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Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts

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Abstract

***Study objectives*—The aims were (1) to compare discharge diagnoses and concurrent medication in a pharmacy based cohort of users of H_2 receptor antagonists to those in a population of users of other drugs in the same period, who did *not* use H_2 receptor antagonists; (2) to compare these results to those of a similar study performed with the Tayside record linkage scheme.**

***Design and setting*—The study was a retrospective cohort study. The morbidity data from the only hospital in one medium sized city (62 000 inhabitants) were linked to the dispensing data of all five community pharmacies on an individual basis (April 1, 1986–December 31, 1989). In the absence of a unique patient identification number, data from pharmacies and hospital were linked by the combination of date of birth, gender, and general practitioner code. For every user of H_2 receptor antagonists two controls were obtained from all patients who had not used these drugs, and matched for age (within 5 years), gender, and general practitioner. All discharge diagnoses which followed this first prescription up to December 31, 1989, in a patient in the index cohort, and during the same period in his or her matched controls, were included in the study.**

***Main results*—In the index cohort (n = 2174) 341 persons were admitted (526 admissions) as against 398 persons (527 admissions) in the control cohort (n = 4348). There was increased morbidity in the index cohort, especially concerning the gastrointestinal system (peptic ulcers and malignancies, abdominal pain, gastrointestinal haemorrhage), but also concerning the musculoskeletal, respiratory, and circulatory systems. The morbidity in the last three groups corresponded with drugs used concomitantly by patients in the index cohort, so it was probably not causally related to the intake of H_2 receptor antagonists but was rather an indicator of higher levels of morbidity in the index cohort.**

***Conclusions*—The figures were grossly comparable to those of the Tayside record linkage scheme. Probabilistic linking with the patient characteristics of gender, date of birth, and general practitioner code can facilitate the undertaking of postmarketing surveillance studies.**

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To conduct postmarketing surveillance, availability of data concerning drug exposure and morbidity is a prerequisite. Since the pioneering work on record linkage and drug monitoring by Skegg and Doll,[1] several automated systems for medical record linkage have been developed during the last decade. The importance of such systems is obvious since, in contrast to voluntary reporting schemes, these facilitate the assessment of relative risks by application of various epidemiological research designs (eg, cohort, case-control). Record linkage systems may be fast, flexible, and relatively inexpensive.[2] In view of the forthcoming concerted registration procedures in the European Community for new chemical entities, with the potential consequences of rapid penetration of a product into the European market, such systems may become very important for the surveillance and assessment of drug risks.

A key feature of these systems is the accuracy of linking data from different registries on an individual basis.[3] Linkage can be performed by using a unique patient identification number (deterministic linkage) or with a combination of patient characteristics (probabilistic linking), available in the registries which are linked.[4–6] Most current systems make use of a unique identification number. Unfortunately, in most countries a patient identification number is not available on a nationwide basis. Even if available (eg, in the United Kingdom), this number is not consistently used for all medical and pharmaceutical registrations.[5] Secondly, public arousal as regards privacy and confidentiality may disable its use for record linkage.[7]

In The Netherlands a unique patient identification number is not available but we showed that it is possible to link exposure and morbidity data with the probabilistic method.[8 9] In this retrospective cohort study we compared the discharge diagnoses in patients on H_2 receptor antagonists with patients not using these drugs. Our results are compared to a similar study with the Tayside record linkage scheme, as published in this journal and elsewhere in 1984.[10 11] Data on concurrent drug use were not available in the Tayside study. Since this may be a proxy of comorbidity, we sought to get more insight into comedication in a cohort of users of H_2 receptor antagonists. A second objective was to test the feasibility of performing a cohort study with probabilistic linkage.

