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The Potential Drug-Drug Interactions in Alzheimer Patients' Treatment

Alzheimer Hastalarının Tedavisinde Potansiyel İlaç-İlaç Etkileşimleri

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Abstract

Objective: Advanced age, as a cause of increased prevalence of co-morbidities, is one of the main risk factors for Alzheimer disease. Co-morbidities accompanying the Alzheimer as well as the disease itself elicit polypharmacy which means two or more drugs used concomitantly. One of the undesirable results of polypharmacy is potential drug-drug interactions (pDDI). The study aimed to evaluate the pDDIs in Alzheimer patients.

Material-Method: Files of patient who applied to a XXX Outpatient Clinic of a tertiary hospital in XXX between 2016-2018 were evaluated retrospectively. Rate of polypharmacy, presence and type of pDDI were determinated.

Results: In the analyses of 115 files, mean age was 75.13+9.38 and frequency of polypharmacy was calculated as 53.9%. Presence of 3 or more co-morbidites was associated with polypharmacy. pDDI was detected in 77.4% of patients and type C interaction was the most common type. Quetiapine, citalopram/escitalopram, donepezil, risperidone and acetylsalicylic acid were the five drugs that interacted with the maximum number of other medications.

Conclusions: The rate of polypharmacy and pDDI as a consequence of polypharmacy could be higher in Alzheimer patients. Some pDDIs could impair the therapeutic effects of Alzheimer drugs in addition to undesirable effects. So the pDDI should be kept in mind when a new drug should be added to Alzheimer patient.

Keywords: Alzheimers Disease, Potential Drug-Drug İnteraction, Elderly, Polypharmacy.

Özet

Amaç: İleri yaş, artan ko-morbidite prevalansının bir sonucu olarak, Alzheimer hastalığı için ana risk faktörlerinden birisini oluşturur. Alzheimer hastalığın kendisi yanında, bu hastalığa eşlik eden ko-morbiditeler, polifarmasi olarak ifade edilen iki veya daha fazla ilacın eş zamanlı kullanımını ortaya çıkarır. Polifarmasinin istenmeyen sonuçlarından biri, potansiyel ilaç-ilaç etkileşimleridir (pDDI). Bu çalışma Alzheimer hastalarında pDDI'ların değerlendirilmesini amaçlamıştır.

Materyal-Metot: 2016-2018 yılları arasında XXX'da bulunan üçüncü basamak bir hastanenin XXX Polikliniğine başvuran hastaların dosyaları retrospektif olarak değerlendirildi. Polifarmasi oranı, pDDI varlığı ve tipi belirlendi.

Bulgular: Analiz edilen 115 dosyada yaş ortalaması 75,13+9,38, polifarmasi sıklığı %53,9 olarak hesaplandı. Üç veya daha fazla ko-morbidite varlığı polifarmasi ile ilişkili bulundu. Hastaların %77,4'ünde pDDI saptandı ve en sık görülen tip C tipi etkileşim olarak belirlendi. En fazla sayıda ilaçla etkileşime giren ilaçlar; ketiapin, sitalopram / essitalopram, donepezil, risperidon ve asetilsalisilik asit olarak sıralandı.

Sonuç: Alzheimer hastalarında polifarmasi ve bunun bir sonucu olarak pDDI oranları daha yüksek olabilir. Bazı pDDI'lar, istenmeyen etkilerin yanı sıra Alzheimer ilaçlarının terapötik etkilerini de bozabilir. Bu yüzden, Alzheimer hastalarına yeni bir ilaç eklenmesi gerektiğinde pDDI akılda tutulmalıdır.

Anahtar kelimeler: Alzheimer Hastalığı, Potansiyel İlaç-İlaç Etkileşimi, Yaşlı, Polifarmasi.

