been recorded on a computer. Östersund has a population of 50,000, and all subjects born on two chosen days of the month were selected, thus corresponding to 1/15 of the total. Age and sex were ascertained by means of their identification number. Data included here are for the period March 1968 to February 1969.

TOTAL DRUG SALES

Swedish sales figures for all drugs are available through Drug Statistics Limited, a joint organization of the pharmaceutical industries, national as well as international.

COMPARISONS MADE

Data on all patients diagnosed as suffering from blood dyscrasias were collected from the Uppsala region of Sweden and compared with data on patients with drug-induced blood dyscrasias from the whole of Sweden. The periods for collection of these data differed by two years owing to the delay in getting information on "all blood dyscrasias" through official channels. To compare the data from these two sources two assumptions were made: (1) that the Uppsala region is representative of Sweden as a whole (the Uppsala health care region reaches through the middle of Sweden (fig. 1) and has 1·2 million inhabitants—15% of the total Swedish population—the composition of the population in the region with regard to age and sex is identical with that of the country as a whole); (2) that no *major* changes regarding drug consumption had taken place in Sweden during the years of the two studies.

FIG. 1—Extent of Uppsala health care region.

Results

As regards age-related incidence (fig. 2), aplastic anaemia and agranulocytosis followed almost identical curves, with a low incidence up to the age of 40 and then a moderate rise. Thrombocytopenia was much more common and had a higher incidence in the younger age groups. Haemolytic anaemia was more common than aplastic anaemia and agranulocytosis but not as common as thrombocytopenia.

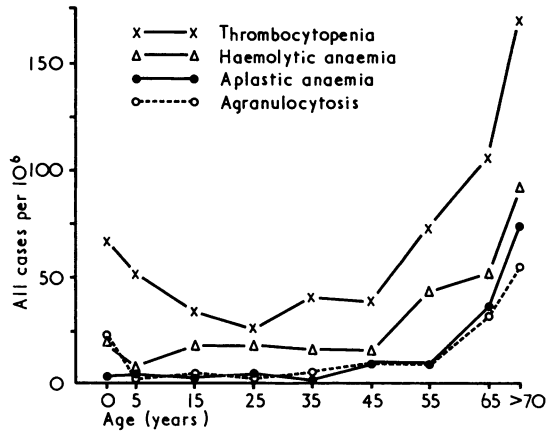

FIG. 2—Age-related incidence of *all cases* of aplastic anaemia, acquired haemolytic anaemia, thrombocytopenia, and agranulocytosis occurring in Uppsala region during 5-year period (1964-8). Curves represent yearly incidence.

The age-related incidence of the drug-induced blood dyscrasias in the whole of Sweden is shown in fig. 3. The incidence for all the cytopenias is seen to be low during childhood and adolescence but increases with age. This effect is seen least with aplastic anaemia, thrombocytopenia and agranulocytosis showing the biggest increase with age.

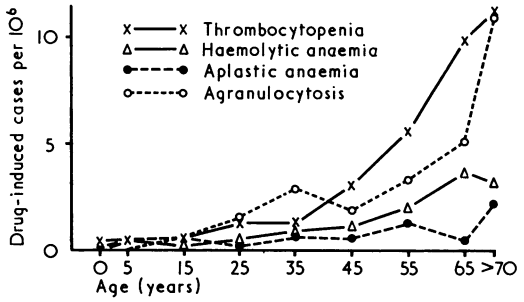

FIG. 3—Age-related incidence of *drug-induced* cases of aplastic anaemia, haemolytic anaemia, thrombocytopenia, and agranulocytosis reported to Swedish Adverse Drug Reaction Committee from all of Sweden during 5-year period 1966-70.

