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Drug Interactions with Cholinesterase Inhibitors

An Analysis of the French Pharmacovigilance Database and a Comparison of Two National Drug Formularies (*Vidal*, *British National Formulary*)

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Abstract

Background: Cholinesterase inhibitors (ChEIs) could be involved in several drug-drug interactions (DDIs) because of their complex pharmacodynamic and/or pharmacokinetic properties.

Aim: To identify spontaneous reports in the French Pharmacovigilance Database containing DDIs with the three ChEIs marketed in France (donepezil, galantamine or rivastigmine) and to compare the informativity of two national drug references, the French national formulary (*Vidal*) and the *British National Formulary* (*BNF*), for their ability to identify ChEI-related DDIs.

Methods: Spontaneous reports submitted to the French Pharmacovigilance Database concerning donepezil, galantamine or rivastigmine were reviewed by two clinical pharmacologists from Toulouse Regional Pharmacovigilance Centre. Spontaneous reports containing DDIs were identified according to *Vidal*, *BNF* or their own judgement (and with use of the interaction supplement of the French independent drug information bulletin *La Revue Prescrire*). Then, the potential of DDIs to result in adverse drug reactions (ADRs) was evaluated. Finally, the presentations of the different ChEIs in the two references (*Vidal*, *BNF*) were compared for their DDI informativity.

Results: A total of 1058 spontaneous reports were identified that involved ChEIs in the French Pharmacovigilance Database up to 31 March 2006; of these 376 (35.5%) contained at least one DDI according to experts' judgement. In total, 118 DDIs (31.4%) were the cause of ADRs. Most of the DDIs were due to pharmacodynamic interactions (247 cases, 65.7%). The most frequently encountered drugs involved in DDIs were bradycardic (205 cases, 54.5%) and anticholinergic (118 cases, 31.4%) drugs. DDIs were found in 309 spontaneous reports (29.2%) according to *Vidal* and in 127 (12.0%) according to *BNF*. In total, 88 'serious' ADRs were related to DDIs (including seven deaths, mainly due to cardiovascular ADRs). The most frequently observed ADRs due to DDIs were cardiovascular (67 cases, mainly bradycardia, atrioventricular block and arterial hypotension) and neurological (33 cases, mainly mental confusion). Comparison of the different presentations of summary of product characteristics (SPC) showed that *Vidal* was

more informative than *BNF* for all the ChEIs, and that galantamine had the most complete data in the two references.

Conclusion: DDIs were present in more than one-third of spontaneous reports including ChEIs registered in the French Pharmacovigilance Database. Approximately, one-third of these DDIs were the cause of ADRs. The informativity of European drug dictionaries differs substantially and *Vidal* was found to be more informative than *BNF* for all the ChEIs.

Background

The selective deficiency of acetylcholine in Alzheimer's disease (AD), as well as the observations that central cholinergic antagonists (such as atropine) could induce a confusional state that bears some resemblance to the dementia of AD, has given rise to the 'cholinergic hypothesis', which proposes that a deficiency of acetylcholine is critical in the genesis of symptoms of AD.[1-3] However, it is important to note that the deficit in AD is far more complex, involving multiple neurotransmitter systems, including serotonin, glutamate and neuropeptides.[4,5] This 'cholinergic hypothesis' led to the development of cholinesterase inhibitors (ChEIs) as first-line treatment for symptoms of AD. Since the introduction of the first ChEI, tacrine in 1994, the use of these drugs has continually increased.

The ChEIs act by inhibiting the breakdown of acetylcholine through the blockade of the enzyme acetylcholinesterase. They produce modest improvements in cognitive scores in patients with AD.[4,6] Adverse effects associated with donepezil, rivastigmine and galantamine are chiefly due to excessive cholinergic stimulation, causing gastrointestinal, neurological or cardiovascular adverse drug reactions (ADRs).[7,8] Moreover, ChEIs could be involved in several drug-drug interactions (DDIs) because of their pharmacodynamic (PD) and/or pharmacokinetic (PK) properties.[9,10]

Antimuscarinic drugs (such as atropine) antagonise the pharmacological effects of ChEIs and tend to aggravate cognitive disorders treated with these drugs.[7-12] Concomitant use of ChEIs and bradycardic drugs (such as β-adrenoceptor antagonists [β-blockers], some calcium channel antagonists and some antiarrhythmics or torsades de pointes [TDP]-inducers) increases the risk of arrhythmias or syncope.[7-10] The action of competitive (non-depolarising) neuromuscular antagonists can be opposed by ChEIs, which increase the local concentration of acetylcholine. Paradoxically, ChEIs can also enhance the action of depolarising neuromuscular blockers, such as suxamethonium chloride, by inhibiting their metabolism.[7-10]