Introduction

Alzheimer disease (AD), which constitutes 50-70% of all cases of dementia, is a neurodegenerative disease that manifests itself in behavioral changes and memory impairment (1, 2). Considering that the age is the most important risk factor, it is not surprising that the prevalence of disease is increasing in aging countries worldwide (3). Increasing age accompanies many other chronic conditions including AD (4, 5). In addition, it has been shown that there may be more than one co-morbid condition in patients with AD regardless of age (6). Especially in patients with severe dementia, combination therapy may be preferable instead of monotherapy (7). Considering all of these factors, the probability of using more than one drug, called polypharmacy, in AD patients increases.

Although the definition of polypharmacy in the literature is mostly done only by the number of drugs, there are also definitions that include the duration of use of the drug or classify the polypharmacy into light-to-medium categories as well. Among these, the most commonly used definition is the numerically defined definition and includes five or more drugs

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(8). The use of polypharmacy reduces patient compliance, and leads to drug-drug interactions and undesirable advers effects. While age is an important cause of polypharmacy due to accompanying co-morbid diseases, lack of enough knowledge about drug effects and interactions in physicians may be an important factor for polypharmacy and its possible results (9).

Drug-drug interaction is defined as the change in the efficacy or toxicity of a drug due to a concomitant or previous medication (10). It is known that 70% of these interactions, which constitute 20-30% of the side effects associated with drugs, are clinically important and 1-2% of them cause life-threatening adverse events (11). While the observed adverse effect of two or more drug combinations on the patient is defined as the actual drug-drug interaction, the potential drug-drug interaction (pDDI) assessment is performed theoretically regardless of whether the patient has an adverse effect. There are several software programs that evaluate pDDIs. These programs are created from text-books, articles and other internet sources, and are updated frequently (12).

The aim of this study was to evaluate the presence of pDDI in patients admitted to a tertiary health care facility with the possible drug combinations in the treatment of AD, as well as the medications added to the treatment due to age and / or, other medical problems associated with AD.

Material and Methods

Ethical Approval

After the approval of XXX University Clinical Research Ethics Committee (Ethic no: 9/07/2019-237), the files of patients who applied to XXX University Medical Faculty Hospital XXX Outpatient Clinic between 2016-2018 were evaluated.

Study Design

A total of 250 files were reached from the hospital admissions. Of 250,115 files that include demographic datas, diagnosis times and drug information were analyzed for polypharmacy and pDDIs. The term of polypharmacy was considered as 5 or more drugs. The duration of drug use was not evaluated, polypharmacy categorization was not performed. Lexi-Interact database was used to evaluate pDDIs. This database has been shown to be the most competent, complete and easy to use program between available ones (12). In the program that describes the pDDIs and these mechanisms, the interactions are classified as A, B, C, D and X according to the severity. There are suggestions as the evaluation of treatment modification or avoidance of combination, for D and X type interactions which are important for clinical reflection (13).

Statistical Analysis

SPSS 23.0 (SPSS Inc., Chicago, IL, US) package program was used to evaluate the data. To compare the mean values of the linear variables, the Student's t-test was used for the groups with a standard distribution and the Mann–Whitney U-test for those that did not have a standard distribution (post hoc pairwise comparison test). $p<0.05$ was determined as the significance value.

Results

A total of 115 patients were included in the study. 46.1% of the patients were female and 53.9% were male. The mean age of all patients was 75.13±9.38 (min-max: 51-95). The mean age of the women (74.87±9.08) and men (75.43±9.80) were similar (p=0.750) (Table 1). The mean number of drugs used was 5.43±2.85 (min-max: 1-12). The frequency of polypharmacy in patients was calculated as 53.9% (n=62). No relation was found between age and number of medications (r=-0.132, p=0.158).

