Relationship of Drug-Drug Interactions with Hospital Diagnoses Associated to Adverse Drug Reactions: a Retrospective Study of Billing Data in Austria

Research Article

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Abstract

Purpose: The objective of this study was to identify hospitalisations in Austria caused by adverse drug reactions (ADR) and to analyse preceding medication for the risk of drug-drug interactions (DDI) based on healthcare billing databases.

Methods: A retrospective study was performed using the billing data of the Austrian health system. The research database of the Main Association of Austrian Social Security Organisations was used, which contains hospital discharge diagnoses and all medications reimbursed from prescriptions for 5,046,325 adult Austrian patients in 2006 and 2007.

Results: 0.4% of the population was discharged with at least one diagnosis indicating an ADR during the observation period. 1.5% of hospitalised patients had a diagnosis related to an ADR. Of these, a DDI was identified in 68% (13,511 subjects) and a severe interaction in 12% (2,412 subjects), respectively.

Conclusions: Billing data provide important information to complement reporting systems for drug safety. These database searches may contribute to signal and hypothesis generation.

Keywords: Adverse Drug Events; Pharmacovigilance; Drug Safety; Hospital Diagnoses; Drug Reimbursement.

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Introduction

The European Directive on Pharmacovigilance [1] defines adverse drug reactions (ADR) as "a response to a medicinal product which is noxious and unintended" including medical errors. While some ADR appear preventable, others are unexpected on the basis of available product information or poorly predictable because of drug-drug interactions (DDI).

ADR affect an unknown quantity of the population and are a common cause for hospital admissions [2]. Several studies have estimated the incidence of ADR-related hospital admissions with data obtained from discharge letters and nationwide analysis, for example in Spain [3], England [4] or in the Netherlands [5].

It is estimated that 2-6% of hospitalisations are due to ADR [6-8]. A review of 25 studies [9] found a median ADR rate of 5.3% with a range between 0.2% and 15.7%. In an effort to estimate patient risks on a population-based level most studies calculate the proportion of ADR-hospital admissions, others the admissions per treated patients. For example Schneeweiss et al. [7] calculate 9.5 admissions per 10.000 treated patient in Germany. ADR admissions occur more often in elderly people [10-13] and are caused by a few number of medications [10]. Besides morbidity and mortality, ADR are responsible for a substantial utilisation of bed capacity and treatment costs in hospital [14-16] and can trigger reduced precriptions [17].

ADR reports emerge from pre- or post-marketing trials or from spontaneous case reports. Similar to other European countries [18] the reporting activity by health care professionals in Austria has increased since 2006, but remains at a very low level. In Austria with approximately 8 million inhabitants the Austrian Agency for Health and Food Safety (AGES) received 323 ADR reported

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in the year 2006, and an average of 704 ADR per year between 2006 and 2013 [19]. Particularly in a country where the spontaneous reporting system is underdeveloped, new highly-efficient approaches that can be realized with limited resources need to be explored.

ADR may be identified from healthcare system databases. The Main Association of Austrian Social Security Organisations maintains a data repository of patient- and treatment- related medical data (GAP-DRG) for accountancy and billing for all subjects treated in Austria. For research purposes this database has added information of all reimbursed medications dispensed at pharmacies and diagnoses from hospital discharges covering the years 2006 and 2007.

The goal of this study was to capture ADR-related hospital discharge diagnoses on a population level in Austria based on billing data and to search for possible DDIs of medications dispensed preceding these hospital stays.

Methods

The study protocol was approved by the Ethics Committee of the Medical University of Vienna (EK #1131/2013).

Study population

Data in the GAP-DRG database from 2006 and 2007 were collected by the Main Association of Austrian Social Security Organisations and anonymised. All hospital diagnoses and reimbursed medications dispensed at pharmacies upon prescription (including resident physicians with in-house pharmacies) for the Austrian population during the years 2006 and 2007 were available for analysis. Data from patients younger than 20 were excluded from analysis.

