December 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.3 • 407-411

Persistent itching associated to silodosin in an elderly patient: Implications for drug-drug interactions and Pharmacogenetics

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Abstract

Itching is a complaint affecting especially the elderly, in whom comorbidities and polypharmacy increase the risk of adverse drug reactions. We reported the case of an 83-year-old man with a generalized itching lasting more than 3 years underwent to our attention during his enrollment in a clinical study at University Hospital of Salerno, Italy where he was planned for a thromboendoarteriectomy because of left internal carotid artery stenosis. His medical history included arterial hypertension, ischemic heart disease, chronic cerebrovasculopathy, dyslipidaemia and prostatic hyperplasia. His therapy was olmesartan medoxomil 10 mg/die, nebivolol 5 mg x 1/2/die, acetylsalicylic acid 100 mg/die, omeprazole 20 mg/die, atorvastatin 20 mg/die, supplements containing EPA and DHA, vitamins K2, B6, B12 and folic acid (vit B9) and silodosin 8 mg/die. The patient's demographic clinic, laboratory data and a pharmacological anamnesis were collected. Screening of two ABCB1 polymorphisms associated to a decrease of P-glycoprotein (P-gp) activity was performed by realtime PCR. An iatrogenic cause of the itching was suspected and the Naranjo algorithm was applied, revealing possible association between such an adverse reaction and all used drugs. Because the patient reported the beginning of the itching in concomitance with the aspirin assumption, this agent was discontinued but without improvement. Then, because silodosin-atorvastatin interaction may increase the silodosin plasma concentration, this drug was switched to doxazosin and the itching disappeared. This clinical case stresses the potential misleading based on the patients' beliefs and the importance to consider all the patients' available information to ascertain the cause of adverse drug reactions.

Keywords: itching, elderly, adverse drug reaction, drug-drug interaction, polypharmacy.

Introduction

Chronic itching is common in the elderly also because of polypharmacy (1). To ascertain an iatrogenic origin of the itching is essential to consider multiple factors, including comorbidities, results of biochemical and functional exams and drug-drug interactions. Moreover, it is important to consider that in the elderly there is an increased risk of inappropriate medications that strongly correlates with age, drugs number, and intervention (1,2).

Case presentation

An 83-year-old male diagnosed with carotid stenosis was admitted to the University Hospital of Salerno for a thromboendoarteriectomy. He suffered from hypertension, chronic cerebrovasculopathy, dyslipidaemia and benign prostatic hyperplasia. The therapy is reported in table 1. The patient has been enrolled in a study (EC approved number 80/2018) evaluating the response to the antiplatelet agent clopidogrel by the screening of polymorphisms in CYP2C19 and ABCB1 gene encoding the glycoprotein P (P-gp). During a check-up visit, the patient reported itching with scratching trauma. The routine blood tests and instrumental exams did not show any impairment (Table 2). No allergies or history of psychiatric pathologies were reported.

The patient was convinced that the itching had started in concurrence with the ASA intake. Therefore, once established the absence of a congenital clopidogrel resistance, a switch from ASA to clopidogrel was done. Fifteen days after, the patient continued to report a generalized itching. The Naranjo Algorithm was applied, showing that all assumed drugs could have caused the itching with a causality assessment classified as possible (score of 3; Table 1). Atorvastatin and silodosin were considered because they were administered at the same time as ASA.

Moreover, the patient was tested for the presence of two polymorphisms in ABCB1 (3435C>T and 1236C>T) associated to decrease of P-gp-mediated efflux (3,4), resulting homozygous for both (Table 2).

The clinical pharmacology and vascular surgery teams decided to switch from silodosin to doxazosin, for which no drug-drug interaction with atorvastatin has been reported. Three days after the suspension of silodosin, the patient referred the disappearance of the itching, confirmed at the follow-up visit (after four weeks). The Naranjo algorithm was applied again revealing a score of 5 corresponding to a "probable" association between itching and silodosin (Table 1).

Discussion

The itching experienced by the patient had long been underestimated and its aetiology was not investigated at all. Just because he was enrolled in a clinical study it has been possible to correct his therapy freeing him from the itching without given up ASA and atorvastatin.

The itching associated to silodosin, is uncommon ADR (<1%) all together with skin rash, urticarial and drug eruption (5). Romano et al. described a case of a man, who was treated with valproic acid, lorazepam, and citalopram. When silodosin 8 mg/die was added, he developed an extensive itching and purpuric skin rash. The Naranjo algorithm was not applied because of lack of data, but drug-drug interaction between valproic acid and silodosin was reported (6). In this case, as well as for that here described, the role of the drug-drug interaction in determining the association between silodosin and itching seems clear. In fact, atorvastatin may increase the plasmatic levels of silodosin by P-gp efflux transporter, thus caution and clinical monitoring are recommended (7).

