ARE MEDICINAL PRODUCTS A RELEVANT SOURCE OF HIDDEN EXTRA-PHOSPHATE LOAD IN CKD PATIENTS ?

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Introduction and aims: Reduction of intestinal phosphorus load is an important aspect for the prevention and treatment of CKD-MBD. However, this strategy is limited by poor adherence to dietary prescription and by hidden sources of phosphorus (P). In addition to phosphate containing additives in foods, recently It was claimed that medicinal products (MP) may contribute to increase the burden of phosphate, mainly present as an excipient.

Methods: With the aim to evaluate the risk of P exposure deriving from long term drug treatment, in this investigation we assessed the prevalence of drugs containing P in the excipient list. We carried out a systematic screening of 14 anatomical therapeutic classes (ATC) of drugs potentially given to CKD patients by oral route and for long term administration.

Results: 311 active pharmaceutical ingredient (API) and 3763 branded or generic medications were examined. Among them, 60 active molecules (19.3%) included at least one medication containing P as an excipient. In total, 472 medications (12.5 %) listed P as an excipient. The prevalence of medications containing phosphate as an excipient was higher for the oral anti-diabetic (23.8%), followed by anti-depressant (19.2%), anti-hypertensive (17.5%) and gastro-intestinal tract (16.4%) medications. All other classes showed a prevalence lower than 10%. Within each ATC class, the APIs at risk of containing phosphate have been identified as well as the prevalence of both branded and generic medications. Calcium hydrogen phosphate was the most prevalent form (77.7 %) of phosphate as an excipient.

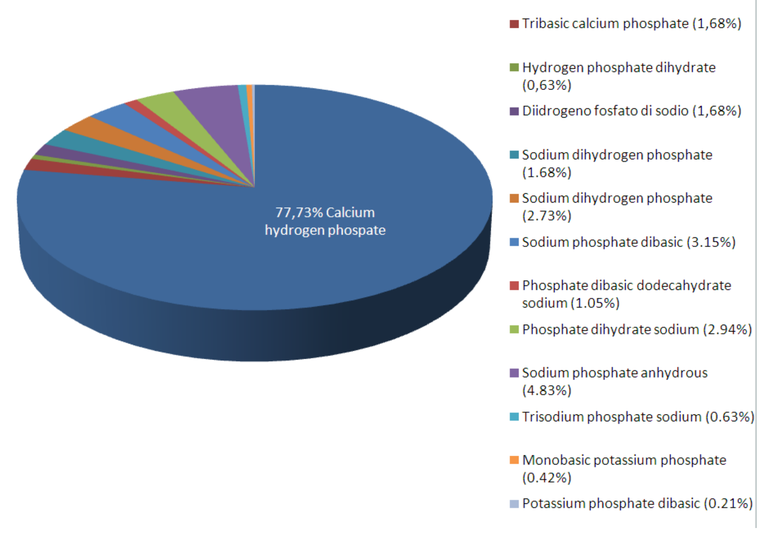

Fig 1 Prevalence of the different types of phosphate salts detected as an excipient component among 472 medications

	ATC	M	M with P		API	API with P	
		n.	n.	%	n.	n.	%
Drugs used in diabetes	A10	239	57	23.8	25	5	20.0
Psychoanaleptics	N06	738	142	19.2	49	17	34.7
Antihypertensives	C02	927	162	17.5	69	10	14.5
Drugs for acid related disorders	A02	274	45	16.4	5	3	60.0
Thyroid therapy	H03	50	4	8.0	8	2	25.0
Lipid modifying agents	C10	354	28	7.9	6	3	50.0
Analgesics	N02	163	11	67	21	5	23.8
Immunosuppressants	L04	67	4	6.0	5	1	20.0
Antihistamines for systemic use	R06	105	3	2.9	11	3	27.3
Drugs for chronic obstructive airway diseases	R03	394	9	2.3	42	5	11.9
Antithrombotic agents	B01A	92	2	2.2	18	2	11.1
Cardiac therapy	C01	238	5	2.1	34	4	11.8
Vitamins	A11	110	0	0.0	16	0	0.0
Antigout preparations	M04	12	0	0.0	2	0	0.0
Total		**3763**	**472**	**12.5**	**311**	**60**	**19.3**

Tab 1. Prevalence of API with at least one medication containing Phosphate as an excipient, and prevalence of Medications (M) containing Phosphate as an excipient within the examined ATC classes. Drugs are identified with the name of the therapeutic subgroups as they appeared in the ATC classification system