Additional data sources

A list of 505 ADR-related diagnoses from a study of Stausberg and Hasford [20] was used to identify a relationship between medicines and hospital discharge diagnosis. The diagnoses were encoded in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification (ICD-10-GM) and grouped in seven categories of ADR likelyhood (Table 1).

For the analysis of possible DDIs the Austria-Codex was integrated into the GAP-DRG-database. The Austria-Codex contains all medications available in Austria and flags DDI information [21]. The Austria Codex categorizes the DDI warnings into severe, moderate and minor interactions. Severe DDIs may be life-threatening or cause permanent damage.

ADR and DDI identification

For this study the ICD-10 list of Stausberg and Hasford [20] was adapted by pharmacological experts. ADR caused by medicines dispensed during hospitalisations were reviewed. Where appropriate, an ADR was removed when the effect was not unexpected. For example, code D 61.10 (Drug-induced aplastic anaemia) was removed when the diagnosis was linked to cytotoxic chemotherapy during a preplanned hospital stay. Further, direct drug-induced ADR such as allergic/hypersensitivity reactions or the code L27.0 "generalized skin eruption due to drugs and medicaments" were not considered for DDI analysis due to the monocausal nature of event. After this careful revision the list of ICD-10 codes in the database was reduced to 161 diagnoses (see Appendix).

Hospital discharge diagnoses from 1.7.2006–30.9.2007 were analysed. The remaining two quarters before and the quarter after this period were taken for the evaluation of medications before and after index hospitalisation. For the analysis of a relationship between an ADR-diagnosis and DDIs, only ICD-10 diagnoses with ≥100 occurences in these five quarters were considered. Other diagnoses were considered as too rare to provide a clinically relevant signal, unless categorized as induced directly by medication.

The prescribed daily dosage was not accessible from the database. Thus, the nominal intake period per drug was set to 30 days. This was intentionally chosen as standard package sizes cover mostly a 30 days period, except for antibiotics. In addition, this conservative definition prevents an overestimation of possible interactions and attributes DDIs mainly to long-term use of medication. Further, this strategy mitigates a bias resulting from different reporting periodicities of the medication data by health insurances.

Data were prepared using the PostgreSQL database Version 9.1.3. Descriptive statistical analyses were performed with Excel.

Table 1. Summary of hospital diagnoses (7 ADR-categories, 5 ADR-categories + expert-selection).

ADR-category	Definition	number of Stausberg codes	number of ICD codes used for selection	number of identified ICD codes	Identified hospital diagnoses
A1	Induced by medication	104	49	46	3,273
A2	Induced by medication or other causes	78	19	19	17,681
B1	Poisoning by medication	133	80	72	1,887
B2	Poisoning by or harmful use from medication or other causes	15	2	2	4
C	ADR very likely	30	11	11	2,968
D	ADR likely	83	0	-	-
E	ADR possible	62	0	-	-
Sum		505	161	150	25,813

Columns show the numbers of the codes taken from the Stausberg study, selected by experts for categories A-C, and identified in the database and the number of the identified diagnoses with these codes.

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Results

5,046,325 subjects had a medical consultation or a prescription reimbursed during the five quarters between 01.07.2006 and 30.09.2007. 1,324,320 subjects were admitted to a hospital in this period, with a total of 2,530,313 hospitalisations.

ADR diagnoses

Direct drug-induced or very likely ADR were found in 25,813 discharge diagnoses of 25,535 hospitalisations from 19,760 subjects. These ADR comprised 150 different ICD codes (Table 1). Thus approximately 0.4% of all subjects had a hospitalisation with an ADR-related diagnosis.

19,760 patients (1.5% of hospitalised subjects) had an ADR-related diagnosis. In this group with an ADR-related diagnosis, a higher proportion of females was observed across all age groups. This sex difference of ADR incidence persisted when data were normalized for age-group proportions in the Austrian population [22] (Figure 1).

