

Identification of Adverse Drug Reactions by Evaluation of a Prescription Database, Demonstrated for “Risk of Bleeding”

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Summary

Objective: Information about adverse drug reactions plays an important role when assessing the benefit/risk profile of a drug. Identifying rare adverse drug reactions, however, is a difficult task. This paper illustrates the advantages of using a prescription database for this purpose.

Methods: The mediplus[®] database used in our analysis covered data from 320,644 outpatients observed between July 1999 and June 2002. The example of bleeding complications during intake of antidiabetic drugs is used to illustrate this approach. The comparison of cohorts and subgroups is nearly always a problem in surveys. For our analyses we considered a set of patients who had taken a selected medication for a certain period of time and compared the frequency of adverse events with those occurring when the same patients did not take this medication. Hence, the comparison with versus without a certain medication is based on the same set of patients as in a cross-over study.

Results: Our evaluations indicate that the rate of bleeding complications is low when taking any of the widely used antidiabetic drugs, glutamate modulators, cholinesterase inhibitors, calcium antagonists or the phyto-medicine Ginkgo biloba.

Conclusion: Basing the comparison of the rates of complications during periods with and without intake of a certain drug on the same set of patients may be a useful tool for assessing adverse drug reactions from data reported in prescription databases.

Keywords

Adverse event, adverse drug reaction, bleeding complication, survey, antidiabetic drugs, Ginkgo biloba, observational cross-over study

Methods Inf Med 2005; 44: 697–703

1. Introduction

In order to identify a previously unknown adverse reaction to a drug, two major problems must be solved. Firstly, an adverse drug reaction may be rare, but it is important to identify a rare adverse drug reaction if it is serious. Detection of rare adverse drug reactions is only possible if the drug is widely used over an extended period of time and with a sufficiently large number of prescriptions. Secondly, a specific event, e.g. headache, diarrhea, bleeding etc., may either be an adverse drug reaction or may be spontaneous, may be caused by a disease or may have another origin or reason. To identify an adverse drug reaction, control groups without exposure to the drug in question as well as statistical considerations are necessary.

The proof of a causal relationship between the occurrence of a complication and exposure to a drug is a difficult task. In 1966, Hill [1] already provided some useful criteria for assessing causality. When a medical problem newly appears or aggravates during the exposure to a treatment, this is called an adverse event (AE). In a randomized trial investigating a pharmacologically active drug versus a placebo, the situation is rather obvious: if a specific adverse event occurs significantly more often in the group with active medication than in the placebo group, this type of adverse event is considered to be caused by the drug under investigation, i.e., it is believed to be an adverse drug reaction (ADR) to the investigated medication. For this conclusion, we assume that the scrupulousness with which undesired events are observed and recorded is the same for the verum group and for the

placebo group. However, an unbiased assessment of AE causality can only be achieved when the treatment groups are completely masked and when a similar degree of watchfulness for adverse events in both treatment groups can be assumed. For example, anticoagulative treatment requires frequent monitoring of bleeding complications by measuring prothrombin time, particularly in the beginning. For this purpose patients undergoing active anticoagulative treatment are admitted to an outpatient clinic every two weeks for taking blood samples. This visit gives the patient the opportunity to report adverse events. However, when the patients from the placebo group are not called into the outpatient clinic at the same time intervals, they have less opportunity to report adverse events. Furthermore, patients who are aware that they are taking a newly prescribed medication that may cause bleeding complications can be assumed to be more attentive to such events than those without anticoagulative treatment, even when a particular event has actually not been caused by the drug. Thus, over-reporting in the group undergoing active medication and under-reporting in the placebo group might pretend an adverse drug reaction which actually does not exist.

As outlined in the following paragraphs, all study designs commonly used in medical research have serious problems identifying rare adverse drug reactions. As a consequence, new approaches are needed.

Controlled randomized trials investigate not only efficacy but also assess aspects of safety, especially adverse events and laboratory measures. The presence of a control

group and the good comparability of the treatment groups create very favorable conditions for distinguishing adverse drug reactions from adverse events not related to the investigational treatment. However, the limited sample sizes of controlled, randomized trials – usually several hundred subjects at the very most – are too small to recognize rare adverse drug reactions.

