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RESEARCH ARTICLE

Exploring co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions: a cross sectional in silico study

Potential novel binding interactions with resins

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Abstract
Background Sevelamer and polystyrene sulfonate are used for treating hyperphosphatemia and hyperkalaemia in chronic kidney disease patients. Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. *Aim* The aim of this study was to explore co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions. *Method* In this in silico study, the 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate in the period 2000–2018 were extracted from the University Groningen IADB.nl database. Drugs dispensed to < 5% of patients, drugs not orally administered, drugs administered once daily before bedtime and drugs for which information on binding interactions with sevelamer or polystyrene was already available were excluded. The likelihood of an interaction (yes or no) of the included drugs was assessed based on pKa- and Log P values. For sevelamer, drugs with a pKa (acid) between 1.5 and 7.4 and or a Log P value > 2.0 were identified as potential interacting drug. For polystyrene sulfonate, drugs with a pKa (base) > 1.5 were identified as potential interacting drug. *Results* Of the top 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate, 22 and 27 potentially clinically relevant new interacting drugs were identified for sevelamer and polystyrene sulfonate respectively. *Conclusion* Several potentially relevant novel binding interactions for sevelamer and polystyrene sulfonate were identified based on dispensing data and assessment of chemical properties for which further interaction research is warranted.

Keywords Drug interactions · Drug utilization · Kidney diseases · Polystyrene sulfonate · Sevelamer

Impacts of practice

- Sevelamer and polystyrene sulfonate, resins used to treat hyperphosphatemia and hyperkalaemia in chronic kidney disease patients, may bind other drugs in the gastrointestinal tract decreasing their bioavailability and clinical effectiveness
- Physicians and pharmacists should take this into consideration when treating patients with sevelamer and or polystyrene sulfonate
- An *in silico* strategy using a prescription database to explore co-dispensed drug use and predicting binding based on chemical properties is a useful tool to identify

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potential novel drug binding interactions with these resins
- Confirmatory *in vitro* and *in vivo* interaction research for these potential binding interactions is necessary to assess the clinical relevance
- Confirmed binding interactions should be monitored using pharmacy electronic medication surveillance systems and provided with recommendations for staggered dosing

Introduction

Resins, such as sevelamer and polystyrene sulfonate, are often used for binding phosphate and potassium to treat hyperphosphatemia and hyperkalaemia, which can cause serious complications in patients with chronic kidney disease (CKD) [1, 2]. Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. CKD patients often use many different drugs, due to comorbidities such as cardiovascular diseases, diabetes mellitus, metabolic disorders, gout and anaemia. Most often prescribed drug groups are cardiovascular drugs, antidiabetic agents, drugs for acid related gastro-intestinal disorders, anti-gout preparations and agents for the treatment of mineral bone disorder [3, 4]. Due to the high number of prescribed drugs, the prevalence of potential drug-drug interactions in CKD patients is high, varying from 75 to 91% [5–9]. For instance phosphate binders, used by 85% of haemodialysis patients, show several drug-drug interactions in clinical practice [10, 11]. Sevelamer is the phosphate binder of first choice because it reduces mortality when used as an alternative or addition to calcium containing phosphate binders [10, 12]. Furthermore, the use of calcium containing phosphate binders needs to be restricted due to an increased risk of metastatic and vascular calcifications [2]. Sevelamer is a non-absorbed polymer, free of metal and calcium. It contains several amines separated by one carbon from the polymer backbone. The amines become partially protonated in the gastro-intestinal tract and interact with phosphate molecules through ionic and hydrogen binding. This binding decreases the bioavailability of phosphate and thereby decreases elevated serum phosphate concentrations. In addition to its phosphate-binding properties, sevelamer acts as a bile acid sequestrant and significantly reduces low-densitiy lipoprotein (LDL) cholesterol levels [13]. Polystyrene sulfonate (available as sodium or calcium salt) is a cation-exchanging resin that has been widely used for several decades as first-line therapy of mild chronic hyperkalaemia in patients with CKD [1, 2]. It lowers the plasma potassium concentration through exchange of potassium and sodium/calcium ions in the gastro-intestinal tract, mainly in the colon and partly in the small intestine. Polystyrene sulfonate itself is not absorbed from the gastro-intestinal tract [14, 15]. The estimated numbers of sevelamer and polystyrene sulfonate users in the Netherlands in 2020 were 7,686 and 6,309 respectively [16].