Drug-drug interactions

All ADR-related hospital diagnoses were analysed for potential DDIs. In 13,511 subjects (68%) an interaction could be identified. This DDI was classified as severe in 2,412 subjects (12%). Most frequent DDI signals are presented in Table 2. Table 3 lists the substance groups involved in the DDI warnings.

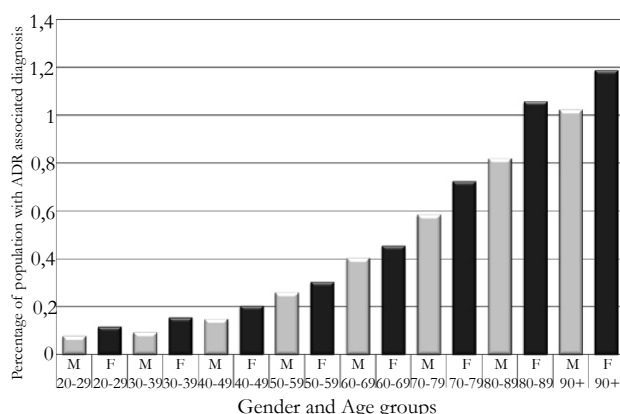---

Figure 1. Proportion of population with ADR-diagnoses.

Table 2. Hospitalisations with ADR-related diagnoses and DDI warnings.

Diagnosis					
ADR-category	Hospital stays with Diagnosis	Warning ID	Interaction warning	Hospital stays with diagnosis and warning	
				n	%
ICD-Code T88.7 Unspecified adverse effect of drug or medicament					
A2	15,437	211	Reduced diuretic and antihypertensive efficacy	3,071	19.9
ICD-Code F13.1 Mental and behavioural disorders due to use of sedatives or hypnotics: Harmful Use					
A2	1,332	464	Increased occurence of severe adverse reactions possible	519	39.0
		27	Increased plasma concentration of benzodiazepines possible	385	28.9
		B45	Increased gastrointestinal bleeding risk	354	26.6
		425	Intoxication risk – increased efficacy of antidepressants	273	20.5
		467	Increased efficacy of benzodiazepines possible	247	18.5
ICD-Code T46.0 Cardiac-stimulant glycosides and drugs of similar action					
B1	1,132	97	Increased efficacy of cardiac glycosides– risk of cardiac glycoside intoxication	660	58.3
		211	Reduced diuretic and antihypertensive efficacy	410	36.2
		192	Inreased bradycardia and AV-prolongation	335	29.6
		232	Initial drop in blood pressure possible	328	29.0
		231	Increased potassium loss – risk of hypokalemia	257	22.7
		1	Reduced antihypertensive potency/increased risk of renal failure	249	22.0
		45	Reduced antihypertensive efficacy	212	18.7
		528	Increased efficacy of anticoagulants	211	18.6
		270	Increased efficacy of cardiac glycosides– risk of cardiac glycoside intoxication	196	17.3
		186	Increased potassium retention – risk of hyperkalemia	189	16.7
ICD-Code G21.1 Other drug-induced secondary parkinsonism					
A1	387	464	Increased occurence of severe adverse reactions possible	156	40.3
		B45	Increased gastrointestinal bleeding risk	86	22.2
		813	Increased efficacy of metoprolol possible	77	19.9
		140	Additive anticholinergic actions	69	17.8
		528	Increased efficacy of anticoagulants	68	17.6
		211	Reduced diuretic and antihypertensive efficacy	67	17.3

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Table 3. Substance groups involved in the identified drug-drug interactions.