Cohort studies often have no second (reference) cohort at all, or the cohorts are not really comparable. For example, a cohort of women taking oral contraceptives and a cohort of women aged 16 to 50 who do not take oral contraceptives may differ in many aspects – e.g. lifestyle, health awareness, nutrition, physical activity, smoking – not only in just taking “the pill”.

Case control studies investigate only one specific disease or medical problem. Therefore, a special assumption, i.e., a precise hypothesis, is required to determine which disease or problem is assumed to be an adverse drug reaction. Furthermore, matching cases and controls as well as recall bias can be problematic.

Spontaneous reports on serious adverse events are often incomplete, are not systematically compiled, and may be extremely biased. Sometimes the assumption of an adverse drug reaction is a self-fulfilling prophecy: if it is publicized that drug ‘x’ may cause problem ‘y’, patients using ‘x’ are likely to be particularly attentive to problem ‘y’. If ‘y’ is observed it is reported as a ‘case’.

Retrospective evaluation of medical records often results in an initial hypothesis regarding an adverse drug reaction. The first obstacle to a well-done retrospective evaluation is the selection of relevant cases. Access to medical records is often only possible via patient identification. While computerized medical records often provide better and more specific access, problems remaining include missing information and lack of control.

Prospective surveys may be the most promising option for systematic screening of adverse drug reactions. However, surveys with appropriate variables and a sufficiently large sample size only become available in recent years.

None of these designs are powerful enough to identify rare adverse drug reactions. Hence, we will examine the utility of surveys for this purpose using the mediplus® database as an example.

Table 1 Patients and prescriptions covered by the excerpt of the mediplus® database used in the analyses

Age (years)	Females	Males	Total
< 35	pat = 13 484 yrs = 2.33 (0.78) med = 4.80 (7.16) exp = 52% (59%)	pat = 9 555 yrs = 2.29 (0.78) med = 4.14 (6.15) exp = 47% (60%)	pat = 23 039 yrs = 2.31 (0.78) med = 4.52 (6.77) exp = 50% (59%)
35 to < 50	pat = 30 515 yrs = 2.45 (0.72) med = 4.66 (9.49) exp = 83% (91%)	pat = 22 218 yrs = 2.38 (0.74) med = 4.01 (10.01) exp = 84% (99%)	pat = 52 733 yrs = 2.42 (0.73) med = 4.38 (9.76) exp = 84% (94%)
50 to < 65	pat = 49 396 yrs = 2.54 (0.69) med = 4.95 (8.17) exp = 144% (138%)	pat = 43 092 yrs = 2.51 (0.70) med = 4.67 (11.15) exp = 153% (148%)	pat = 92 488 yrs = 2.53 (0.69) med = 4.82 (9.68) exp = 148% (143%)
65 to < 80	pat = 57 437 yrs = 2.60 (0.68) med = 5.88 (9.43) exp = 218% (184%)	pat = 44 731 yrs = 2.60 (0.66) med = 5.44 (12.61) exp = 215% (182%)	pat = 102 168 yrs = 2.60 (0.67) med = 5.69 (10.94) exp = 217% (183%)
≥ 80	pat = 36 331 yrs = 2.59 (0.70) med = 6.37 (12.57) exp = 225% (193%)	pat = 13 729 yrs = 2.61 (0.68) med = 6.33 (19.77) exp = 220% (190%)	pat = 50 060 yrs = 2.59 (0.69) med = 6.36 (14.89) exp = 224% (192%)
Total	pat = 187 242 age = 62.9 (17.97) yrs = 2.53 (0.71) med = 5.45 (9.71) exp = 166% (167)	pat = 133 401 age = 60.4 (16.29) yrs = 2.51 (0.71) med = 4.95 (12.41) exp = 162% (165%)	pat = 320 644 age = 61.8 (17.33) yrs = 2.53 (0.71) med = 5.24 (10.92) exp = 164% (166%)

pat = Number of patients

age = Mean age in years

yrs = Mean observation time in years

med = Number of different medications per year

exp = Exposure time in % of observation time. In this table exposure to any medication is shown. If a patient took > 1 medication at the same time, the time of intake is counted for each medication. Hence, exposure time may exceed 100%. This way of calculating the time of exposure to medication is in accordance with version B in Table 3.

Numbers in parentheses are standard deviations.

Patient numbers in subgroups do not sum up to totals due to partly missing data for age or sex.