Studies and case reports investigating binding interactions of sevelamer show that sevelamer binds to levothyroxine, ciprofloxacin, mycophenolic acid, tacrolimus, cyclosporine, vitamin D analogs, lipid soluble vitamins like vitamin A, E and K, folic acid, quetiapine and furosemide [11, 13–15, 17–24]. For polystyrene sulfonate, binding interactions have been described with lithium, quetiapine and levothyroxine [23, 25, 26]. Based on the chemical mechanism of the known binding interactions there are possibly many more drugs that bind to sevelamer and/or polystyrene sulfonate. The Summary of Product Characteristics (SmPC) of polystyrene sulfonate underlines this by discouraging taking other oral medication three hours before or after polystyrene sulfonate intake [27]. In the Netherlands, only the known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing between drugs. However, this advice is difficult to accomplish in a patient group using on average 8 different drugs per day [3, 4]. In addition, nephrologists may not be aware of binding interactions of these resins with comedication and their clinical implications [11]. Therefore, more knowledge about potential binding interactions with sevelamer and polystyrene sulfonate is relevant for tailored management in clinical practice. To be able to identify clinically relevant binding interactions, co-dispensed drug use of patients using sevelamer and or polystyrene sulfonate should be investigated.

Aim

The aim of the present study was to explore co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions. Drugs for which further interaction research is warranted were identified based on their chemical properties.

Ethics approval

The study database IADB.nl uses de-identified medical records that could not lead to individual patients. According to the Code of Conduct for Health Research by the Foundation Federation of Dutch Medical Scientific Societies, approved by the Dutch Data Protection Authority in 2004, no ethics committee approval is needed for research using anonymous medical records [28].

Method

Design and setting

This study used an in silico strategy to detect potential novel drug-drug interactions. An in silico experiment is performed by computer or via computer simulation. We used a prescription database to explore co-dispensed drug use with sevelamer and polystyrene sulfonate and predicted binding based on chemical properties.

In a cross sectional study, we used pharmacy dispensing data from the population-based prescription database, University Groningen IADB.nl [29, 30]. The database comprises prescription drug dispensing data from more than 70 community pharmacies in the northern and eastern part of the Netherlands since 1994, covering a population of approximately 700,000 people. Prescription rates among this database population have been found to be representative for the Netherlands as a whole and the database is widely used in research [29]. The database includes demographic information such as date of birth and gender and medication information with Anatomical Therapeutic Chemical (ATC) codes, dispensing date, amount and dose dispensed, number of defined daily doses dispensed and period of drug coverage, i.e. the period of time in days for which the patient had drugs dispensed [29]. Due to a high patient pharmacy commitment in the Netherlands and sophisticated software, the medication records for each patient are virtually complete, except for over-the-counter drugs and medicines dispensed during hospitalization.

Study population and outcome definition

From the IADB database all patients using sevelamer (ATC-code V03AE02) and/or polystyrene sulfonate (ATC-code V03AE01) for at least 90 days in a period of 12 consecutive months between 1st January 2000 and 31st December 2018 were selected. The different options for identification of co-dispensed drugs are graphically depicted in Fig. 1 using drugs A, B, C and D as examples. Drugs were identified as 'co-dispensed' when they were dispensed before the first/follow up date of dispensing sevelamer/polystyrene sulfonate and the use covered a period ending after the dispensing date of sevelamer/polystyrene sulfonate (drug A and B). Furthermore, all drugs, which were dispensed after the first/follow up dispensing date of sevelamer/polystyrene sulfonate, but before the last day of coverage with sevelamer/polystyrene sulfonate, were included (drug C and D).

The number of patients who received a drug which was co-dispensed with sevelamer/polystyrene sulfonate during the study period was extracted from the database. A co-dispensed drug in combination with sevelamer or polystyrene sulfonate was counted only once for every individual patient. Therefore, this number is further referred to as 'unique drug-sevelamer/polystyrene sulfonate combination'.