Donepezil and galantamine are metabolised via the cytochrome P450 (CYP) system. Their plasma concentrations may be raised by drugs that inhibit the isoenzyme CYP3A4 (such as ketoconazole, itraconazole and erythromycin) and by those inhibiting the isoenzyme CYP2D6 (such as fluoxetine and quinidine). Plasma concentrations of donepezil could be reduced by enzyme inducers (such as rifampicin [rifampin], phenytoin, carbamazepine or alcohol).[7-10]

Furthermore, ChEIs are prescribed to elderly patients. This population generally presents with coexisting diseases that require them to take multiple drugs (polypharmacy). Moreover, aging results in changes in PK and PD factors[2,13,14] and a decline in hepatic blood flow is normally associated with aging.[14,15] In addition, liver size decreases with aging, which is associated with a decline in functional hepatocyte number and enzyme content.[13-16] Glomerular filtration rate decreases by approximately 10% per decade after 20 years of age.[13,14,16] Even in the absence of kidney disease, renal clearance is generally reduced by as much as 50% in elderly patients.[14,17] With aging, the response to a drug on its target organ may be increased, decreased or unchanged.[18] Consequently, older adults are generally more sensitive to some drugs and less sensitive to others.[14,15] Thus, elderly patients are at increased risk of DDIs and ADRs (19% of ADRs reported in

the French Pharmacovigilance Database involve patients aged >75 years, whereas this population comprises only 7.7% of the general population in France[19]) and ChEIs because of their PK and/or PD properties further potentiate this risk.

Thus, the aim of the present study was to identify all cases of DDIs among spontaneous reports including ChEIs in the French Pharmacovigilance Database to determine their potential to induce ADRs. In addition, we compare the informativity of two main national drug references on drug information in routine clinical practice – the French national formulary (*Vidal*)[20] and the *British National Formulary* (*BNF*)[21] – for their ability to identify ChEI-related DDIs.

Methods

The French pharmacovigilance system was first established in 1973 and consists of a network of 31 regional centres. The French Pharmacovigilance Database was subsequently established in 1985 to record spontaneous reporting of ADRs.[22,23] Reporting 'serious' or 'unlabelled' ADRs to the French regional centres has been mandatory for any drug prescriber, physician, dentist or midwife in France since 1995.[24]

A 'serious' ADR is defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity or is life threatening.[25] An 'unlabelled' (or unexpected) ADR is defined as an ADR whose nature or severity is not consistent with data contained in domestic labelling or market authorisation or expected from characteristics of the drug.[25]

The present study assessed spontaneous reports submitted to the French Pharmacovigilance Database from the first day of marketing of each ChEI in France (3 September 1997 for donepezil [Aricept® [1]], 12 May 1998 for rivastigmine [Exelon®] and 7 January 2005 for galantamine [Reminyl®]) to 31 March 2006. All ChEIs available in France, donepezil, galantamine and rivastigmine were included in the analysis. Tacrine was excluded from this study because it was withdrawn from the market in 2000.

All spontaneous reports containing a ChEI (whatever the level of imputability) were extracted to analyse all DDIs and their potential to result in ADRs. In this work, we considered all potential DDIs and not only those associated with clinical consequences. For each report, the following data were recorded: age, sex, type of ADR, seriousness of ADR and associated drugs.

Spontaneous reports were reviewed by two clinical pharmacologists from the Toulouse Regional Pharmacovigilance Centre. The spontaneous reports containing DDIs were identified according to *Vidal*,[20] *BNF*[21] or the two experts' judgement (who also used the interaction supplement of the French independent drug information bulletin *La Revue Prescrire*).[26]

Subsequently, the potential of each DDI to result in an ADR was evaluated. Furthermore, the presentations of the different ChEIs in the two references (*Vidal*, *BNF*) were compared for their DDI informativity.

Table I shows the list of DDIs involving ChEIs registered in the two references and those found by the Toulouse pharmacovigilance experts. Interactions between antipsychotic drugs and ChEIs (which could induce extrapyramidal ADRs) were excluded from this study, because they remain mainly theoretical. Moreover, the European Medicines Agency recently extended the approved indications of rivastigmine to include the treatment of moderate dementia in patients with Parkinson's disease.