Methods

EXPOSURE AND MORBIDITY DATA

The "pharmaco-morbidity linkage" (PHARMO)

system comprises a database in which dispensing data from 30 pharmacies are collected on an ongoing basis. Five of these community based pharmacies provide for the medicines prescribed to the patients (except for inpatient prescriptions) in a medium sized and isolated city of 62 000 inhabitants. Since the participating pharmacies make use of different software, all data are converted to one database format in which drugs are coded according to the WHO recommended anatomical-therapeutic-chemical (ATC) classification.[12] For every patient discharged from the only hospital in this city the main medical condition and up to nine other conditions are coded according to the 9th revision of the *International classification of diseases*.[13]

LINKAGE

In this study the reasons for admission (main medical condition) to the hospital in a four year period 1986–1989 (n = 36 000) were linked to the patient exposure data on the basis of the date of birth, gender, and general practitioner reference number (GP code) of every individual. In those cases in which the GP code was not present in the pharmacy files, the most frequently prescribing general practitioner was assumed to be the general practitioner of the patient. In a random sample of 1713 individuals the validity of this linking index was assessed by reference to the original name and address registers in hospital and pharmacy. In this sample the combination date of birth, gender and GP code facilitated linkage with a sensitivity and specificity of 91% and 96% respectively.[8 9]

PATIENT AND CONTROL SELECTION

The index cohort consisted of all patients who had received one or more prescriptions of an H_2 receptor antagonist between the start of the registration period per pharmacy and January 1, 1990. The starting point of the observation period per patient was the date of the first recorded dispensing of an H_2 receptor antagonist (cimetidine, ranitidine, and famotidine), whereas the endpoint was December 31 1989. Two controls were obtained for each index patient from the same pharmacy and matched for age (within five years), gender, and general practitioner. To ensure that they were eligible for health care in this period, only controls were enrolled who had received one or more prescriptions (but *no* H_2 receptors antagonists) in the observation period of the matched index patient.

DATA ANALYSIS

The index and control cohorts were linked to the disease registry and the reasons for and numbers of admissions which occurred in the study period of the index patients were compared to those of their matched controls. For the observation period of every index patient the indentical time interval of its matched controls was studied and the numbers of diagnoses in index and control groups were expressed as relative risks. Rate ratio estimations were made by dividing overall admission rates. The concomitant drug use in the study period in index and control cohorts was assessed per ATC group by counting every patient who had received one or more drugs classified within this ATC group, irrespective of the dose or duration of intake. Concomitant drug use was expressed as the "risk" of using a drug classified within a specified ATC group in the study period in the index cohort, relative to the "risk" of using a drug classified within the same ATC group in the control cohort. No adjustment was made for multiple comparisons of ATC groups. All rate ratios/relative risks are expressed as point estimates with 95% confidence intervals.[14]

Table I Hospital discharges among H_2 receptor antagonist users and controls

	PHARMO (n = 62 000)[1]			*Tayside (n = 400 000)*[2]		
	H_2 antagonist (n = 2174)	*Control (n = 4348)*	*Ratio*	*Cimetidine (n = 3802)*	*Control (n = 3802)*	*Ratio*
Patients with one or more discharges	341	398	1·7	929	401	2·3
Male	153	179	1·7	513	236	2·2
Female	188	219	1·7	416	165	2·5
Total number of discharges	526	527	2·0	1613	654	2·5
Male	270	239	2·3	903	388	2·3
Female	256	288	1·8	710	266	2·7

[1,2] Between the date of issue of the first H_2 receptor antagonist prescription and [1]31 December 1990, [2]31 December 1981

Results

A total of 831 109 prescriptions were dispensed between April 1, 1986, and January 1, 1990 in a mean observation period of 28·9 months. In this period 9785 prescriptions (1·2%) of H_2 receptor antagonists were dispensed to 2296 patients, 3·7% of the city population, with a mean of 4·3 prescription per index patient. Excluded were 122 patients since their date of birth and/or GP code

Table II Number of discharges in major disease groupings among H_2 receptor antagonist users and controls