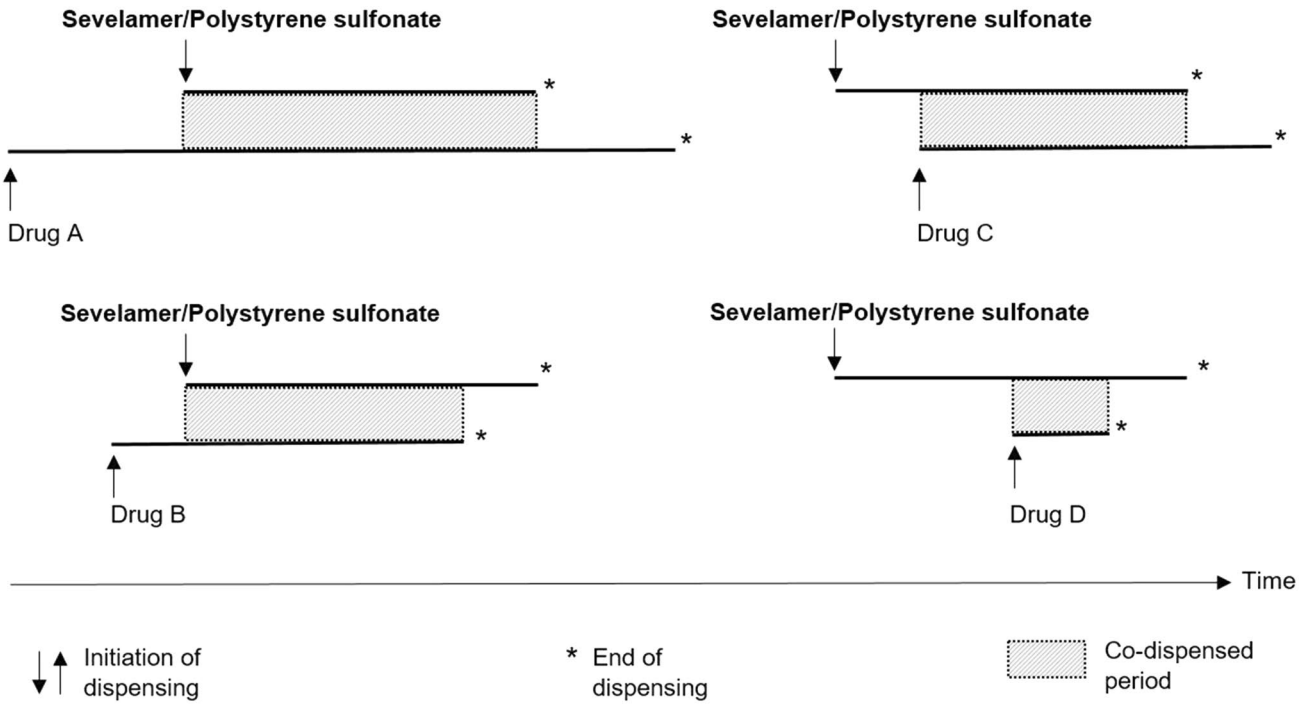

Fig. 1 Graphic presentation of the identification of drugs A, B, C and D that were co-dispensed with sevelamer or polystyrene sulfonate

Analysis

Patient characteristics

We determined the mean age (including standard deviation and range) of sevelamer/polystyrene sulfonate users on July first of each study year from 2000 to 2018. Because there were no relevant differences between these results, we only reported the age data of 2009, the middle of the study period, in the results section.

Top 100 co-dispensed drugs—first level of ATC classification

The 100 drugs most frequently co-dispensed with sevelamer or polystyrene sulfonate during the study period were categorized in the first ATC-class level to identify the main therapeutic groups of co-dispensed drugs. The ATC classification system includes 14 main anatomical or pharmacological groups: A Alimentary tract and metabolism B Blood and bloodforming organs C Cardiovascular system D Dermatologicals G Genito urinary and sex hormones H Systemic hormonal preparations, excluding sex hormones and insulins J Anti-infectives for systemic use L Antineoplastic and immunomodulating agents M Musculo-skeletal system N Nervous system P Antiparasitic products, insecticides and repellants R Respiratory system S Sensory organs V Various [31]. Therefore, we combined the number of unique drug-sevelamer/polystyrene sulfonate combinations within the defined ATC-class first level. Subsequently, we calculated the percentage by dividing this number by the total number of unique drug-sevelamer/polystyrene sulfonate combinations in the top 100.