2. Methods

2.1 Database

IMS-Health is a commercial organization located in Frankfurt/Main, Germany. It provides a permanent survey of a representative panel of more than 1000 medical practices in Germany. The database includes more than 5 million outpatients and over 75 million prescriptions.

The mediplus® database is updated monthly and currently covers nearly 15 years. Further details on the database, panel selection, data collection and data quality can be found in [2]. The version of the database used for our evaluations includes demographic data as well as the diagnoses and prescriptions of 320,644 patients observed between 1999, July 1, and 2002, June 30. Table 1 provides information on the size of the database.

2.2 Bleedings as a Model Adverse Drug Reaction

A bleeding can be a serious issue. The patient can often diagnose it himself or herself. However, in most cases of bleeding a patient

will consult a physician. For these reasons we used bleeding as an example for adverse drug reactions to be investigated by use of a prescription database.

Bleeding complications were identified by the relevant ICD-10 codes (see Appendix 1). If several bleeding complications of the same type (criterion: same four-digit ICD-10 code) were documented within seven days, only the first complication was included in the evaluation.

It was not possible for us to assess the completeness of the *mediplus*[®] database. However, it seemed reasonable to assume that signs of bleeding were documented in a comparable manner during periods with and without a specific medication.

2.3 Antidementives as Model Drugs

In an aging population antidementia drugs are of specific interest. The most widely prescribed drugs of this type include glutamate modulators, cholinesterase inhibitors, calcium antagonists and herbal extracts from *Ginkgo biloba*. We investigated the bleeding risk of these drugs with and without the simultaneous intake of anticoagulative or antiplatelet medication.

Many herbal medications have a very long tradition and are often considered to be safer than chemically defined drugs. We are especially interested in herbal medicines. In our opinion they have to be investigated with the same rigorousness as chemically defined medications. *Ginkgo biloba* extract is produced from dried leaves of the *Ginkgo* tree. The clinical efficacy of the *Ginkgo biloba* special extract EGb 761[®] has been demonstrated in patients with impaired cerebral function or dementia as well as in other indications in numerous randomized, placebo-controlled, double-blind studies [3]. To avoid heterogeneity of results by combining data for different drugs or extracts, our analyses were restricted to EGb 761[®].

Tolerability of EGb 761[®] has been shown to be very good in clinical studies as well as during many years of use in hospitals and general practice. However, suspected involvement of *Ginkgo biloba* preparations in

Table 2 Prevalence of bleeding

	No. of patients	Years of observation	No. of bleedings	No. of bleedings per 100 years of observation
Females	187 242	474 629	12 393	2.61
Males	133 401	335 448	10 193	3.04
Age < 35 years	23 039	53 248	903	1.70
35 to < 50	52 733	127 532	2 759	2.16
50 to < 65	92 488	233 841	6 102	2.61
65 to < 80	102 168	265 418	8 836	3.33
≥ 80 years	50 060	129 787	3 984	3.07
Total	320 644	810 077	22 586	2.79

Prevalence of bleeding is based on all patients and the total observation period
Patient numbers in subgroups do not sum up to totals because of missing data for age or sex.

bleeding complications was expressed in several case reports published between 1997 and 2001 [4-9]. For most of the *Ginkgo biloba* preparations involved, origin and quality were unknown.

The duration of intake of an investigated medication was calculated on the basis of the date of prescription, the amount of medication prescribed, and the schedule of intake. In case of missing values, the modal value of the duration of intake for the respective medication was used. Exposure time was calculated as the sum of the duration of intake and a medication-specific latency period defined prior to evaluation (see Appendix 2).

2.4 Methods of Assessment

Our first approach was to calculate the prevalence of bleeding based on all 320,644 patients and the total observation period included in *mediplus*[®] (Table 2).

In a second approach we estimated the prevalence of bleeding during periods of treatment with any type of medication (Table 3). All patients included in the *mediplus*[®] database had at least one medication intake during the period of observation. Hence, all 320,644 patients were included in the table. However, we only evaluated time intervals (periods) during which an exposure to any medication existed.