The incidence of all blood dyscrasias in the Uppsala region and the incidence of blood dyscrasias reported to be due to drugs in the whole of Sweden are shown in table I. Figs. 2 and 3 show that incidence could be related to age, and table II shows estimates of the proportion of the various blood dyscrasias

TABLE I—*Yearly Incidence of "All" and of "Drug-induced" Blood Dyscrasias of Various Cytopenias per 10⁶ Population*

	All Blood Dyscrasias	Drug-induced Dyscrasia	Drug-induced Dyscrasias as % of All Cases
Aplastic anaemia	13·2	0·7	5
Agranulocytosis	12·8	2·5	19
Thrombocytopenia	59·0	3·1	5
Acquired haemolytic anaemia	26·6	1·1	4

TABLE II—*Estimates of Drug-induced Blood Dyscrasias as a Percentage of all Dyscrasias*

Age in Years	Agranulocytosis	Aplastic Anaemia	Thrombocytopenia	Haemolytic Anaemia
≤4	—	—	0·5	—
5-24	6·7	11·0	1·0	1·6
25-44	53·9	11·8	3·8	3·0
45-64	24·6	9·4	8·6	4·3
≥65	18·6	2·7	7·4	3·4
Average	19·3	5·3	5·3	4·1
Average multiplied by 3 (see text)	58	16	16	12

which were due to drugs in patients of different ages. Only a small proportion of the cases of haemolytic anaemia (4%) were caused by drugs and there was no significant change with age. Aplastic anaemia and thrombocytopenia were caused by drugs in 5% of all the cases. For aplastic anaemia the proportion of drug-induced cases went down and for thrombocytopenia went up with increasing age. Agranulocytosis had the highest average figure (19%) for drug-induction, and this rose sharply with age.

The "drug-induced" groups of patients differed in age and sex composition from the "all blood dyscrasias" patients (tables III and IV). The patients with drug-induced thrombocytopenia, haemolytic anaemia, and agranulocytosis were older than those with drug-induced aplastic anaemia. All the "drug-induced" groups contained more women than did the "all blood dyscrasias" groups.

Mortality varied widely (table V). Drug-induced thrombocytopenia had the best prognosis with only a 1% mortality, followed by drug-induced haemolytic anaemia with a 4% mortality. The highest figures were found with agranulocytosis (30%) and aplastic anaemia (66%).

TABLE III—*Percentage of Patients over 45 Years of Age with Blood Dyscrasias*

	All Blood Dyscrasias	Drug-induced Cases
Thrombocytopenia	57	85
Aplastic anaemia	82	68
Haemolytic anaemia	63	78
Agranulocytosis	71	75
Population of City of Östersund	39	
Total population of Sweden	40	
All drug consumers (City of Östersund)	49	

TABLE IV—*Sex Ratio of Patients with Blood Dyscrasias*

	All Cases		Drug-induced Cases	
	% Women	Women/Men Ratio	% Women	Women/Men Ratio
Thrombocytopenia	62	1·6:1	72	2·6:1
Aplastic anaemia	50	1:1	57	1·3:1
Haemolytic anaemia	62	1·6:1	84	5·3:1
Agranulocytosis	72	2·6:1	74	2·8:1
Mean			73	2·7:1

DRUGS CAUSING BLOOD DYSCRASIAS

The drugs causing the individual cytopenias are listed in table V, together with the number of deaths in each category. Oral diuretics and quinine/quinidine are the drugs that most commonly cause thrombocytopenia. Butazones (oxyphenbutazone and phenylbutazone) and chloramphenicol are the most common causes of aplastic anaemia, methyldopa and sulphonamides of haemolytic anaemia, and dipyrone (Novalgin) and antithyroid drugs of agranulocytosis. Drugs that appear on more than one list are shown in table VI.

TABLE VI—*Drugs appearing on more than One List causing more than a Single Reported Case of the Individual Cytopenias. Figures indicate Position of Drug on the respective List in Table V*

	Thrombocytopenia	Aplastic Anaemia	Haemolytic Anaemia	Agranulocytosis
Phenylbutazone	3	3		5
Oxyphenbutazone	8	1		6
Carbimazole	5			2
Sulphonamides	9	4	2	3

The numbers of consumers in the City of Östersund of the four drugs that most frequently caused cytopenias during the year 1968-9 are shown in fig. 4 as a percentage of the total population in the area. There was a remarkable increase with age in the consumption of oral diuretics not found with the other drugs studied. The risk of a specific cytopenia from the use of an individual drug was calculated from the number of drug consumers in Östersund and from the number of reported adverse reactions for the whole country. The results are given in table VII.