Top 100 co-dispensed drugs

We determined the percentage of sevelamer/polystyrene sulfonate users who received each drug from the top 100 during the study period, by dividing the number of unique drug-sevelamer/polystyrene sulfonate combinations by the total number of patients using sevelamer/polystyrene sulfonate.

Drugs for which further interaction research is warranted

From the list of 100 most frequently co-dispensed drugs we excluded all drugs, which were registered in duplicate. For example, calcium carbonate and cholecalciferol were amongst the top 100 drugs included as mono-preparations as well as a combination product. In this case, we excluded the combination product. We also excluded drugs dispensed to < 5% of the patients to narrow down the list of drugs to assess. These drugs were considered less relevant because they were not frequently used together with sevelamer/polystyrene sulfonate. Drugs not orally administered were excluded, because binding interactions in the gastrointestinal tract are not applicable for these drugs. Furthermore, we excluded drugs usually administered once daily at bedtime, since for this dosage regimen an interaction with sevelamer or polystyrene sulfonate is unlikely. Finally, all the drugs for which there is evidence for an interaction or evidence that there is no interaction based on literature were excluded. For sevelamer, this concerned levothyroxine, ciprofloxacin, mycophenolic acid, vitamin D analogs, folic acid, furosemide and proton pump inhibitors for which an interaction has already been described, and metoprolol, enalapril and digoxine for which there is evidence for no interaction [13, 17–22, 24, 32–34].

For polystyrene sulfonate, this concerned levothyroxine for which an interaction has already been established [14, 15, 26, 27, 34]. This resulted in a list of drugs co-dispensed with sevelamer or polystyrene sulfonate, the number of unique drug-sevelamer/polystyrene sulfonate combinations and the percentage of patients having received the combination during the study period.

Thereafter the likelihood of an interaction with sevelamer was assessed based on the pKa (acid) and Log P value of the drugs [34]. The binding of sevelamer with drugs is based on ionic binding of the protonated amines of sevelamer with negatively charged drugs in the gastrointestinal tract [13]. The pH in the gastrointestinal tract varies between 1.5 and 7.4. Drugs with a pKa (acid) between 1.5 and 7.4 were identified as potentially binding to sevelamer because these drugs are at least for 50% available as negatively charged in the gastrointestinal pH range. Additionally, drugs with a Log P > 2.0 were identified as potentially binding to sevelamer. Sevelamer acts as a bile sequestrant and because drugs with a Log P value > 2.0 are associated with potential binding to colesevelam (also a bile sequestrant) this threshold value was used [35].

The binding of polystyrene sulfonate with drugs is based on exchange of positively charged sodium/calcium for positively charged drugs in the gastrointestinal tract [14, 15]. Drugs with a pKa (base) > 1.5 were identified as potentially binding to polystyrene sulfonate because these drugs are at least for 50% available as positively charged in the gastrointestinal pH range. The drugs were categorized as 'Yes' (binding interaction expected) or 'No' (binding interaction not expected).

Results

From the IADB-data base, 1,083 patients using sevelamer and 716 patients using polystyrene sulfonate for at least 90 days in a period of 12 consecutive months between

January 2000 and December 2018 were identified. The patient characteristics are depicted in Table 1.

Seven hundred and fifty-five different drugs were dispensed to the sevelamer users during this study period, which resulted in 20,801 unique drug-sevelamer combinations; 654 different drugs were dispensed to the polystyrene sulfonate users, which resulted in 10,311 unique drug-polystyrene sulfonate combinations.

We selected the 100 most frequently co-dispensed drugs with sevelamer and with polystyrene sulfonate. For these 100 drugs, 14,739 unique drug-sevelamer combinations and 7,123 unique drug-polystyrene sulfonate combinations were extracted from the database, which covered about 70% of the total unique drug-sevelamer/polystyrene sulfonate combinations.

Table 2 shows the categorization of these 100 drugs in ATC-class first level.