Table 1. Age, number of drugs used, and presence of polypharmacy in patients

	Women (n=53)	Men (n=62)	Total (n=115)	p value
Age (mean±SD)	74.87±9.08	75.43±9.80	75.13±9.38	0.750
Number of drugs used (mean±SD)	5.34±2.56	5.50±3.09	5.42±2.85	0.765
Polypharmacy (5 or more drugs) (n) (%)	29 (54.7)	33 (53.2)	62 (53.9)	0.873

SD: Standard Deviation

Comorbid diseases in patient files are shown in Table 2 below. There were no comorbid diseases in 14 of these patients, 1 comorbid disease in 17 patients, 2 comorbid diseases in 22 patients, and 3 or more comorbid diseases in 62 patients. The most common chronic diseases accompany to AD were listed as depression (n=61), hypertension (HT) (n=53), cardiovascular system disease other than HT (n=50). A significant relationship was found between the presence of three and more comorbid disease and polypharmacy.

pDDI was detected in 77.4% (n=89) of the 115 files. Among these interactions group A was 13.9% (n=16), group B was 20.0% (n=23), group C was 68.9% (n=79), group D was 46.1% (n=53), and group X was 20.0% (n=23). When each type of interaction was evaluated separately, the mean number of group A interaction per person was 0.14±0.38, group B interaction number was 0.36±0.61, group C interaction number was 3.94±5.21, in group D was 1.11±1.92 and in group X was 0.34±0.78. The table showing the interaction types and numbers is given below (Table 3).

Table 3. Interaction rates ant types

Group	Interaction rate (%)	Number of interaction per person (Mean±SD)
A	13.9%	0.14±0.38
B	20%	0.36±0.61
C	68.9%	3.94±5.21
D	46.1%	1.11±1.92
X	20%	0.34±0.78

Table 2. Presence of co-morbid diseases and drugs used in these patients

Co-morbid Diseases		Number of patients n (%)	Number of drugs used (mean±SD)	p value
Number of co-morbid disease	0	14 (12.2%)	2.57±1.16	<0.001*
	1	17 (14.8%)	3.82±1.51	
	2	22 (19.1%)	3.91±1.45	
	≥3	62 (53.9%)	7.05±2.74	
Depression	+	61 (53.0%)	6.36±2.88	<0.001*
	-	54 (47.0%)	4.37±2.44	
Hypertension (HT)	+	53 (46.1%)	6.83±2.79	<0.001*
		62 (53.9%)	4.23±2.31	
Cardiovascular system disease other than HT	+	50 (43.5%)	6.78±2.87	<0.001*
	-	65 (56.5%)	4.38±2.38	
Other psychiatric diseases	+	39 (33.9%)	6.51±2.75	0.003*
		76 (66.1%)	4.87±2.75	
Diabetes mellitus	+	21 (18.3%)	7.19±3.12	0.001*
	-	94 (81.7%)	5.03±2.65	
Vitamin or mineral deficiency	+	17 (14.8%)	6.29±2.69	0.175
		98 (85.2%)	5.28±2.86	
Parkinson's	+	17 (14.8%)	7.65±2.85	0.002*
	-	98 (85.2%)	5.04±2.68	
Gastrointestinal systems disease	+	10 (8.7%)	8.30±2.21	0.001*
	-	105 (91.3%)	5.15±2.76	
Thyroid function disorders	+	8 (7.0%)	7.13±2.70	0.080
	-	107 (93.0%)	5.30±2.83	
Epilepsy	+	7 (6.1%)	6.86±3.24	0.172
	-	108 (93.9%)	5.33±2.82	
Chronic obstructive pulmonary disease	+	7 (6.1%)	5.57±2.76	0.890
	-	108 (93.9%)	5.42±2.87	
Cardiovascular disease	+	6 (5.2%)	7.50±2.74	0.067
	-	109 (94.8%)	5.31±2.82	

Regarding pDDI, the first five drugs that have an interaction with the maximum number of other medications are; quetiapine (intercations with 40 different drugs) citalopram/escitalopram (intercations with 33 different drugs), donepezil (intercations with 28 different drugs), risperidone (intercations with 23 different drugs) and acetyl-salicylic acid (ASA) (intercations with 19 different drugs). In present study, interactions belong to these five drugs were detailed.