Table 3 Prevalence of bleeding during medication intake

	No. of patients	Years of medication		No. of bleedings	No. of bleedings per 100 years of medication	
		version A	version B		version A	version B
Females	187 242	294 553	830 711	9 578	3.25	1.15
Males	133 401	204 432	574 804	7 950	3.89	1.38
Age < 35 years	23 039	16 384	26 401	422	2.58	1.60
35 to < 50	52 733	58 172	110 002	1 687	2.90	1.53
50 to < 65	92 488	147 453	363 916	4 475	3.03	1.23
65 to < 80	102 168	191 772	602 958	7 480	3.90	1.24
≥ 80 years	50 060	85 122	301 959	3 463	4.07	1.15
Total	320 644	498 986	1 405 516	17 528	3.51	1.24

All 320,644 patients represented in the *mediplus*[®] database took at least one medication. The prevalence of bleeding is based on all patients, but only periods with medication intake (any medication) are considered.
If a patient took more than one medication simultaneously, the years of medication are computed in two versions: In version A periods with multiple drug intake are counted once. In version B the duration of a period with multiple drug intake is counted for each drug and summed up. Example: If 3 medications were taken simultaneously over half a year, this is counted as half a year in version A and as 1.5 years of medication in version B.
During 62% of the observation time at least one medication was taken (498,986 years of medication (Table 3) within 810,077 years of observation (Table 2)).

Table 4 Prevalence of bleeding without medication intake

	No. of patients	Years without any medication	No. of bleedings	No. of bleedings per 100 years without medication
Females	164 036	180 076	2 815	1.56
Males	117 758	131 015	2 243	1.71
Age < 35 years	22 674	36 864	481	1.30
35 to < 50	50 683	69 360	1 072	1.55
50 to < 65	83 440	86 388	1 627	1.88
65 to < 80	83 421	73 646	1 356	1.84
≥ 80 years	41 424	44 665	521	1.17
Total	281 795	311 091	5 058	1.63

Out of the 320,644 patients of the mediplus® data base 281,795 patients (88%) had a period without any medication intake. In this table only periods without any medication intake are used for deriving the baseline prevalence of bleeding.

Table 5 Prevalence of bleeding for various antidementia drugs

	Years of medication	Years without medication	No. of bleedings	No. of bleedings per 100 years of medication per 100 years without medication	Relative risk for bleeding
Glutamate modulators, pat = 1 757					
yes	1 171		73	6.23	1.35
no	3 520		163	4.63	
Cholinesterase inhibitors, pat = 998					
yes	581		24	4.13	1.44
no	1 953		56	2.87	
Calcium antagonists, pat = 392					
yes	275		10	3.63	0.84
no	832		36	4.33	
Other chemically defined antidementia drugs, pat = 5 563					
yes	2 987		187	6.26	1.28
no	12 238		598	4.89	
Any Ginkgo preparation, pat = 13 093					
yes	10 547		319	3.02	0.96
no	25 130		793	3.16	
EGb 761®, pat = 9 794					
yes	7 696		235	3.05	0.99
no	18 765		576	3.07	
Any antidementia drug, pat = 20 087					
yes	15 250		601	3.94	1.05
no	39 154		1 470	3.75	

For a certain drug (e.g. EGb 761®) only those patients were included who took the drug for some time but had a period without this drug as well. Patients who never took the drug of interest (e.g. EGb 761®) were excluded. Furthermore, patients who took the drug of interest (e.g. EGb 761®) throughout the total period of observation were excluded as well. Consequently, for a certain drug the lines "yes" and "no" are based on the identical set of patients and denote "periods with intake of the drug" and "periods without intake of the drug".
pat = Number of patients

Some patients had periods in which they took two or more medications simultaneously. To account for this situation, two different computational methods were applied. In version A we counted such a period only once when calculating the exposure time, while in version B we counted such a period for each drug separately and summed up the exposure times for all drugs, which resulted in longer total exposure times.

To estimate the baseline risk, the prevalence of bleeding without any medication was determined. The mediplus® database contains no patients without medication intake during the entire observation period. We decided not to use controls from other data sources to avoid bias by lack of comparability to the patients represented in mediplus®. Therefore, we determined the required estimates from the same database by analyzing the prevalence of bleeding during the time intervals in which no drugs were taken. Thus we evaluated only (i) those 281,795 patients with at least one period without any medication, and (ii) we used only periods without any medication (Table 4). The cumulative period without any medication was a total of 311,091 years contributed by 281,795 patients, resulting in an average time of 1.1 years per patient.