		PHARMO (n = 62 000)			*Tayside (n = 400 000)*		
Disease group	*ICD-9-CM*[a]	*H_2 antagonist (n = 2174)*	*Control (n = 4348)*	*Relative risk (95% CI)*	*Cimetidine (n = 3802)*	*Control (n = 3802)*	*Relative risk*[b] *(95% CI)*
Digestive system	(520–579)	73	28	5·2 (3·38–8·04)*	515	52	9·9 (7·47–13·1)*
Signs, symptoms and ill defined conditions	(780–799)	67	54	2·5 (1·74–3·57)*	195	62	3·1 (2·37–4·17)*
Musculoskeletal system	(710–739)	46	62	1·5 (1·00–2·23)*	72	38	1·9 (1·28–2·79)*
Neoplasms	(140–239)	47	27	3·5 (2·17–5·57)*	163	87	1·9 (1·45–2·41)*
Respiratory system	(460–519)	31	35	1·8 (1·10–2·86)*	93	53	1·8 (1·26–2·45)*
Circulatory system	(390–459)	84	108	1·6 (1·18–2·06)*	199	116	1·7 (1·37–2·15)*
Genitourinary system	(580–629)	18	30	1·2 (0·67–2·15)	89	58	1·5 (1·11–2·13)*
Diseases of the skin	(680–709)	1	7	0·3 (0·04–2·32)	30	26	1·2 (0·68–1·95)
Nervous system and sense organs	(320–389)	37	51	1·5 (0·95–2·21)	42	39	1·1 (0·70–1·68)

CI = confidence interval
[a] 9th Revision of *International classification of diseases*
[b] Adapted from [10 11]
* Significant difference in discharges use among H_2 receptor antagonist users and controls

had not been recorded. Because two controls were matched with each index patient the control cohort had twice as much person-year experience as the index cohort. The average person-year experience in both cohorts was 1·61 year. The mean age in both the index (n = 2174) and control (n = 4348) cohorts was 60 years. In both cohorts 53% of patients were female. The total number of prescriptions in the index group was 59 668 (27·5 prescriptions/patient) as against 63 173 (14·5 prescriptions/patient) in the control group.

ADMISSIONS

A total of 6635 patients who had used one or more prescriptions was admitted to the hospital, thus representing 10·7% of the city population (n = 62 000). In the index cohort 341 out of 2174 patients (15·7%) had been admitted once or several times (total number of admissions: 526) during the study period, whereas the 398 control patients (9·2%) accounted for a total of 527 admissions. The admission rate in the index cohort was 1/6·5 person-years as against an admission rate in the control cohort of 1/13·1 person-years. The admission rate ratio in index versus control cohort was calculated at 2·0 (95% confidence interval: 1·8–2·2). Analysis by gender and by number of discharges gave similar results (table I).

Discharge diagnoses in index and control groups in this study are compared to those of the Tayside system in table II. Increased morbidity concerning diseases of the digestive system was present in the index cohorts in both systems but increased morbidity was also noted in other disease categories, such as neoplasms, and diseases of the musculoskeletal, circulatory and respiratory systems. No significantly increased morbidity was seen in our study for diseases of the skin, genitourinary, and central nervous systems. Table III represents a more detailed analysis of discharge diagnoses of the digestive system. Besides the expected increase in the numbers of index patients with peptic and duodenal disease, gastrointestinal haemorrhage, and abdominal pain, there was also a substantial increase in the discharge diagnoses concerning the gallbladder and biliary tract and hiatus hernia. The number of cancers of the oesophagus and stomach was relatively high.

CONCURRENT MEDICATION

The pharmacy files contain information on all drugs dispensed during the study period. A comparison of the concomitant drug use as distinguished in several ATC groups is presented in table IV. For every ATC group a relative risk was calculated for index patients and controls, and separately for those who had (inpatients) and had not (outpatients) been admitted. Drugs classified within most ATC groups were more frequently used in the index cohort than in the control cohort (table IV, column VI). This was shown most clearly in the outpatient groups (table IV, column IV). In the inpatient group (table IV, column II) the use of drugs for treating gastointestinal problems (ATC groups A03, A04, and A06) predominated but the use of vitamins A11,