The relative change in the total sale of some individual drugs in Sweden during the study period is shown in fig. 5. The total sales went up for most drugs, in some instances very markedly

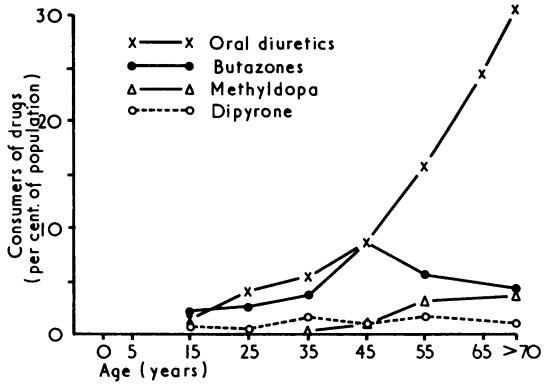

FIG. 4—Drug-consumers in Östersund area as percentage of total population in various age groups.

TABLE V—*Drugs causing Cytopenia of Various Types*

Thrombocytopenia			Aplastic Anaemia			Haemolytic Anaemia			Agranulocytosis		
Drug	No. of Cases	Deaths	Drug	No. of Cases	Deaths	Drug	No. of Cases	Deaths	Drug	No. of Cases	Deaths
Oral diuretics	52		Oxyphenbutazone	10	5	Methyldopa	21	2	Dipyrone	27	7
Quinine/quinidine	26		Chloramphenicol	5	4	Sulphonamides	10		Antithyroid drugs	16	3
Phenylbutazone	7	1	Phenylbutazone	4	2	Dapsone	3		(methimazole 7,		
Indomethacin	6		Sulphonamides	2	1	Miscellaneous	11		thiouracil 5,		
Carbimazole	4		Miscellaneous	8	7				carbimazole 4)		
Phenytoin	3								Sulphonamides	16	4
Nitrofurantoin	3								Phenothiazines	7	3
Oxyphenbutazone	2								Phenylbutazone	5	2
Sulphonamides	2								Oxyphenbutazone	3	1
Miscellaneous	29	1							Procainamide	2	1
									Sulphonylurea	2	
									Miscellaneous	16	7
Total	134	2 (1%)	Total	29	19 (66%)	Total	45	2 (4%)	Total	94	28 (30%)

TABLE VII—*Calculated Risk of Cytopenia from Various Drugs*

Type of Cytopenia	Drug	Calculated Risk	
		From Reported Numbers*	From Estimated Numbers*
Thrombocytopenia ..	Oral diuretics (thiazides, frusemide, chlorthalidone, clopamide)	1:47,000	1:15,000
Aplastic anaemia ..	Butazone (phenylbutazone, oxyphenbutazone, mofebutazone)	1:99,000	1:33,000
	Chloramphenicol	1:19,000	1:6,000
Haemolytic anaemia	Methyldopa	1:18,000	1:6,000
Agranulocytosis ..	Dipyrone	1:10,000	1:3,000

*"Reported numbers" refer to our findings. "Estimated numbers" refer to estimations, based on the reporting frequencies, such as they appear from table VIII. Thus the latter figures are approximately three times as high as the former.

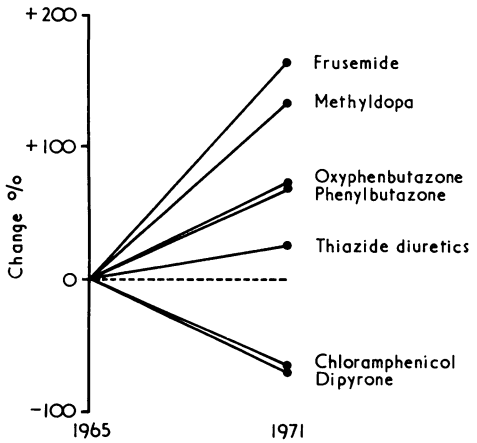

FIG. 5—Relative change in Swedish sales figures for individual drugs during 1965-71.

during the study period. For chloramphenicol and dipyrone, however, a decrease was noted (falls of 68% and 66% respectively). The effects of warnings issued by the Swedish Adverse Drug Reaction Committee is illustrated in figs. 6 and 7. Fig. 6