When comparing the prevalence of bleeding with and without medication (Table 3 versus Table 4), we must keep in mind that these two tables are based on at least partly different sets of patients: Table 4 includes 281,795 patients while Table 3 includes 320,644 patients. During the time of observation the 38,849 patients excluded from Table 4 never had a period without any medication. The comparison of the prevalence of bleeding with (Table 3) and without medication (Table 4) might therefore be biased.

In order to obtain a more reliable comparison of the prevalence of bleeding with and without a certain drug, we used a third approach in which we included only those patients who took the selected drug for some time, but had a period without this drug as well. In Table 5 two estimates for the prevalence of bleeding are presented for six different medications: one estimate for periods during which a drug was taken and a second one for periods without intake of this

medication. Hence, these two estimates are based on an identical set of patients. The achieved comparability is much better than using different sources of data and adjusting for sex, age, body mass index etc., as often employed in epidemiological research. The use of an identical set of patients for the assessment of bleedings during periods with and without exposure justifies the computation of the relative risk of bleeding for the investigated medications.

Finally, we looked for drug interactions (Table 6). For a pair of drugs, e.g. EGb 761[®] and ASS, four different prevalence estimates for bleeding were obtained: One estimate for periods during which both drugs were taken, two estimates for periods in which only one of the two drugs was taken, and finally an estimate for periods when neither of the two drugs was used. According to the procedure used to calculate Table 5, all four prevalences in a subtable of Table 6 are based on the identical set of patients. Hence, in a subtable of Table 6 the data of only those patients could be used who had (i) a period during which they used both drugs, (ii) a period with only one of the drugs, (iii) a period with only the other drug, and finally (iv) a period with neither of the two drugs of interest. This procedure provides a base for intra-individual comparisons under different types of exposure. However, the numbers of patients where all four different schemes of drug intake were observed were rather small, even in a large database like mediplus[®].

3. Results

From Table 1 we can see that exposure to drugs (exp) is increasing much more by age than the number of different medications (med). We interpret that the older the patients are, the longer they take a medication.

Disregarding the distinction between periods with or without medication, the prevalence of bleeding for patients treated by physicians in practices was estimated to be 2.79 bleeding episodes per 100 years of observations (Table 2). The prevalence for the entire population is assumed to be lower since individuals not consulting a physician

Table 6
Prevalence of bleedings per 100 years with or without medication intake of EGb 761[®] and anticoagulative or antiplatelet medication

	EGb 761 [®]	
	yes	no
ASS	pat = 1 627	
yes	2.82	2.65
no	3.67	2.96
	rr = 0.86	
Phenprocoumon	pat = 193	
yes	9.05	6.81
no	8.92	4.61
	rr = 0.69	
Any anticoagulative or antiplatelet medication	pat = 1 903	
yes	3.22	3.16
no	4.38	3.53
	rr = 0.82	

The table includes patients with at least one simultaneous intake of EGb 761[®] and ASS, EGb 761[®] and phenprocoumon, or EGb 761[®] and another anticoagulative or antiplatelet medication.
Table 6 consists of 3 subtables, each of size 2 × 2. All four prevalences of each subtable are based on the identical patients. Example: The prevalence of 2.82 bleedings per 100 years of exposure for “EGb 761[®] = yes, ASS = yes” was computed from periods when the 1627 patients took both EGb 761[®] and ASS. The prevalence of 2.65 bleedings per 100 years of exposure for “EGb 761[®] = no, ASS = yes” was observed in the same 1627 patients, but from periods when the patients took ASS but no EGb 761[®]. The other two prevalences of the subtable were derived accordingly.
pat = Number of patients
rr = Ratio of relative risks (interaction) for simultaneous intake of EGb 761[®] and the specified anticoagulative or antiplatelet medication. An example, how rr is calculated, is given in Section 3.

in practice are not included in Table 2. On the other hand, hospitalized patients with a higher risk are also excluded from Table 2. The prevalence of bleeding during intake of any medication was estimated as 3.51 (Table 3) while it was 1.63 bleeding episodes per 100 years of observation (Table 4) when no medication was taken.

The prevalence of bleeding was higher for males than for females (Tables 2-4). It increased with age, except for patients aged 80 years and above (Table 2, Table 3 version A, Table 4). However, in Table 3, version B, the prevalence of bleeding decreased with age. We assume that the increasing use of medications in older patients is the reason for the decreasing prevalence when performing the computations according to method B.