Table III Number of discharges among H_2 receptor antagonist users and controls

		PHARMO (n = 62 000)		*Tayside (n = 400 000)*	
Disease group	*ICD-9-CM*[a]	*H_2 antagonist (n = 2174)*	*Control (n = 4348)*	*Cimetidine (n = 3802)*	*Control (n = 3802)*
All digestive system	(520–579)	73	28	515	52
Oesophagus, stomach and duodenum	(530–537)	16	1	331	9
Peptic ulcers	(531–533)	8	0	207	2
Diseases of the oesophagus	(530)	0	0	87	3
Other diseases of the stomach and duodenum	(534–537)	8	1	37	4
Gastrointestinal haemorrhage	(578)	5	0	27	1
Hiatus hernia	(553·3)	8	0	15	2
Gallbladder and biliary tract	(574)	14	2	35	2
Cancer of the oesophagus and stomach	(150–151)	9	2	40	1

[a] 9th Revision of the *International classification of diseases*

Table IV Concurrent medication among H_2 receptor antagonist users and controls for the most frequently used ATC drug groups

		I	*II*	*III*	*IV*	*V*	*VI*
ATC group	*Anatomical therapeutic chemical classification*	*Index/control n = 341/n = 398*	*Inpatients RR (95% CI)*	*Index/control n = 1833/n = 3950*	*Outpatients RR (95% CI)*	*Index/control n = 2174/n = 4348*	*Total RR (95% CI)*
A03	Gastrointestinal antispasmodics and anticholinergics	69/37	2·2 (1·50–3·16)*	223/156	3·1 (2·53–3·75)*	292/193	3·0 (2·54–3·60)*
A04	Antiemetics and antinausea	50/16	3·6 (2·12–6·28)*	214/98	4·7 (3·73–5·94)*	264/114	4·6 (3·74–5·73)*
A06	Laxatives	110/72	1·8 (1·38–2·31)*	281/261	2.3 (1·98–2·72)*	391/333	2·3 (2·05–2·69)*
A07	Antidiarrhoeals, intestinal anti-inflammatory agents	35/36	1·1 (0·73–1·77)	107/169	1·4 (1·08–1·73)*	142/205	1·4 (1·13–1·71)*
A10	Antidiabetics	23/29	0·9 (0·55–1·57)	53/121	0·9 (0·69–1·30)	76/150	1·0 (0·77–1·33)
A11	Vitamins	76/54	1·6 (1·20–2·26)*	213/354	1·3 (1·10–1·52)*	289/408	1·4 (1·23–1·63)*
B01	Anticoagulants	34/27	1·5 (0·91–2·38)	49/65	1·6 (1·13–2.34)*	83/92	1·8 (1·35–2·42)*
B03	Antianaemic preparations	3/40	1·5 (1·05–2·27)*	122/117	2·2 (1·75–2·88)*	175/157	2·2 (1·81–2·75)*
C01	Cardiac therapy	88/99	1·0 (0·81–1·33)	173/306	1·2 (1·02–1·46)*	261/405	1·3 (1·11–1·49)*
C02	Hypotensives	78/69	1·3 (0·99–1·76)	155/338	1·0 (0·82–1·19)	233/407	1·1 (0·98–1·33)
C03	Diuretics	119/94	1·5 (1·18–1·86)*	256/535	1·0 (0·90–1·18)	375/629	1·2 (1·06–1·34)*
C04	Peripheral vasodilators	32/33	1·1 (0·71–1·80)	96/145	1·4 (1·11–1·84)*	128/178	1·4 (1·15–1·79)*
C07	β Blocking agents	74/71	1·2 (0·91–1·63)	178/429	0·9 (0·76–1·06)	252/500	1·0 (0·87–1·16)
G04	Urologicals	26/26	1·2 (0·69–1·97)	76/127	1·3 (0·98–1·70)	102/153	1·3 (1·04–1·70)*
H02	Systemic corticosteriods	41/33	1·5 (0·94–2·24)	126/177	1·5 (1·23–1·91)*	167/210	1·6 (1·31–1·94)*
J01	Systemic antibiotics	181/169	1·3 (1·07–1·45)*	603/1212	1·1 (0·99–1·16)	784/1381	1·1 (1·06–1·22)*
J03	Systemic chemotherapeutics	52/61	1·0 (0·71–1·40)	171/257	1·4 (1·19–1·73)*	223/318	1·4 (1·19–1·65)*
J07	Vaccines	77/55	1·6 (1·19–2·24)*	185/299	1·3 (1·12–1·59)*	262/354	1·5 (1·27–1·72)*
M01	Anti-inflammatory and antirheumatic products	164/142	1·3)1·14–1·60)*	521/1061	1·1 (0·97–1·16)	685/1203	1·1 (1·05–1·23)*
N02	Analgesics	164/142	1·3 (1·14–1·60)*	507/745	1·5 (1·33–1·62)*	671/887	1·5 (1·39–1·65)*
N05	Psycholeptics	177/150	1·4 (1·17–1·62)*	545/899	1·3 (1·19–1·43)*	722/1049	1·4 (1·27–1·49)*
N06	Psychoanaleptics	23/20	1·3 (0·75–2·40)	99/92	2·3 (1·76–3·06)*	122/112	2·2 (1·69–2·80)*
R01	Nasal preparations	42/55	0·9 (0·61–1·30)	232/390	1·3 (1·10–1·49)*	274/445	1·2 (1·07–1·42)*
R03	Anti-asthmatics	59/52	1·3 (0·94–1·87)	179/285	1·4 (1·13–1·62)*	238/337	1·4 (1·21–1·65)*
R05	Cough and cold preparations	121/115	1·2 (1·00–1·52)*	433/862	1·1 (0·98–1·20)	554/977	1·1 (1·04–1·24)*
R06	Systemic antihistamines	72/82	1·0 (0·77–1·36)	258/457	1·2 (1·06–1·40)*	330/539	1·2 (1·08–1·39)*
S01	Ophthalmologicals	78/75	1·2 (0·92–1·61)	269/497	1·2 (1·02–1·34)*	347/572	1·2 (1·07–1·37)*