Quetiapine

Quetiapine, interacted with 40 different drugs, caused pDDI in the 19.1% of the patients (n=22). In Table 4 drugs that interacted with quetiapine and number of patients who had this inteaction were shown. Donepezil (13%) and rivastigmine (8.7%) were the first two drugs interacted with quetiapine.

Table 4. Drugs that interacted with quetiapine

Drugs that interact with quetiapine	Number of patients (n=115)	Percentage (%)
Donepezil	15	13
Rivastigmine	10	8.7
Sertraline	7	6.1
Escitalopram	5	4.3
Rasagiline	4	3.5
Risperidone, pramipexole, metformin, levodopa, haloperidol (each one separately)	3	2.6
Trazodone, tamsulosin, indapamide, amlodipine, metoprolol, olanzapine (each one separately)	2	1.7
Alfuzosin, alprazolam, amantadine, amitriptyline, barnidipine, bisoprolol, domperidon, glimepirid, hydrochlorothiazide, insulin aspart, irbesatran, candesartan, lamotrigine, levatiracetam, levocarbidopa, memantine, nebivolol, olmesartan, perindopril, citalopram, tramadol, trandolapril, valsartan	1	0.9*

*Each drug had only one interaction

Citalopram / Ecitalopram

The drugs that caused interactions with citalopram/ escitalopram in 24.3% (n=28) of the patients were shown in Table 5. Donepezil (15.6%) and ASA (10.4%) were the first two drugs interacted with citalopram/escitalopram.

Table 5. Drugs that interacted with citalopram / escitalopram

Drugs that interacted with citalopram / escitalopram	Number of patients (n=115)	Percentage (%)
Donepezil	18	15.6%
ASA	12	10.4%
Ginkgo, quetiapine, piracetam	5	4.3%
Metformin	3	2.6%
Alfuzosin, clopidogrel, trazodone	2	1.7%
Acemetacin, dexketoprofen, diclofenac, gliclazide, haloperidol, hydroxychloroquine, insulin aspart, candesartan, levetiracetam, olanzapine, rasagiline, sertraline, sitagliptin, tramadol, valsartan, venlafaxine, indapamide, irbesartan, memantine, risperidone, galantamine	1	0.9%*

*Each drug had only one interaction, ASA:Acetyl-salicylic Acid

Table 6. Drugs that interacted with donepezil

Drugs that interact with Donepezil	Number of patients (n=115)	Percentage (%)
Quetiapine, sertraline	15	13.0
Metoprolol	9	7.8
Indapamid, citalopram, venlafaxine	4	3.5
Olanzapine, propranolol	3	2.6
Risperidone, trazodon	2	1.7
Amantadine, alfuzosin, aripiprazole, budesonide, dipyridamole, domperidone, fluoxetine, formoterol, haloperidol, hyoscine-N-butylbromide, carvedilol, memantine, paroxetine, propiverine	1	0.9*

*Each drug had only one interaction

Table 7. Drugs that interacted with donepezil

Drugs that interacted with risperidone	Number of patients (n=115)	Percentage (%)
Rivastigmin, pramipexole, quetiapine	3	2.6
Venlafaxine, bisoprolol, donepezil, metformin, olanzapine	2	1.7
Amantadine, amitriptyline, biperiden, diltiazem, escitalopram, fluoxetine, glimepride, insulin, indapamide, levodopa, olmesartan, ramipril, rasagiline, metoprolol	1	0.9*

*Each drug had only one interaction

Table 8. Drugs interacted with ASA

Drugs interacted with ASA	Number of patients (n=115)	Percentage (%)
Ginkgo	14	12.2
Escitalopram	12	10.4
Piracetam	8	7.0
Clopidogrel	7	6.1
Sertraline, metformin	5	4.3
Ramipril	4	3.5
Fluoxetine, venlafaxine, perindopril	3	2.6
Paroxetine	2	1.7
Diltiazem, dipyridamole, duloxetine, enalapril, gliclazide, pentoxifylline, pioglitazone, sitagliptin	1	0.9*

*Each drug had only one interaction, ASA: Acetyl-salicylic Acid

Donepezil

Almost half of the patients had interactions between donepezil and another drug. (n=65, 47.8%). Quetiapine (13%) and metoprolol (7.8%) were the first two drugs interacted with donepezil. Drugs that interacted with donepezil were shown in Table 6.