In Table 5 we present the relative risk of bleeding for glutamate modulators, cholinesterase inhibitors, calcium antagonists, other chemically defined antidementia drugs, EGb 761[®] and for any antidementia drug. Among these, the cholinesterase inhibitors had the highest relative risk (1.44), while EGb 761[®] had a relative risk of less

than 1, indicating that there was no increased risk of bleeding.

Interactions are more difficult to estimate and to explain than primary effects. In Table 6 patients with at least one simultaneous intake of EGb 761[®] and ASS, phenprocoumon or another anticoagulative or antiplatelet medication were considered. The prevalences for bleeding ranged from 2.65 to 9.05 episodes per 100 years of observation. As a measure of interaction between EGb 761[®] and anticoagulative or antiplatelet medication we calculated the ratio (“rr” in Table 6) between the relative risk of bleeding complications under exposure to EGb 761[®] (with simultaneous intake of an anticoagulative or antiplatelet medication) and the relative risk during non-exposure to EGb 761[®]. While rr = 1.0 indicates no interaction of the two medications, a value of rr > 1.0 indicates a higher risk while rr < 1.0 indicates a lower risk during simultaneous exposure to EGb 761[®].

For illustration we consider the combination of EGb 761[®] and ASS as an ex-

ample (first subtable of Table 6): the baseline risk for bleeding (no EGb 761[®], no ASS) was 2.96 bleeding episodes per 100 years. Intake of ASS modified the risk by a factor of $2.65/2.96 = 0.90$. During periods with intake of EGb 761[®] the risk increased by a factor of $3.67/2.96 = 1.24$. With both

medications taken simultaneously we expect – if no interaction is present – a risk of $0.90 \times 1.24 = 1.11$ over the baseline. With the baseline value of 2.96 bleeding episodes we would therefore expect $1.11 \times 2.96 = 3.29$ bleeding episodes per 100 years during intake of both medications. Only 2.82

bleeding episodes per 100 years were observed, and therefore the risk of bleeding during intake of both EGb 761[®] and ASS was less than expected under the assumption of no interaction. The ratio (rr) is given by observed risk versus expected risk, i.e., $2.82/3.29 = 0.86$.

Appendix 1: ICD-10 Codes and Related Diagnostic Terms Considered to Be Bleeding Complications