CI = confidence intervals
* Significant difference in drug use among H_2 receptor antagonist users and controls

antianaemic preparations (B03), diuretics (C03), systemic antibiotics (J01), anti-inflammatory and antirheumatic products (M01), analgesics (N02), psycholeptics (N05), and cough and cold preparations (R05) was also increased compared to controls.

Discussion

In this feasibility study there was a significantly increased rate ratio of admissions in the cohort of patients treated with H_2 receptor antagonists as compared to the control cohort. This increase was partly explained by an enhanced number of discharge diagnoses of gastrointestinal problems, but in addition the number of discharge diagnoses related to morbidity in several other bodily systems was also increased.

Three types of morbidity could be distinguished in the index cohort. Firstly, there was the morbidity or comorbidity due to peptic complications, which may be directly related to the reason for use of H_2 receptor antagonists, eg, peptic ulcers, abdominal pain, or dyspepsia. The increase of diagnoses concerning the gallbladder and biliary tract, as seen in both the Tayside scheme and in our study, is possibly explained by those cases in which the initial symptoms were wrongly attributed to peptic ulcer disease. Similarly, some of the cases of gastrointestinal malignancy may be due to misjudgment of symptoms. Secondly, some discharge diagnoses may be related to adverse effects of H_2 receptor antagonists. These may be difficult to detect since the incidence of adverse effects due to these drugs as a cause for hospital admission is probably low. Large record linkage systems and a well chosen research hypothesis are essential to identify and quantify these effects. Thirdly, there is the unexplained increase in admissions due to morbidity in other systems. The complex morbidity pattern in users of H_2 receptor antagonists has also been noted in other studies.[15] As drugs are prescribed to treat prevailing morbidity, concurrent drug use is an indicator for (co-)morbidity. It is obvious from table IV (column VI) that most ATC groups were used more frequently in the index than the control cohort. This is consistent with the higher overall number of prescriptions used in the index cohort. This strongly suggests that the prevalence of morbidity in the index cohort was higher than in the control cohort. Interestingly, in the hospital inpatient group (table IV, column II) the increase in disorders of the gastrointestinal, musculoskeletal, respiratory, and circulatory systems was compatible with the significantly increased use of gastrointestinal antispasmodics and anticholinergics (A03), antiemetics and antinauseants (A04), laxatives (A06), vitamins (A11), antianaemic preparations (B03), diuretics (C03), anti-inflammatory and antirheumatic products (M01), analgesics (N02), and cough and cold preparations (R05). It is unlikely that these effects reflect adverse effects to H_2 receptor antagonists. More likely, these drugs are relatively frequently used in patients with other illnesses and not causally related to these diseases.