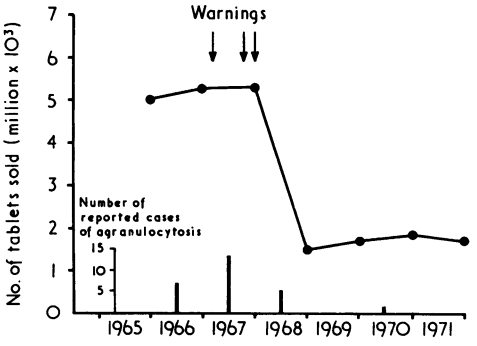

FIG. 6—Reduction in sale of drugs containing dipyrone after three warnings (arrowed) during 1967 from Swedish Adverse Drug Reaction Committee. Number of patients with dipyrone-induced agranulocytosis reported during years 1966-70 are indicated at bottom of chart.

shows the marked drop in the nation-wide sale of drugs containing dipyrone after three warnings during 1967 (February, September, and December). The number of reported patients with dipyrone-induced agranulocytosis is also included in fig. 6. Fig. 7 shows the less spectacular but noticeable effect of one warning against the indiscriminate use of chloramphenicol issued in May 1968.

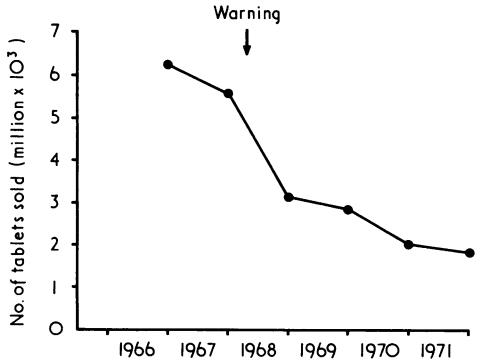

FIG. 7—Reduction in sale of chloramphenicol during 1960. Arrow indicates time of warning against indiscriminate use issued by Swedish Adverse Drug Reaction Committee.

Discussion

Adverse reaction to drugs is a growing problem the world over. In Sweden haematological complications account for about 10% of all reports to the Adverse Drug Reaction Committee. Four separate studies[3 4 6 9] have shown that drug-induced cytopenias in Sweden are reported with a frequency of 25-34% (mean 31%) of the total number of cases that one is able to find through a perusal of *all* patient records (table VIII). The figures for drug-induced cytopenias reported to the Committee should thus be multiplied by 3 to give the true frequency of drug-induced blood dyscrasias, and the estimated proportion of all dyscrasias which are drug-induced shown in table VIII is likely to be an under-estimate.

TABLE VIII—*Reporting Frequency of Drug-induced Blood Dyscrasias*

	Percentage of All Cases
Thrombocytopenia	33
Aplastic anaemia	34
Haemolytic anaemia	25
Agranulocytosis	31
Average	31

The risk figures given in table VII were calculated from comparatively small numbers of drug consumers. The population basis for the figures is about 0·6% of the Swedish population. Nevertheless, the figures correspond well with those from other parts of the world. Worlledge *et al.*[10] found identical figures for the risk of autoimmune haemolytic anaemia from methyldopa therapy (0·02%, corresponding to 1:6,000). Wallerstein *et al.*[11] found the risk of aplastic anaemia from the use of chloramphenicol to be 1:25,000-1:41,000—our figures are 1:6,000-1:19,000. Both Wallerstein's and our figures are higher than those previously reported. Wallerstein *et al.* in the same study analysed the risks of aplastic anaemia from the use of butazones and found the figure for oxyphenbutazone alone to be 1:124,000—our figures for phenylbutazone and oxyphenbutazone together are 1:33,000-1:99,000.

More women than men suffer haematological drug reactions. In Sweden the female to male ratio is 1:1. A recent study[2] showed that the ratio for total drug consumption in a Swedish county was 1·3:1, and for analgesic drug consumption 1·5:1. The ratio among the cytopenias studied varied from a 1·3:1 for aplastic anaemia to 5·3:1 for drug-induced haemolytic anaemia, the mean being 2·7:1. The difference between the sexes is apparent also when "all blood dyscrasias" are compared with drug-induced cases—the latter contained a significantly higher proportion of women in the thrombocytopenia and haemolytic anaemia groups (table IV).