Results

A total of 1058 spontaneous reports including ChEIs were sent to the French Pharmacovigilance Database up to 31 March 2006. The patients had a mean age of 79.3 ± 7.9 years (31–96 years) and most of them were women (n = 683, 64.6%) [table II]. Of these spontaneous reports, 376 (35.5%) con-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Drug-drug interactions (DDIs) concerning cholinesterase inhibitors (ChEIs) registered in *Vidal*[20] (V), *British National Formulary* [*BNF*][21] (B) and those found by the Toulouse pharmacovigilance experts (E)

Interacting drug	DDI information source			Results
	donepezil	rivastigmine	galantamine	
Pharmacodynamic interactions				
Depolarising muscle relaxants (suxamethonium chloride)	E, V, B	E, V, B	E, V	Enhancing effects of muscle relaxants
Non-depolarising muscle relaxants	E, B	E, B	E	Antagonising effects of muscle relaxants
Anticholinergic drugs (atropine, scopolamine, UI drugs, antitussives, some antimuscarinic antiparkinsonian drugs, imipramine antidepressants, atropinic bronchodilators, atropinic antispasmodic agents, antihistamines, some antiarrhythmics, phenothiazine derivatives and mydriatic eye drops)[a]	E, V, B	E, V, B	E, V, B	Pharmacological antagonism
Cholinergic drugs	E, V	E, V	E, V	Enhancing cholinergic effects
Bradycardic drugs	E	E	E, V	Bradycardia
β-adrenoceptor antagonists	E, V	E	E, V	Bradycardia
Digoxin	E	E	E, V	Bradycardia
Calcium channel antagonists	E	E	E, V	Bradycardia
Amiodarone	E	E	E, V	Bradycardia
Torsade de pointes inducers	E	E	E, V	Torsades de pointes
Pharmacokinetic interactions				
CYP3A4 inhibitors (amiodarone, diltiazem, verapamil, imidazole antifungals, protease inhibitors, erythromycin, clarithromycin, josamycin)[b]	E, V		E, V	Inhibition of ChEI metabolism and increase of its plasma concentrations
Erythromycin	E, V		E, V, B	Inhibition of ChEI metabolism and increase of its plasma concentrations
Ketoconazole	E, V		E, V, B	Inhibition of ChEI metabolism and increase of its plasma concentrations
CYP2D6 inhibitors (fluoxetine, paroxetine, quinidine, thioridazine)[b]	E, V		E, V, B	Increase of ChEI metabolism and reduction of its plasma concentrations
Hepatic microsomal enzymes inducers (alcohol, antiepileptic drugs, rifampicin [rifampin], rifabutin, efavirenz, nevirapine, griseofulvine)[b]	E, V			Increase of ChEI metabolism and reduction of its plasma concentrations

a List of atropinic drugs in the 'Interaction Supplement' of the French independent drug information bulletin *La Revue Prescrire*.[26]

b *Vidal* classification concerning the CYP inhibitors or inducers.

CYP = cytochrome P450; **UI** = urinary incontinence.

tained at least one DDI according to expert judgment, with 118 (31.4%) of these DDIs assessed as having the potential to result in an ADR (figure 1). Mean age of the patients in these three groups (spontaneous reports including ChEIs [n = 1058], spontaneous reports containing DDIs with ChEIs [n = 376] and those including ADRs related to DDIs [n = 118]) did not differ significantly (table II).

Only 33 (8.8%) of the DDIs were qualified as 'interactions' in the French Pharmacovigilance Database. Donepezil was the most frequently involved drug (650 cases) followed by rivastigmine (235 cases) and galantamine (173 cases). The percentage of DDIs was quite similar for the three drugs (37.1%, 32.3% and 34.1%). However, the percentage of ADRs due to DDIs was lower for rivastigmine (7.2%) than for donepezil (12.5%) or galantamine (11.6%).

DDIs were found in 309 (29.2%) case reports according to *Vidal* and in 127 (12.0%) according to *BNF* (figure 2). In comparison to the two experts' judgement, *Vidal* reflects approximately 80% of

DDIs with ChEIs. This rate is nearly 34% for *BNF* (table I). In 78 cases, more than one DDI was identified.

Figure 3 represents the distribution of DDIs according to their main mechanism: PD or PK. In 247 cases (65.7%), at least one PD interaction was found. PK interactions were identified in 57 cases (15.2%). Moreover, both types of interaction (PD and PK) were found in 72 cases (19.1%). No PK interaction was found for rivastigmine in contrast to donepezil, which showed a high number of such interactions (109 cases).