ATC	API	Branded		Generic		all M	
		n.	%	n.	%	n.	%
C07AA07	Sotalol	0/3	0	2/7	28,5	2/10	20
C07AB02	Metoprolol	1/5	20	2/8	25	3/13	23
C07AB07	Bisoprolol	27/27	100	22/43	51	49/70	70
C07BB07	Bisoprolol hydrochlorothiazide	3/3	100	0/3	0	3/6	50
C07CA02	Oxprenelol+Chlorthalidone	1/1	100	-	0	1/1	100
C07CB02	Metoprolol+Chlorthalidone	1/1	100	-	0	1/1	100
C03BB04	Amiloride+ Chlorthalidone	1/1	100	-	0	1/1	100
C09AA04	Lisinopril dihydrate	8/8	100	25/25	100	33/33	100
C08CA01	Amlodipine	18/35	51	39/53	74	57/88	64
C08DA51	Verapamil	8/8	100	0/12	0	8/20	40
C10AA03	Pravastatin	0/19	0	9/34	26	9/53	17
C10AA05	Atorvastatin	0/71	0	7/80	8,7	7/151	4,6
C10AA07	Rosuvastatin	12/12	100	0/4	0	12/16	75
N05AG02	Pimozide	1/1	100	-	-	1/1	100
N05AX13	Clozapine	0/2	0	2/7	28	2/9	22
N05AH03	Olanzapine	4/29	13,7	0/66	0	4/95	4
N05AH04	Quietapine	21/21	100	44/69	63,7	65/90	72,2
N05AX08	Risperidone	3/8	37,5	0/34	0	3/42	7
N05AX12	Aripripazole	2/8	25	-	-	2/8	25
N05AX13	Paliperidone	5/9	56	-	0	5/9	56
N06AA04	Clomipramine	1/4	25	-	-	1/4	25
N06AA09	Amitriptyline	4/7	57	-	-	4/7	57
N06AA16	Dosulepin	1/1	100	-	-	1/1	100
N06AB04	Citalopram	1/27	3,7	0/51	0	1/78	1,2
N06AB05	Paroxetine	6/14	43	8/15	53	14/29	48,2
N06AB06	Sertraline	7/9	78	26/34	76	33/43	76,7
N06AX03	Mianserin	2/3	66,6	-	-	2/3	66,6
N06AX05	Trazodone	2/8	25	-	-	2/8	25
N06AX18	Reboxetine	1/1	100	-	-	1/1	100
4AA2F31	Hypericum	1/2	50	-	-	1/2	50
D04AA13	Dimetindene	1/2	50	-	-	1/2	50
R06AX02	Cyproheptadine	1/2	50	-	-	1/2	50
R06AX17	Ketotifen	1/5	20	0/1	0	1/6	17
R01AD04	Flunisolide	0/42	0	3/5	60	3/47	6,3
R03AK11	Fluticasone	2/14	14,2	-	-	2/14	14,2
R03BB02	Ipratropium bromide	1/3	33,3	0/1	0	1/4	25
R03CC13	Clenbuterol	1/4	25	-	-	1/4	25
R03DA04	Theophylline	2/9	22	-	-	2/9	22
A10BB09	Glicazide	2/7	28,6	1/12	8	3/19	15,7
A10BH01	Sitagliptin	9/9	100	-	-	9/9	100
A10BX02	Repaglinide	3/3	100	39/42	92,8	42/45	93,3
A10BX04	Exenatide	1/1	100	0/3	0	1/4	25
A10BX07	Liraglutide	2/3	66,6	-	-	2/3	66,6
A02BC01	Omeoprazole	9/25	36	19/32	59	28/57	49,1
A02BC02	Pantoprazole	0/17	0	2/34	5,9	2/51	3,9
A02BC03	Lansoprazole	7/26	26,9	8/46	17,3	15/72	20,8
L04AA10	Sirolimus	4/4	100	-	-	4/4	100
C01AA04	Digoxin	2/7	28	-	-	2/7	28
C01DA14	Isosorbide mononitrate	1/20	5	0/19	0	1/39	2
C01EB09	Ubidecarenone	1/11	9	-	-	1/11	9
C01EB21	Regadenoson	1/1	100	-	-	1/1	100
H03AA03	Liothyronine+Levothyroxine sodium	2/2	100	-	-	2/2	100
H03AA05	Thyroglobulin	2/2	100	-	-	2/2	100
N02BE01	Acetaminophen	3/68	4,4	2/40	5	5/108	4,6
N02BE51	Acetaminophen + Salicylic acid	1/1	100	-	-	1/1	100
N02BE51	Acetaminophen+ Clorphenamine	1/1	100	-	-	1/1	100
N02BE51	Acetaminophen + sobrerol	2/4	50	-	-	2/4	50
B01AC02	Cloricromene	1/2	50	-	-	1/2	50
B01AC24	Ticagrelor	1/1	100	-	-	1/1	100

Tab 2: List of the API with at least one medications containing P as an excipient. Number of Medications (M) listing phosphate within the excipients over the total existing, either as branded, generic or both forms

Conclusions: our results suggest that the prevalence of phosphate containing MP is quite low and it is possibile to identify, within each ATC, the MP containing P as excipient. The bibasic calcium phosphate was the most prevalent form, which has a lower bioavailability rate than most of other P salts. We have not measured the P content as excipient but the existing data by Sherman et al.[1] and by Sultana et al.[2] show that it is generally low, apart from very few MP that can be easily identified; the median P load from drugs was estimated to 39 mg/d. The excipient seem to be a quite negligibile source of P, which could be further limited by correct information and prescription. The extra-phosphate load from phosphate-containing additives present in food and beverages remains the main hidden source of P in CKD patients.

[1] Sherman RA, Ravella S, Kapoian T. A dearth of data: the problem of phosphorus in prescription medications. Kidney Int. 2015 Jun; 87 (6): 1097-9. 2015.67.

[2] Sultana J, Musazzi UM, Ingrasciotta Y et al. Medications in additional source of phosphate in chronic kidney disease patients. Nutr Metab Cardiovasc disease. 2015 Oct; 25: 959-967.

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