Age is also a factor. More drug-induced cases were found in

the higher age groups (table III), the difference being especially marked for drug-induced thrombocytopenia. In contrast, patients with drug-induced aplastic anaemia were younger than those in the "all blood dyscrasias" category. Idiopathic aplastic anaemia is a disease of unknown aetiology, often terminating the life of an old person.

The differences with regard to age and sex between "all blood dyscrasias" and drug-induced cases are greatest for thrombocytopenia and smallest in agranulocytosis. This implies that in thrombocytopenia only a small proportion of cases are drug-induced, whereas in agranulocytosis most of the cases are, in fact, drug-induced. Such an interpretation is compatible with the figures given in table II.

It is important to follow the pattern of drug-induced complications and to be aware of the dangers that are involved in the prescribing of drugs. The pattern changes gradually. In 1962 Erslev and Wintrobe[12] found that chloramphenicol was the drug most often associated with pancytopenia, antibacterial sulphonamides with thrombocytopenia, and phenothiazines with leucopenia. In our study (table V) the findings are quite different. We now find—in Sweden—that oxyphenbutazone is the drug that most often causes aplastic anaemia, that dipyrone is the most common cause of agranulocytosis, and that oral diuretics together (thiazides, chlorthalidone, frusemide, and clopamide) by far outnumber all other drugs as the cause of drug-induced thrombocytopenia.

Some drugs are found on several lists (table VI). Dausset and Contu[13] pointed out that several drugs are known to be capable of inducing more than one type of cytopenia, though rarely in the same patient. Variations in the total sale of drugs (fig. 5) must also be taken into account when discussing drug complications. It is evident that the sale of many of the compounds that most frequently cause drug-induced cytopenias has gone up during the past five years, in some instances very markedly. Thus the sale of oral diuretics (all varieties) has gone up 69% and the sale of methyldopa 132%. As noted previously, the frequency of methyldopa-induced haemolytic anaemia seems to be increasing.[9] Two drugs show a decreasing sales curve, probably to a large extent due to the warnings issued by the Swedish Adverse Drug Reaction Committee. There has, for example, been a decrease in the number of patients with dipyrone-induced agranulocytosis.

The effects of warnings issued by the Swedish Adverse Drug Reaction Committee are illustrated in figs. 6 and 7. Such warnings are mailed to all physicians and published in the weekly issue of the journal of the Swedish Medical Association (*Läkartidningen*). The effect of the warning against dipyrone-containing preparations was remarkably effective. The effect of warning against the indiscriminate use of chloramphenicol was less spectacular, though quite noticeable. A downward trend in the sales figures was present before the warning, probably caused by the appearance of newer antibiotics.

Conclusions

It is evident that results of great importance have been derived from the comparison of data on all blood dyscrasias occurring in Uppsala with those of blood dyscrasias reported to the Swedish Adverse Drug Reaction Committee as due to drugs. Examples are, among others, the total dominance of oral diuretics as the cause of drug-induced thrombocytopenia and that of methyldopa with regard to drug-induced haemolytic anaemia.

Reports on "Intensive hospital monitoring of adverse reactions to drugs"[14] and on "Comprehensive drug surveillance"[15] have been published, emphasizing the necessity of finding better reporting systems for adverse drug reactions, the subject also of a recent W.H.O. report.[16] Our experiences in Sweden with a voluntary reporting system clearly indicate that this is not sufficient. We feel that the reporting of adverse drug reactions should be as mandatory as the reporting of a discharge diagnosis on all hospital records. Computer systems will definitely aid in our efforts to keep better track of what drugs do to our patients and could help physicians to report complications immediately and authorities to keep track of what is happening. Hospital computer systems allowing such integrated functions are being built and used in Sweden (the Danderyd system).[17] Furthermore, it is necessary to have up-to-date and accurate morbidity statistics—at present such figures from official sources become available only after a considerable delay, often a year or more.

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