Figure 4 shows that the PD interactions were the cause of ADRs in 74 cases and the PK interactions in 18 cases. In 26 cases, the two types of interactions were found to explain the ADRs.

The most frequently encountered drugs involved in DDIs were: drugs used in cardiovascular diseases in 205 cases (β-blockers in 83 cases, digoxin in 49 cases and amiodarone in 45 cases), anticholinergics in 118 cases and CYP inhibitors in 118 cases (table III). The most frequent ADRs were induced by bradycardic drugs (73 cases), followed by CYP inhibitors (43 cases). The most frequent PK interaction was CYP enzymatic inhibition mainly by amiodarone, paroxetine or fluoxetine (data not shown). In total, 88 (74.6%) 'serious' ADRs were related to DDIs, including seven deaths (mainly due to cardiovascular ADRs including cardiac arrest, syncope and sudden death), threatening of vital prognosis in nine cases and hospitalisation or prolongation of hospitalisation in 72 cases. The most frequently observed ADRs due to DDIs were cardiovascular (bradycardia, atrioventricular block and arterial hypotension) in 67 cases and neurological (mental confusion) in 33 other cases.

Table II. Demographic characteristics of patients in spontaneous reports including cholinesterase inhibitors (ChEIs) recorded in French Pharmacovigilance Database up to 31 March 2006

Characteristics	Spontaneous notifications including ChEIs (n = 1058)	DDIs with ChEIs (n = 376)	ADRs related to DDIs (n = 118)
Age in years [mean (range)]	79.3 ± 7.9 (31–96)	79.1 ± 10.0 (31–95)	78.4 ± 13.5 (31–94)
Women [n (%)]	683 (64.6)	236 (62.8)	74 (62.7)
Men [n (%)]	375 (35.4)	140 (37.2)	44 (37.3)

ADRs = adverse drug reactions; **DDIs** = drug-drug interactions.

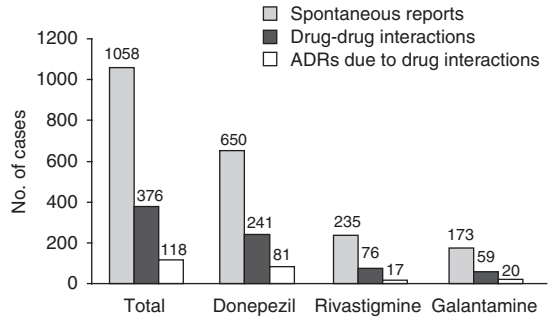

Fig. 1. Number of cases of drug-drug interactions with cholinesterase inhibitors recorded in French Pharmacovigilance Database up to 31 March 2006. **ADRs** = adverse drug reactions.

Discussion

ChEIs are commonly prescribed to elderly patients. This population generally presents with coexisting diseases that require them to take multiple drugs (polypharmacy), which increases the risk of DDIs. Moreover, ChEIs because of their PK and/or PD properties further potentiate this risk. Thus, we decided to use the French Pharmacovigilance Database to identify cases of DDIs involving ChEIs and to compare the informativity of two main national drug references largely used in routine clinical practice in France (*Vidal*)[20] and in England (*BNF*).[21]

An important factor in conducting a study of this type is the representative nature of the dataset in terms of prescriptions. The French Pharmacovigilance Database is an interesting tool indirectly reflecting drug consumption in the patient population. This database contains a description of drug use in the population presenting with an ADR. If we assume that the occurrence of ADRs in a population is random, the population reflected in the French Pharmacovigilance Database could be considered as representative of the general population using drugs, as previously demonstrated.[27] It was shown in previous studies using the French Pharmacovigilance Database that the characteristics of the populations of patients with Parkinson's disease,[28] HIV infection[29] or diabetes mellitus[30] are in accordance with

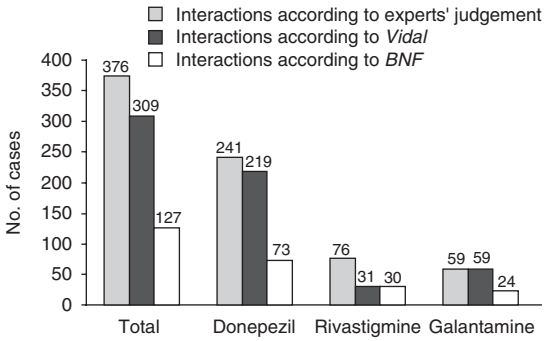

Fig. 2. Informativity of references (*Vidal*[20] and *British National Formulary* [*BNF*][21]).