In sevelamer users, 8,634 unique drug-sevelamer combinations (58.6%) regarded to ATC-classes A, B and C, while in polystyrene sulfonate users, this was 4,760 (66.8%). These included proton pump inhibitors, laxatives, vitamin D analogs, antidiabetic agents as insulins, drugs for treating renal anaemia, antiplatelet coagulation drugs, antithrombotics, antihypertensive drugs, heart failure treatment and lipid

Table 1 Characteristics of patients using sevelamer or polystyrene sulfonate for at least 90 days in a period of 12 consecutive months in 2000–2018

	Sevelamer N = 1083	Polystyrene sulfonate N = 716
Age*, years (mean (sd) [range])	62 (17) [1–89]	58 (20) [10–95]
Gender (N (%))		
Male	619 (57)	471 (66)
Female	464 (43)	245 (34)
Duration S / PSP use, days(mean (sd) [range])	840 (759) [90–5247]	576 (628) [90–3813]
Unique drug-S/PSP combinations (N (%))		
< 10	278 (25.7)	293 (40.9)
11–20	403 (37.2)	275 (38.4)
21–30	226 (20.9)	95 (13.3)
31–40	115 (10.6)	41 (5.7)
41–50	37 (3.4)	10 (1.4)
> 50	24 (2.2)	2 (0.3)

*Age measured on 1st July 2009

SD: standard deviation

S: sevelamer

PSP: polystyrene sulfonate

Table 2 One hundred most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate, by ATC-class first level

Drug category (ATC-first level)	Sevelamer (N*, (%)) Ntotal = 14,739	Polystyrene sulfonate (N*, (%)) Ntotal = 7123
A. Alimentary tract and metabolism	3,597 (24.4)	1,660 (23.3)
B. Blood and blood forming organs	1,806 (12.3)	1,026 (14.4)
C. Cardiovascular system	3,231 (21.9)	2,074 (29.1)
D. Dermatologicals	958 (6.5)	416 (5.8)
G. Genito-urinary system and sex hormones	50 (0.3)	34 (0.5)
H. Systemic hormonal preparations, excluding sex hormones and insulines	541 (3.7)	259 (3.6)
J. Anti-infectives for systemic use	1,378 (9.3)	579 (8.1)
L. Antineoplastic and immunomodulating agents	66 (0.4)	72 (1.0)
M. Musculo-skeletal system	374 (2.5)	207 (2.9)
N. Nervous system	1,408 (9.6)	455 (6.4)
R. Respiratory system	474 (3.2)	156 (2.2)
S. Sensory organs	293 (2.0)	120 (1.7)
V. Various	563 (3.8)	65 (0.9)

*Number of unique drug-sevelamer/polystyrene sulfonate combinations

lowering treatment. Other frequently co-dispensed drugs were dermatologicals (indifferent dermatological products, dermal corticosteroids, anti-infective treatment), ATC class H (prednisolone, cincacalcet, levothyroxine) ATC class L (mycophenolic acid, tacrolimus), ATC class M (allopurinol, colchicine), and ATC-class N (pain medication, benzodiazepines). The individual top 10 drugs co-dispensed with sevelamer (number of unique drug combinations and percentage of patients who received the combination during the study period) were alfacalcidol 643 (59.4%), metoprolol 541 (50.0%), omeprazole 471 (43.5%), calcium carbonate 429 (39.6%), furosemide 421 (38.9%), acetylsalicylic acid 393 (36.3%), amlodipine 358 (33.1%), macrogol 341 (31.5%), ferrofumarate 307 (28.3%) and prednisolone 290 (26.8%). For polystyrene sulfonate the individual top 10 included alfacalcidol 325 (45.4%), metoprolol 311 (43.4%), omeprazole 254 (35.5%), furosemide 233 (32.5%), amlodipine 220 (30.7%), calcium carbonate 212 (29.6%), ferrofumarate 200 (27.9%), acetylsalicylic acid 188 (26.3%), simvastatin 175 (24.4%) and prednisolone 164 (22.9%).

After application of the described exclusion criteria, a list of 39 drugs co-dispensed with sevelamer and 47 drugs co-dispensed with polystyrene sulfonate was compiled for further exploration of interaction potential (Fig. 2). Table 3 presents the selected drugs, the number of unique drug-sevelamer/polystyrene sulfonate combinations, the percentage of sevelamer/polystyrene sulfonate users having received these drugs and the results of the analysis of potential new binding interactions based on pKa- and Log P values. We identified 22 and 27 potentially new binding interactions for sevelamer and polystyrene sulfonate, respectively.

Discussion

This study identified several novel potential binding interactions for sevelamer and polystyrene sulfonate using an in silico approach.