Risperidone

Risperidone that was found to interact with 23 different drugs caused pDDI in 6 patients (5.2%). Rivastigmin (2.6%) and venlafaxine (1.7%) were the first two drugs interacted with risperidone. Table 7 shows the drugs that interacted with risperidone.

ASA

It was determined that ASA caused interaction with 19 different drugs (29.6%). Ginkgo (12.2%) and escitalopram (10.4%) were the first two drugs interacted with ASA (Table 8).

Discussion

AD, the most common cause of dementia, is one of the leading disease occuring with the advanced age (14). Studies show that women with a diagnosis of AD are more that men (15). Parallel to this general informations, the mean age of 115 patients whose files were evaluated was 75.13, but the number of male patients was found to be higher in our study. This numerical difference was not statistically significant and can be explained by the short interval which the files were evaluated.

Age-related changes and co-morbidities occuring with the increasing age cause an elevation in the number of drugs used by patients. Although this condition, called polypharmacy, means the simultaneous use of two or more drugs as a term, in the studies polypharmacy is generally evaluated as five or more drugs (16). In the literature, the rate of polypharmacy determined in elderly patients varies between 30% and 86% in different countries, but this value is around 30% in developed countries (17, 18). In a study conducted with outpatients over 65 years of age in our country, the rate of use of at least 3 drugs was 91%, and the rate of using at least 5 drugs in nursing homes was calculated as 39.3% (16, 19). On the other hand, there are studies which reported that 40% of the elderly outpatients used 5 or more drugs (20). In present study, the rate of use of 5 or more drugs was found as 53.9%. Although this rate seems to be higher than the rate of developed countries, factors such as the variability in the definition of polypharmacy and the associated parameters (duration of drug use, etc.), and the diversity of the patient population make it difficult to make a comparison.

While no comorbid disease could detect in the files of 14 patient, at least 1 co-morbidity was determined in the remainings. Depression and hypertention (HT) were the first and second common co-morbidity, recpectively, in the co-morbidity list. In present study, we found 3 or more comorbid diseases in 53.9% of the patients and there was a significant relationship between this condition and polypharmacy. In a Brazilian study, the most common co-morbidities in AD patients were HT, depression, DM and hypercholesterolemia, respectively (21). Similarly, in another study evaluating co-morbidities in patients with Parkinson's and AD, it was reported that both patient groups had more co-morbidities than healthy controls, and circulatory system disease, endocrine system diseases and metabolic diseases were the most common diseases in

all groups (22). These co-morbid conditions can explain the polypharmacy in our country as well as in the world.

Different pDDI rates have been shown in studies conducted in different countries and in different sample groups. In present study, pDDI rate was detected as 77.4%. In a study including 6 European countries and conducted in 2002, the rate of 1 and more pDDI was found to be 46%, while there are countires that this rate was estimated as 80% (23, 24). If dementia patients are considered, in recent studies performed with this patient group 1 and more pDDI rates were determinated as 43.2% to 59.1% (25, 26). The fact that our rates were higher than the other countries in terms of both the general population and dementia patient population, it might be due to the differences in the drug prescribing habits, polypharmacy perception and access to medicines among countries

Among the pDDIs identified, the most common was C-type interaction, as shown in other studies (16). Although such interactions that are considered to be "potentially clinically relevant" and can be controlled by dose adjustment, it should still be kept in mind during prescribing that this potential may continue (27).