D50.0	IRON DEFICIENCY ANAEMIA SECONDARY TO BLOOD LOSS (CHRONIC)	K27.0	PEPTIC ULCER, ACUTE WITH HAEMORRHAGE
D62	ACUTE POSTHAEMORRHAGIC ANAEMIA	K27.2	PEPTIC ULCER, ACUTE WITH BOTH HAEMORRHAGE AND PERFORATION
D65	DISSEMINATED INTRAVASCULAR COAGULATION [DEFIBRATION SYNDROME]	K27.4	PEPTIC ULCER, CHRONIC OR UNSPECIFIED WITH HAEMORRHAGE
D68.3	HAEMORRHAGIC DISORDER DUE TO CIRCULATING ANTICOAGULANTS	K28.0	GASTROJEJUNAL ULCER, ACUTE WITH HAEMORRHAGE
D68.9	COAGULATION DEFECT, UNSPECIFIED	K28.2	GASTROJEJUNAL ULCER, ACUTE WITH BOTH HAEMORRHAGE AND PERFORATION
D69.9	HAEMORRHAGIC CONDITION, UNSPECIFIED	K28.4	GASTROJEJUNAL ULCER, CHRONIC OR UNSPECIFIED WITH HAEMORRHAGE
H11.3	CONJUNCTIVAL HAEMORRHAGE	K29.0	ACUTE HAEMORRHAGIC GASTRITIS
H21.0	HYPHAEMA	K62.5	HAEMORRHAGE OF ANUS AND RECTUM
H31.3	CHOROIDAL HAEMORRHAGE AND RUPTURE	K66.1	HAEMOPERITONEUM
H35.6	RETINAL HAEMORRHAGE	K92.0	HAEMATEMESIS
H43.1	REOUS HAEMORRHAGE	K92.1	MELAENA
H92.2	OTORRHAGIA	K92.2	GASTROINTESTINAL HAEMORRHAGE, UNSPECIFIED
I31.2	HAEMOPERICARDIUM, NOT ELSEWHERE CLASSIFIED	M25.0	HAEMARTHROSIS
I60.0	SUBARACHNOID HAEMORRHAGE FROM CAROTID SIPHON AND BIFURCATION	N42.1	CONGESTION AND HAEMORRHAGE OF PROSTATE
I60.1	SUBARACHNOID HAEMORRHAGE FROM MIDDLE CEREBRAL ARTERY	N83.6	HAEMATOSALPINX
I60.2	SUBARACHNOID HAEMORRHAGE FROM ANTERIOR COMMUNICATING ARTERY	N83.7	HAEMATOMA OF BROAD LIGAMENT
I60.3	SUBARACHNOID HAEMORRHAGE FROM POSTERIOR COMMUNICATING ARTERY	N85.7	HAEMATOMETRA
I60.4	SUBARACHNOID HAEMORRHAGE FROM BASILAR ARTERY	N89.7	HAEMATOCOLPOS
I60.5	SUBARACHNOID HAEMORRHAGE FROM VERTEBRAL ARTERY	N92.1	EXCESSIVE AND FREQUENT MENSTRUATION WITH IRREGULAR CYCLE
I60.6	SUBARACHNOID HAEMORRHAGE FROM OTHER INTRACRANIAL ARTERIES	N92.2	EXCESSIVE MENSTRUATION AT PUBERTY
I60.7	SUBARACHNOID HAEMORRHAGE FROM INTRACRANIAL ARTERY, UNSPECIFIED	N92.3	OVULATION BLEEDING
I60.8	OTHER SUBARACHNOID HAEMORRHAGE	N92.4	EXCESSIVE BLEEDING IN THE PREMENOPAUSAL PERIOD
I60.9	SUBARACHNOID HAEMORRHAGE, UNSPECIFIED	N92.6	IRREGULAR MENSTRUATION, UNSPECIFIED
I61.0	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, SUBCORTICAL	N93.0	POSTCOITAL AND CONTACT BLEEDING
I61.1	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, CORTICAL	N93.8	OTHER SPECIFIED ABNORMAL UTERINE AND VAGINAL BLEEDING
I61.2	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, UNSPECIFIED	N93.9	ABNORMAL UTERINE AND VAGINAL BLEEDING, UNSPECIFIED
I61.3	INTRACEREBRAL HAEMORRHAGE IN BRAIN STEM	N95.0	POSTMENOPAUSAL BLEEDING
I61.4	INTRACEREBRAL HAEMORRHAGE IN CEREBELLUM	N95.3	STATES ASSOCIATED WITH ARTIFICIAL MENOPAUSE
I61.5	INTRACEREBRAL HAEMORRHAGE, INTRAVENTRICULAR	R04.0	EPISTAXIS
I61.6	INTRACEREBRAL HAEMORRHAGE, MULTIPLE LOCALIZED	R04.1	HAEMORRHAGE FROM THROAT
I61.8	OTHER INTRACEREBRAL HAEMORRHAGE	R04.8	HAEMORRHAGE FROM OTHER SITES IN RESPIRATORY PASSAGES
I61.9	INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED	R04.9	HAEMORRHAGE FROM RESPIRATORY PASSAGES, UNSPECIFIED
I62.0	SUBDURAL HAEMORRHAGE (ACUTE)(NONTRAUMATIC)	R23.3	SPONTANEOUS ECCHYMOSES
I62.1	NONTRAUMATIC EXTRADURAL HAEMORRHAGE	R 31	UNSPECIFIED HAEMATURIA
I62.9	INTRACRANIAL HAEMORRHAGE (NONTRAUMATIC), UNSPECIFIED	R58	HAEMORRHAGE, NOT ELSEWHERE CLASSIFIED
I85.0	OESOPHAGEAL VARICES WITH BLEEDING	S06.4	EPIDURAL HAEMORRHAGE
K25.0	GASTRIC ULCER, ACUTE WITH HAEMORRHAGE	S06.5	TRAUMATIC SUBDURAL HAEMORRHAGE
K25.2	GASTRIC ULCER, ACUTE WITH BOTH HAEMORRHAGE AND PERFORATION	S06.6,	TRAUMATIC SUBARACHNOID HAEMORRHAGE
K26.0	DUODENAL ULCER, ACUTE WITH HAEMORRHAGE	S06.8	OTHER INTRACRANIAL INJURIES
K26.2	DUODENAL ULCER, ACUTE WITH BOTH HAEMORRHAGE AND PERFORATION	T81.0	HAEMORRHAGE AND HAEMATOMA COMPLICATING A PROCEDURE, NOT ELSEWHERE CLASSIFIED
K26.4	DUODENAL ULCER, CHRONIC OR UNSPECIFIED WITH HAEMORRHAGE		
K26.6	DUODENAL ULCER, CHRONIC OR UNSPECIFIED WITH BOTH HAEMORRHAGE AND PERFORATION		