The 100 most frequently co-dispensed drugs with sevelamer or polystyrene sulfonate found in this study are in line with other drug utilization studies done in patients with CKD and haemodialysis patients [2–7, 9]. Drugs for the treatment of cardiovascular diseases, diabetes mellitus, metabolic disorders, gastrointestinal disorders, anaemia, gout, infections, dermatological disorders and pain were the main drug categories reported in those studies [2–7, 9]. This confirms the suitability of the IADB database for this research [29].

The high number of unique drug-sevelamer/polystyrene sulfonate combinations found in this study can be explained by polypharmacy of this population, switching of drugs because of inefficacy or adverse effects, prescription of drugs for short duration, for example antibiotics and the long study period of 19 years.

In several studies the prevalence of drug-drug interactions in CKD patients is reported to be high, i.e. 75–91%, and is associated with the number of prescribed drugs, age, the stage of CKD, as well as comorbidities as diabetes

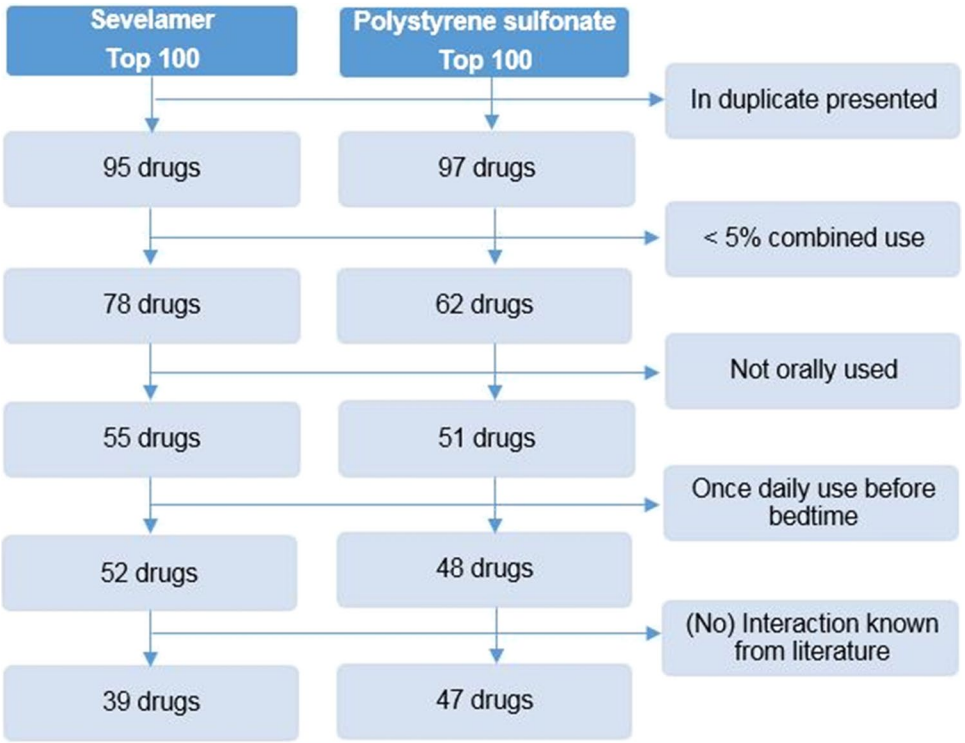

Fig. 2 Selection of co-dispensed drugs with sevelamer or polystyrene sulfonate for further interaction research

Table 3 Most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate and assessment of potential binding interactions