In the analysis of files, the first drug that has an interaction with the maximum number of other medications was quetiapine. Quetiapine interacted with other drugs in 19.1% of the patients and interacted with 40 different drugs. Quetiapine was most frequently interacted with donepezil (n=15) and rivastigmine (n=10). These drugs, which are both acetylcholine esterase inhibitors, interac with quetiapine in form C interaction type. When acetylcholinesterase inhibitors, that are the standard treatment modalities used to stabilize or ameliorate the cognitive dysfunction in AD (28), are used with an anticholinergic drug such as quetiapine, expected effect of drug may decrease because of the mechanism of action opposite to each other. In addition, an elevation in anticholinergic load may increases the frequency of undesirable side effects. A study in Korea showed that approximately 6% of patients who were started on acetylcholinestarase inhibitor treatment due to dementia were exposed to other drugs with high anticholinergic load in the first 3 months of treatment, and this was related to delirium and increased mortality as well as treatment modification (29). Similarly, increased anticholinergic load has been reported to enhance the occurrence of delirium by 40% in palliative care patients (30). The present study progressed only through pDDI assessment. Furthermore, due to its retrospective design, the associated clinical data could not be fully obtained or questioned. Therefore, the effect of cholinergic load increase on AD treatment was not evaluated clinically in our study. However, given that the treatment of AD is started in the early period and the drugs used for the longest period are donepezil and rivastigmine, every drug which will be added in the treatment of patients should be carefully investigated in order to not to increase the potential cholinergic load. In the interacting-drug list of current study, there are drugs which have numerically few but clinically significant interactions with quetiapine. Parkinsonian drugs such as pramipexole, L-dopa and amantadine interac with quetiapine in form D interaction type. The antipsychotic-antiparkinsonian drug interaction is discussed below.

In the analysis, the second drug that has an interaction with the maximum number of other medications was citalopram. Depression, commonly accompany to AD and is treated mainly with antidepressants, is important as it adversely affects the patient's results and quality of life. The possibility of using antidepressants in patients with dementia or cognitive dysfunction is known to be two times higher than those without dementia (32). However, current studies have shown controversial results about the efficacy of antidepressants in AD and a superiority to placebo has not been shown for antidepressants (33). In present study, ıt was shown that sertaline mostly interacted with donepezil by means of number. However, this interaction is a type A interaction, which is not considered clinically significant. In a study conducted in healthy volunteers, concurrent use of sertaline and donepezil showed no significant change in drug pharmacokinetics (34). Numerically significant sertraline-ASA interaction is a type C interaction, which is important because of the possible antiplatelet effect of the sertraline to increase the risk of bleeding. Ginkgo preparations used in the treatment of AD also have anticoagulant-antiplatelet properties (13). Citalopram-Ginkgo interaction is classified as type D interaction and indicates a serious risk of bleeding in the patient. Interactions of citalopram with drugs used for both AD treatment and other co-morbidities appear to be mainly interactions that do not change the results and treatment of AD, but rather increase the risk of bleeding. One of the interactions in the intercating drug list that creates a difference apart from the increase in bleeding is the interaction between sertraline and quetiapine. This type C interaction can cause a psychomotor impairment that can be deepening by clustering both drug-induced depressant effects, and may accelerate the cognitive decline in the patient. As the use of antidepressants have already begun to be controversial in AD, they should be prescribed by considering the side effects of these drugs alone, as well as the increased risk of bleeding.

In the analysis, the thirth drug that has an interaction with the maximum number of other medications was donepezil. This molecule mostly interacted with metoprolol, after quetiapine and sertraline. The interaction with sertraline was a type A interaction and no clinical effect was expected, whereas interaction with metoprolol is a type C interaction and may manifest as bradycardia.