The design of this feasibility study was largely similar to that performed with the Tayside record linkage system,[10 11] but there were some differences. Firstly, because of the smaller population we made our study period longer. Secondly, at the moment of performing the Tayside study, cimetidine was the only agent marketed in the United Kingdom. Despite the fact that more H_2 receptor antagonists were involved in our study, however, the results were remarkably similar. There was, however, in both index and control patients a much lower overall admission rate in this study than in the Tayside study. It is uncertain whether this is due to a variation in regional and/or national morbidity patterns, health care service, or both. Although the admission rate ratios in both studies were comparable, the ratios in our study were consistently lower. Also the relative risk for diseases of the digestive system is of lower magnitude in our study. There are three possible explanations for this difference. Firstly, and most likely, our study was performed 10 years after the introduction of H_2 receptor antagonists on the market in a phase when these agents are increasingly used for all kinds of dyspeptic complaints and abdominal pain.[16] In the Tayside study cimetidine had been introduced fairly recently, and it is likely that at that time its use was more rigorously restricted to patients with demonstrated peptic ulcer disease. This is compatible with the much lower overall percentage of users of H_2 receptor antagonists in the Tayside study. Obviously, as regards peptic ulcer related admissions, this would lead to a relative risk of higher magnitude. Secondly, in the Tayside study community based controls were enrolled. The use of community based controls would inflate the relative risk estimation if the control has died or moved to another area. In our study each control patient had had a prescription in the study period. This guaranteed that both index and control patients were eligible for medical services, and thus were alive and present in the area. Thirdly, one might argue that pharmacy based controls are generally more ill than community based controls, which would ultimately lead to more admissions. This is, however, not a likely explanation since over a three year period more than 90% of the population obtains one or more prescriptions (Herings R M C, unpublished data). This means that a randomly chosen pharmacy based control is probably representative of the total city population. Moreover, the much lower overall admission rate in the controls in our study than in those of the Tayside study is not consistent with higher morbidity.

The PHARMO system has some advantages. Although probabilistic linkage seems to be a disadvantage because of potential misclassification, this is not a great problem with a specificity of 96%. Moreover, misclassification will be non-differential and does not influence the rate ratio of cohort studies because it will occur to the same extent in the index and control cohort.[17] Although the use of a unique patient identification number makes linking more simple, the confidentiality of such numbers has raised public and political discussions.[6] Moreover large indentification numbers are difficult to recall for the average individual, and hence such numbers

are not consistently used.[5] In the Tayside study no NHS number was found in 24% of prescriptions.[10] In our study only the absence of gender and date of birth makes linking impossible, and so the percentage that could not be linked (approximately 7%) was much smaller. Another advantage of our system is that all drug data are automated and that, in contrast to the Tayside scheme, no manual extraction and coding of prescriptions is needed. As the collection of drug data is an integral part of the administrative procedures in automated pharmacies in The Netherlands—unlike the Tayside scheme—we have data on all other drugs dispensed to the index and control patients in the same period. This facilitates a further assessment of the concurrent morbidity in these patients. In the Tayside study, for instance, the increase in disease categories concerning the respiratory system led to speculation as regards smoking habits. Although the increased use of respiratory drugs could be compatible with this hypothesis, it could also be explained by underlying respiratory diseases. Another advantage of the availability of dispensing data is the recognition of other drug risk factors, drug-drug interactions, and detection of potential confounding variables.[18] At this moment our scheme is much smaller than the Tayside scheme, but it is currently expanded to a population of 250 000 individuals.

In conclusion probabilistic linkage with dispensing data from pharmacies and morbidity data from hospitals facilitates the performance of cohort studies. Similarly, with diagnoses as a starting point, case-control studies are possible. On the condition that both consumption and morbidity data are validated, this scheme could be a useful resource for the performance of postmarketing surveillance studies.

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