Atorvastatin may have caused an increase of the silodosin plasmatic levels by inhibiting the P-gp in the patient carrying two well-known polymorphisms associated to a decrease of P-gp efflux activity.

To identify the cause of a certain ADR might be difficult, especially when it is misled by the patient's beliefs. In particular, the itching may be easily misdiagnosed due to the presence of other pathological conditions.

This clinical case stresses the importance to monitor the drugs side effects by considering all the patients' available and evaluable information.

Acknowledgments

We thank the patient for giving his written informed consent to participate in the study and to publish his clinical, diagnostic and anamnestic data for scientific purposes.

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Table 1. Naranjo Algorythm scores at baseline, after the changes from ASA to clopidogrel and from silodosin to doxazosin. The drugs associated with the suspected adverse reaction and the respective Naranjo Algorithm score are reported. After the switch from ASA (suspected drug) to clopidogrel, itching persisted. In concomitance with such a switch, omeprazole was changed with pantoprazole. The Naranjo score for ASA became 2 (see the green cell). Silodosin was discontinued and doxazosin was introduced. After stopping silodosin the itching disappeared. This drug was associated to the itching with a probability score of 5 according to the Naranjo algorithm (see the red cell).

NA: Naranjo Algorithm; ASA: acetylsalicylic acid; Ω3-vit: Omega-3-vitamins B6, B9, B12, vitamin k2 or menaquinones.

Itching				No itching	
Baseline		After switch from ASA to clopidogrel		After switch from silodosin to doxazosin	
DRUG	**NA score**	**DRUG**	**NA score**	**DRUG**	**NA score**
ASA 100 mg/die	3	ASA (dechallange)	2	/	/
omeprazole 20 mg/die	3	pantoprazole	3	pantoprazole	3
atorvastatin 20 mg/die	3	atorvastatin	3	atorvastatin	3
olmesartan medoxomil 10 mg/die	3	olmesartan medoxomil	3	olmesartan medoxomil	3
nebivolol 5 mg x 1/2/die	3	nebivolol	3	nebivolol	3
Ω3-vit. K2,B supplements	3	Ω3-vit. K2,B supplements	3	Ω3-vit. K2,B supplements	3
silodosin 8 mg/die	**3**	**silodosin**	**3**	**silodosin** (dechallange)	**5**

Table 2. Results of Laboratory Tests and Genotyping. The results of the laboratory tests carried out by the patient, as well as the patient's genotype relative to the three tested polymorphisms, are shown in the table.

HCT: hematocrit; RBC: red blood cells; Hb: hemoglobin; WBC: white blood cells; PLT: platelet count; MPV: mean platelet volume; PDW: platelet distribution width ; PCT: plateletcrit; PT: prothrombin time ; aPTT: activated partial thromboplastin time; GFR: glomerular filtration rate corrected for body surface (1.73 mq) and sex (Male); LDL: low density lipoproteins; HDL: high density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase. ABCB1 C3435T: single nucleotide polymorphism in gene encoding the P glycoprotein ; ABCB1 C1236T: single nucleotide polymorphism in gene encoding the P glycoprotein CYP3A4*1B (-392A>G): single nucleotide polymorphism in gene encoding the CYP3A4; WT: wild type.

VARIABLES	PATIENT'S VALUE	NORMAL RANGE
HCT (%)	45,3	42 – 52
RBC (x106/uL)	4,74	4.7 - 6.1
Hb (g/dl)	14	13 - 16
WBC (x103/uL)	8,01	4.8 - 10.8
PLT (x103/uL)	204	130 - 400
MPV (fL)	10,8	9,7 - 12,8
PDW (fL)	12,5	9 -14
PCT (%)	0,22	0,20 - 0,36
PT (sec)	11,4	10 -13
aPTT (sec)	30	28 - 40
Fibrinogen (mg%)	191	150 - 400
GFR (ml/min/1.73 mq)	54	46 - 70
Triglycerides (mg/dl)	115	50 - 150
Total cholesterol (mg/dl)	126	120 – 220
LDL (mg/dl)	72	70 - 180
HDL (mg/dl)	41	40 - 80
AST (U/l)	25	0 - 41
ALT (U/l)	24	0 - 41
GammaGT (U/l)	28	1 - 30
Pseudocholinesterases (U/l)	8725	5100 – 11700
Total bilirubin (mg/dl)	0,74	0 - 1.2
Direct bilirubin (mg/dl)	0,13	0 - 0.51
Indirect bilirubin (mg/dl)	0,30	0 - 0.59
Albumin(g/dl)	3,6	3,5 - 5,0
TESTED POLYMORPHISMS	**PATIENT'S GENOTYPE**	**WT GENOTYPE**
ABCB1 C3435T	TT	CC
ABCB1 C1236T	TT	CC
CYP3A4*1B (-392A>G)	AA	AA