Warning ID	Substance Group 1	Substance Group 2
1	ACE-inhibitors	Nonsteroidal anti-inflammatory drugs
27	Benzodiazepines	Proton-pump inhibitors
45	Beta-Blocker	Nonsteroidal anti-inflammatory drugs
97	Cardiac glycosides	Diuretics, potassiuretic
140	Neuroleptics	Anticholinergic drugs
186	ACE-inhibitors	Potassium-sparing diuretics
192	Cardiac glycosides	Beta-Blocker
211	Diuretics, potassiuretic	Nonsteroidal anti-inflammatory drugs
231	Diureticsa, potassiuretic	Glucocorticoides
232	ACE-inhibitors	Diuretics, potassiuretic
270	Cardiac glycosides	Glucocorticoides
425	Tricyclic antidepressants and analogues	Serotonin re-uptake inhibitors
464	Neuroleptics	Serotonin re-uptake inhibitors
528	Anticoagulants	Serotonin re-uptake inhibitors
813	Beta-Blocker	Serotonin re-uptake inhibitors
B45	Nonsteroidal anti-inflammatory drugs	Serotonin re-uptake inhibitors

Diagnosis T88.7 "Unspecified adverse effect of drug or medicament" was found in 15,437 hospital records. In 19.9% of these cases, the DDI warning "reduced diuretic and antihypertensive efficacy" was available for the combination of the prescribed medication. No other signal was detectable in this group, suggesting that a majority of these diagnoses is a non-specific effect from multiple medicines or caused by a single drug.

The second most frequent diagnosis suggesting drug-drug interaction with 1,332 records was coded as ICD-10 F13.1 "Mental and behavioural disorders due to use of sedatives or hypnotics: Harmful Use". In this group, available interaction flags included "Increased occurence of severe adverse reactions possible" (39.0%), "Increased plasma concentration of benzodiazepines possible" (28.9%), „Increased gastrointestinal bleeding risk" (26.6%), "Intoxication risk – increased efficacy of antidepressants" (20.5%), and "Increased efficacy of benzodiazepines possible" (18.5%).

1,132 cases were found for the third most frequent diagnosis T46.0, "Poisoning by agents primarily affecting the cardiovascular system: Cardiac-stimulant glycosides and drugs of similar action". Most DDI warnings were "Increased efficacy of cardiac glycosides– risk of cardiac glycoside intoxication (58.3%)", followed by "Reduced diuretic and antihypertensive efficacy" (36.2%). Of note, the interaction warning "Increased efficacy of cardiac glycosides– risk of cardiac glycoside intoxication" also occurred in a second set of DDI (Table 3) with 196 cases, adding clinical relevance for the association between use of cardiac glycosides, co-medication and hospitalisations.

Other diagnosis were less frequent and included G21.1 "Other drug-induced secondary parkinsonism" (387 cases; most frequent DDI warning "Increased occurence of severe adverse reactions possible" in 40.3%), G44.4 "Drug-induced headache, not elsewhere classified" (298 cases, interaction warning "Increased gastrointestinal bleeding risk" in 34.2%), E16.0 "Drug-induced hypoglycaemia without coma" (296 cases, interaction warning "Reduced glucose-lowering efficacy" in 40.9%, "Increased glucose-lowering efficacy" in 36.8%), and I95.2 "Drug-induced hypotension" (282 cases, "Reduced diuretic and antihypertensive efficacy" in 34.4%).

Discussion

It is generally accepted that ADR monitoring can prevent hospital admissions [23]. However, public awareness is limited and under-reporting of ADRs is a challenge for implementation of pharmacovigilance surveillance systems. Current legislation addresses primarily reporting and distribution of drug safety information but not analysis of collected data. In addition, discussions about data protection and personalisation of therapies deflect from the usefulness of drug safety databases. A public European database and validated methodology is not available to benchmark regional or national data or to gather information about the incidence or clinical severity of DDIs.

Collected medical and billing data are not popular as a source of pharmacovigilance signal generation. An analysis of healthcare reimbursement information linked with clinical diagnoses may represent a powerful complementary tool to support pharmacovigilance activities. In the present retrospective study the GAP-DRG administrative database enabled the analysis of associations between ADR-related hospital discharge diagnosis and preceding medication on a population level. In our cohort, approximately 26% of subjects had a hospitalisation during the observation period, with direct or very likely ADR as a discharge diagnosis in 1.5% of hospitalised subjects.