Appendix 2: Latent Periods for Medications

Anticoagulative and antiplatelet medication:

ASS	10 days
Dipyridamole	7 days
Ticlopidine	7 days
Clopidogrel	7 days
Warfarin	5 days
Phenprocoumon	10 days

Antidementia drugs:

Egb 761 [®] and other Ginkgo preparations	42 days	
Memantine	glutamate modulator	42 days
Donepezil	cholinesterase inhibitor	29 days
Rivastigmine	cholinesterase inhibitor	3 days
Galantamine	cholinesterase inhibitor	4 days
Nimodipine	calcium antagonist	4 days
Piracetam	others	3 days
Pyritinol	others	3 days

Other drugs: 7 days

The estimated values of $rr = 0.86$, 0.69 and 0.82 for ASS, phenprocoumon, and any anticoagulative or antiplatelet medication, respectively, do not provide any indication of an increased risk (positive interaction) of bleeding complications induced by a simultaneous intake of these drugs and Egb 761[®].

No increase in the prevalence of bleeding during Ginkgo biloba intake compared to periods without Ginkgo biloba was seen either for ASS, for phenprocoumon, or for any anticoagulative or antiplatelet medication. Example: When taking phenprocoumon alone, the relative risk was $6.81/4.61 = 1.48$. With simultaneous intake of Egb 761[®] phenprocoumon had a relative risk of $9.05/8.92 = 1.01$. However, this difference was observed in the subtable with the smallest number of patients.

In **conclusion**, with respect to the risk of bleeding no indication of an interaction between Egb 761[®] on the one hand and ASS, phenprocoumon, or any anticoagulative or antiplatelet medication on the other hand was detected.

4. Discussion

A large and hopefully unbiased survey is a good basis to investigate adverse drug reac-

tions. Taking the mediplus[®] database as an example, we describe some evaluation strategies for pursuing this goal. The final concept was to compare periods with and without a certain medication in only one set of patients. This concept has some similarity to a cross-over study where the same patients are observed under different conditions of exposure. However, a cross-over study is controlled and randomized: (i) the duration of periods for treatment A and B (e.g. verum and placebo) are exactly the same, (ii) the patients are randomized to either the sequence AB or BA, and (iii) there is usually a washout phase between the treatments. Although these three features are not present in our analysis, it may nevertheless be regarded as an 'observational cross-over study'.

As a baseline risk (i.e. in periods without any medication) we found 1.63 bleeding episodes per 100 years (Table 4) based on 281,795 patients. According to Table 6 there were 2.96 bleeding episodes per 100 years without Egb 761[®] and without ASS based on 1627 patients, 4.61 without Egb 761[®] and without phenprocoumon based on 193 patients, and finally 3.53 without any anticoagulative or antiplatelet medication including Egb 761[®] (1903 patients). The three mentioned risks for bleeding from Table 6 are calculated from different sets of patients. The range of estimates from 2.96 to 4.61 demonstrates the importance of determining the risk with and without a certain medication from the identical set of patients in an observational cross-over design. Otherwise the comparison between the complication risks with and without a certain medication could be biased by the special characteristics of the sets of patients analyzed.

The results of our descriptive evaluations indicate that none of the widely used antidementia drugs poses a serious risk of bleeding complications. The highest relative risk we found was 1.44 for cholinesterase inhibitors (Table 5). For Ginkgo biloba we found no increased risk of bleeding at all (relative risk = 0.96). Furthermore, we did not observe any interaction between the Ginkgo preparation Egb 761[®] and ASS, phenprocoumon, or other anticoagulative or antiplatelet medication.

Detecting rare adverse drug reactions is still a challenge for physicians, health data administrators and statisticians. We propose that the applied 'observational cross-over design' is an additional tool for working on this important task.

Acknowledgments

We would like to thank Drs Carola Walther and Stephan Köhler of Schwabe Pharmaceuticals for their valuable medical input.

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