Drug	pKa (acid) [34]	Log P [34]	Sevelamer (N=1,083)			Drug	pKa (base) [34]	Polystyrene sulfonate (N=716)		
			Unique drug combination (N)	Patients (%)	Potential new binding interaction (Yes/No)			Unique drug combination (N)	Patients (%)	Potential new binding interaction (Yes/No)
Calcium carbonate	6.1	0.3	429	39.6	No[a]	Alfacalcidol	−2.8	325	45.4	No
Acetylsalicylic acid	3.4	1.2	393	36.3	Yes	Metoprolol	9.7	311	43.4	Yes
Amlodipine	19.1	1.6	358	33.0	No	Omeprazol	4.8	254	35.5	Yes
Macrogol	–	–	341	31.5	No	Furosemide	−1.5	233	32.5	No
Ferrofumarate	3.4	< 0	307	28.3	No[a]	Amlodipine	9.5	220	30.7	Yes
Prednisolone	12.6	1.27	290	26.8	No	Calcium carbonate	–	212	29.6	No[b]
Amoxicillin/clavulanic acid	3.2/3.3	< 0	285	26.3	Yes / Yes	Ferrofumarate	–	200	27.9	Yes[c]
Acenocoumarol	5.8	2.7	272	25.1	Yes	Acetylsalicylic acid	−7.1	188	26.3	No
Lanthanum carbonate	6.1	0.3	259	23.9	No[a]	Prednisolone	−2.9	164	22.9	No
Polystyrenesulfonate	–	–	245	22.6	No	Macrogol	–	157	21.9	No
Acetaminophen	9.5	0.9	214	19.8	No	Acenocoumarol	−6.8	149	20.8	No
Lactulose	10.3	< 0	213	19.7	No	Enalapril	5.2	138	19.3	Yes
Tramadol	13.8	2.5	212	19.6	Yes	Pantoprazol	3.6	121	16.9	Yes
Cinacalcet	–	6.3	184	17.0	Yes	Amoxicillin/clavulanic acid	7.4/−2.6	111	15.5	Yes / No
Bumetanide	4.7	2.4	165	15.2	Yes	Acetaminophen	−4.4	102	14.2	No
Doxycycline	3.3	< 0	156	14.4	Yes	Ciprofloxacin	8.7	95	13.3	Yes
Doxazosin	12.7	2.1	145	13.4	Yes	Allopurinol	1.3	88	12.3	No
Flucloxacillin	3.8	2.4	125	11.5	Yes	Bumetanide	2.7	86	12.0	Yes
Allopurinol	8.5	0	125	11.5	No	Doxazosin	7.2	84	11.7	Yes
Metoclopramide	14.5	1.4	121	11.2	No	Colecalciferol	−1.3	81	11.3	No
Oxazepam	10.6	2.9	121	11.2	Yes	Lactulose	−3.0	78	10.9	No
Codeine	13.8	1.3	121	11.2	No	Bisoprolol	9.7	75	10.5	Yes
Oxycodone	13.6	1.0	120	11.1	No	Tramadol	9.2	74	10.3	Yes
Nifedipine	–	1.8	116	10.7	No	Isosorbide mononitrate	−3.5	72	10.0	No
Colchicine	15.1	1.5	116	10.7	No	Colchicine	0	70	9.8	No
Bisoprolol	14.1	2.2	112	10.3	Yes	Doxycyclin	8.3	69	9.6	Yes
Isosorbide mononitrate	13.3	< 0	105	9.7	No	Hydrochlorothiazide	−2.7	69	9.6	No

Table 3 (continued)

Drug	pKa (acid) [34]	Log P [34]	Sevelamer (N=1,083)			Drug	pKa (base) [34]	Polystyrene sulfonate (N=716)		
			Unique drug combination (N)	Patients (%)	Potential new binding interaction (Yes/No)			Unique drug combination (N)	Patients (%)	Potential new binding interaction (Yes/No)
Lisinopril	3.2	<0	103	9.5	Yes	Lanthanum carbonate	–	65	9.1	Yes[b]
Clopidogrel	–	4.0	101	9.3	Yes	Nifedipine	5.3	65	9.1	Yes
Clindamycin	12.4	1.0	97	9.0	No	Lisinopril	10.2	64	8.9	Yes
Amitriptyline	–	4.8	88	8.1	Yes	Oxazepam	−1.5	62	8.7	No
Sulfamethoxazol/trimethoprim	6.2/17.3	0.8/1.3	88	8.1	Yes / No	Oxycodone	8.8	58	8.1	Yes
Losartan	7.4	5.1	85	7.8	Yes	Flucloxacillin	−0.9	52	7.3	No
Diclofenac	4.0	4.3	84	7.8	Yes	Irbesartan	4.1	52	7.3	Yes
Irbesartan	7.4	5.5	81	7.5	Yes	Spironolactone	−4.9	50	7.0	No
Hydrochlorothiazide	9.1	<0	71	6.6	No	Diclofenac	−2.1	49	6.8	No
Loperamide	14.0	4.8	71	6.6	Yes	Clopidogrel	5.1	48	6.7	Yes
Vitamin B complex/vitamin C	15.5/4.4	<0 / <0	64	5.9	No / Yes	Cinacalcet	10.3	48	6.7	Yes
Bisacodyl	–	3.6	55	5.1	Yes	Perindopril	5.5	48	6.7	Yes
						Mycophenolic acid	−4.1	46	6.4	No
						Codeine	9.2	44	6.1	Yes
						Amitriptyline	9.8	43	6.0	Yes
						Gliclazide	1.4	43	6.0	No
						Esomeprazole	4.8	43	6.0	Yes
						Losartan	4.1	37	5.2	Yes
						Dipyridamole	6.6	36	5.0	Yes
						Metformin	12.3	36	5.0	Yes