The present analysis has associated hospitalisations with drug prescriptions preceding the index event. However, due to its dependence on billing data, the study has several limitations. Firstly, the actual intake of medicines cannot be derived from the database information. For this reason, a nominal intake per drug was used. Secondly, the database does not contain over-the-counter drugs, herbal medicines or medication dispensed in hospitals and does not include data from medicines which are not reimbursed such as oral contraceptives. Consequently, DDIs resulting from those

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substances may have been underreported, even if self-medication may play only a limited role in ADR and DDI leading to hospitalisation [24]. Retrospective drug utilisation reviews show that the incidence of potentially serious DDIs is <1% in ambulatory settings, depending on the case finding methods [25]. In this Austrian cohort, a severe DDI was identified in approximately 12% of hospitalised patients with an ADR-related diagnosis. While this number is small compared to total hospitalisations, it nevertheless indicates a significant and potentially preventable group of ADRs, as flaging of DDIs can be implemented easily as prescription quality check in physician's electronic drug prescription and pharmacy's dispense systems. However, in the absence of a control group, the descriptive natur of a DDI does not allow for risk quantification or qualification of the clinical relevance of drug interactions.

The results obtained in this study are difficult to compare with the settings in the various other studies. For example, in Austria the admission diagnoses of hospitalisations are not available as in Germany and this analysis is limited to discharge diagnoses accordingly. In addition, this limits the causality assessment between the drugs taken before hospitalisation and the ADR diagnoses as a measure of clinical relevance. Nevertheless, the results are similar to other findings, i.e. with regard to the highest risk group of elderly females [12] and the increase of ADR-diagnosis with age. For example, the proportions of ADR-related hospitalisations in 2001 varied between 1.3% for the age group 18-64 years and 2.8% for subjects aged>64 years in the Netherlands [5]. Likewise, the finding that non-steroidal anti-inflammatory drugs are frequently involved DDI is consistent with reviews [26].

The interpretation of DDI warnings with clinical discharge diagnoses is also hampered by the fact that some interactions denote symptoms contrary to the actual clinical presentation, eg., E16.0 drug-induced hypoglycaemia or I95 hypotension. Likewise, the frequent flag for "increased GI bleeding risk" is obviously not an ADR related to the index hospital discharge code F13.1 "Mental disorder due to sedatives or hypnotics", but confounded by co-prescription of serotonin re-uptake inhibitors with non-steroidal anti-inflammatory medicines or antithrombotic drugs. Guidance from automated warning systems for the prescribing physician may therefore result in incorrect clinical expectations or too hesitant dose adjustments. Surprisingly the discharge diagnosis of "Drug-induced headache" (G44.4) was not frequently found in the database. This typical symptom of analgesic medication overuse is commonly observed in chronic pain patients [27], which suggests that some discharge diagnoses may be underreported in the present cohort.

The GAP-DRG database does not provide information on in-hospital medication, over-the-counter medicines, or non-reimbursed medications. It is therefore unknown if the clinical course of patients admitted to hospitals is complicated by ADRs from this analysis. Further, other medications, nutrients or products that might interfere with pharmacokinetics or –dynamics of medicines cannot be assessed or risk attributed. The current data does no allow for a comparison of ADR trends over time. The growing importance of this topic is shown by a study in England [4], where an increased rate of ADR admissions as well as in-hospital mortality due to ADR admissions is evident from ten-years trends between 1999 and 2009.

Conclusion

Systematic studies of administrative databases such as GAP-DRG can be used to identify ADRs. As recently reported from hospitals in England, USA and Germany, observed differences in the adverse event rates are smaller using routine date than those of other study types [28]. However, the analysis of coded hospital discharge diagnoses does not capture the clinical relevance of drug interactions and cannot be extrapolated to ADRs observed in outpatient care. Additional medical information would be necessary to analyse the severity of DDIs and to avoid hospitalisations early.

Acknowledgments

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