In the analysis, the fourth drug that has an interaction with the maximum number of other medications was risperidone and this drug mostly interacted with rivastigmine, pramipexol and quetiapine respectively, by means of number. Psychotic symptoms or agitation, commonly associated with AD, are negatively impact the quality of life of patients and their relatives, and accelerate the cognitive impairment (35). At this point, antipsychotic drugs are preferred in the treatment of dementia-related behavioral disorders (36). Among these interactions, the interaction between antipsychotic risperidone and an antiparkinsonian molecule, pramipexole, is remarkable. The types of dementia that develop in Parkinson's disease are considered as Lewy body dementia and Parkinson's dementia, and the co-existence of AD and Parkinson's

disease is rarely seen in the literatüre (37, 38). Although this co-existence is rare, the drug-drug interaction seen in these patients is classified as D-type interaction that needs to be considered clinically important, and a result of interaction the antiparkinson activity of pramipexole may be reduced. This interaction does not directly change the course of AD, but may worsen Parkinsonism, leading to increased mortality and morbidity. Atypical antipsychotics are preferred more frequently because of the weak dopaminergic D2 blockade in patients with psychotic symptoms, and quetiapine is known as the least harmful molecule (39). In present study an interaction between quetiapine and risperidone was determinated. C-type interaction between these two antipsychotics, prescribed rarely together in clinical practice, may manifest with prolonged QT time. Similar to the interaction between donepezil-rivastigmine, interaction between quetiapine and risperidone does not affect the primary disease course, but may cause significant problems in the elders who are already vulnerable to cardiovascular disease. Therefore, it should be kept in mind that the potential interactions of antipsychotic drugs may have serious clinical implications and that the use of antipsychotics in patients with Parkinson's disease may increase the risk of death more than 2 times (40). In present study, an interaction was determined between risperidone and rivastigm in 3 patient files. Type C interaction suggests that rivastigmine may increase the neurotoxic effects of antipsychotic drugs. In a recent clinical study, it was shown that the simultaneous use of these two drugs caused more neurological side-effects in addition to more physiological effects (41).

In the analysis, the fifth drug that has an interaction with the maximum number of other medications was ASA and mostly interacted with Ginkgo, by means of number. Ginkgo is the only drug used in the treatment of AD among other drugs which interacted with ASA. Ginkgo preparations that have anticoagulant-antiplatelet features has an interaction with ASA as type D. Despite some studies that have reported spontaneous hemorrhages with co-administration of ASA (325 mg/oral) and Ginkgo (42, 43), there are other studies concluded that concurrent Gingko use with ASA, with the same or higher dose (500 mg), caused no significant differences in coagulation indices or advers bleeding rates (44, 45). Although the clinical data on the simultaneous use of ASA and Ginkgo preparations are controversial, haemorrhage that may occur as a result of this potential interaction should be kept in mind. The interactions of ASA with other drugs apart from Gingko are C-type interactions, and often associated with the increased risk of bleeding. The use of ASA in combination with angiotensin converting enzyme (ACE) inhibitor may theoretically reduce the beneficial effects of ACE inhibitör, in addition to increased bleeding (46). However, there are also studies suggesting that the use of two groups of drugs does not result in a decrease in ACE inhibitor activity (47, 48). In present study, a type C interaction by the use of ASA with metformin that consequently resulting decreased hypoglycemic effect of metformin was determined. However, it was reported that ASA should be used in high doses to induce hypoglycemia (49).

Conclusion

The drug-drug interactions evaluated within the scope of this study are "potential" interactions and it is not known exactly whether each patient will have the same interaction or whether each interaction will be at the same severity. However, it should be kept in mind that patients with AD are vulnerable to pDDI because of both aging and accompanying co-morbidities, so pDDIs should be considered when prescribing drugs. It is also very important to inform the family members who are responsible for care of AD patients about the interactions due to inevitable drug pairs. This information will help to take the necessary precautions in the case of a clinical reflection of the possible interaction, and more importantly, will prevent to perceive the side effect as a new clinical situation and consequently to treat this side effect with another drug that has a risk of interaction.

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