[a]Sevelamer may bind carbonate or fumarate but not the clinically effective ions calcium, iron and lanthanum

[b]Although theoretically polystyrene sulfonate could bind the positively charged calcium, this would not lead to a binding interaction in clinical practice, considering the availability of a polystyrene sulfonate product as a calcium-salt

[c]Polystyrene sulfonate may bind the positively charged iron and lanthanum ions

mellitus, hypertension and obesity [5–9]. However, these studies did not report binding interactions among the top 10 drug-drug interactions, despite the fact that several binding interactions with sevelamer and polystyrene sulfonate are already known and both drugs are widely used by patients with CKD stage 4 or 5 [10, 11, 17–26, 34]. The lack of reporting of binding interactions may be because previous studies included patients with all stages of CKD instead of only patients with CKD stage 4 and 5. In addition, different (software) methods for identifying drug-drug interactions are used in these studies. Furthermore, the study of Sommer et al. focused on pharmacodynamic interactions instead of pharmacokinetic interactions [8].

We identified 22 and 27 potential binding interaction candidates for sevelamer and polystyrene sulfonate respectively for further interaction research. We suggest performing in vitro experiments for those drugs to validate these findings and to assess the extent of binding by simulating gastro-intestinal conditions in the laboratory in the presence and absence of sevelamer or polystyrene sulfonate. Walker et al. showed that in vitro binding studies using colesevelam are very sensitive but have a low specificity for identifying compounds binding to the drug [35]. No binding in vitro meant that the likelihood for binding in vivo was very small. On the other hand, when there is binding in vitro this will not automatically imply there is binding in vivo. This is because drug absorption from the gastro-intestinal tract is affected by many different factors as absorptive surface area, pH, food effects, intestinal transit time, passive intestinal permeability, intestinal transporters and enzymes, which are not all accounted for in in vitro experiments [36]. So confirmatory in vivo studies are necessary to assess the clinical relevance of in vitro binding findings. In vitro screening is however, a valuable tool to test a large number of drugs, to limit the number of candidates for subsequent clinical drug interaction studies.

Strengths of this study are extracting the most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate from a large, up-to-date and representative database and analysing these for their interaction potential based on pKa and Log P values. The analysed top 100 co-dispensed drugs covered about 70% of the unique drug-sevelamer/polystyrene sulfonate combinations and the analysed top 100 covered all drugs used by more than 5% of the sevelamer/polystyrene users. A limitation of our study is that we considered combinations received by less than 5% of the sevelamer/polystyrene sulfonate users as less relevant to assess for potential interactions because they were not frequently used together with sevelamer/polystyrene sulfonate. However, consequently, we may have excluded drugs for which a binding interaction may have important clinical consequences for individual patients.

The interaction potential was assessed based on a minimum of 50% negatively or positively charged availability of the drugs at gastrointestinal pH levels based on pKa-values. For sevelamer also lipophilicity was assessed by taking into account Log P values. Computational approaches have also been developed to identify novel drug-drug interactions in silico [37]. Which approach is most successful in determining clinically relevant drug-drug interactions has not been determined yet. Another limitation of our study is that prescribing in this patient group may be different in other regions of the world or in other health care systems, so we may have missed clinically relevant drugs with potential to interact, which are infrequently prescribed in the Netherlands.

Conclusion

In conclusion, we identified several candidates for potential novel binding interactions with sevelamer and polystyrene sulfonate from data on co-dispensed drugs and through an assessment of the chemical properties of these drugs. Further in vitro studies should be performed with those candidates.

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