epidemiological data (i.e. in terms of prevalence). Thus, the French Pharmacovigilance Database can be used to study drug prescription and to investigate drug interactions in real practice.[27]

Moreover, we attempted to compare the epidemiological data and French Pharmacovigilance Database data concerning dementia. Approximately 3.5% of the French population aged >75 years old and experiencing dementia is treated with ChEIs or memantine.[19,31,32] In the French Pharmacovigilance Database, the proportion of patients aged >75 years old experiencing ADRs and treated by ChEIs or memantine between 3 September 1997 and 31 March 2006 was 3.14%. These data show that the French Pharmacovigilance Database could be a reliable source of information concerning ChEIs prescription in real practice.

Our data show that more than one-third of spontaneous reports including ChEIs and recorded in the French Pharmacovigilance Database contain potential DDIs and almost one-third of these DDIs could explain the occurrence of ADRs. The main mechanism explaining these interactions was found to be a PD interaction (85% of cases). This is rather surprising since one could think that physicians have a better knowledge on PD than PK mechanisms. However, this finding is in accordance with a previous study performed in general practice by our group.[33]

The most frequent PD interaction found in the present study was the interaction between ChEIs and bradycardic drugs (β-blockers, digoxin, amiodarone, calcium channel antagonists) in 205 cases, followed by the unexpected association with anticholinergic drugs (118 cases). The combination of atropinic drugs and ChEIs leads to pharmacological antagonism. This combination is therefore illogical. ChEIs counter the effects of atropinic drugs used to treat urinary incontinence. Urinary incontinence is also a recognised adverse effect of ChEIs.[7,8,20,21] Moreover, atropinic drugs aggravate cognitive deficits (memory disturbances, confusion and disorientation), can cause behavioural disturbances (i.e. visual hallucinations, agitation and irritability) or decrease cognitive performance among elderly people due to their effects on the CNS.[9,34] Thus, drugs with atropinic effects can aggravate symptoms of dementia, whether or not the patient is also receiving a ChEI.[9] However, the rate of reported ADRs among DDIs with anticholinergic drugs is very low (24 of 118 cases, 20%) compared with bradycardic agents (73 of 205, 36%) and CYP inhibitors (43 of 118, 36%). Finally, association with cholinergic drugs was only observed in 11 cases.

As far as we know, there are relatively few studies investigating DDIs with ChEIs in clinical practice. For example, Doucet et al.[35] found that among a small group of 58 inpatients with AD, 19 (32.7%) received an association of ChEIs and antimuscarinic drugs. Roe et al.[11] found that older adults with

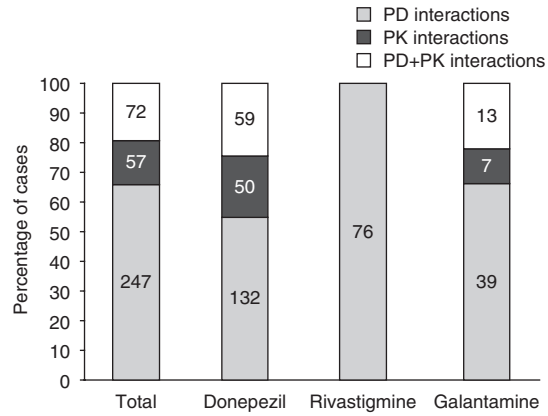

Fig. 3. Pharmacodynamic (PD) and/or pharmacokinetic (PK) interactions in spontaneous reports including cholinesterase inhibitors recorded in the French Pharmacovigilance Database up to 31 March 2006.

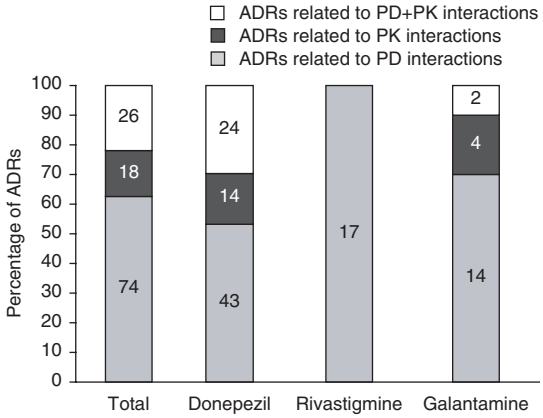

Fig. 4. Adverse drug reactions (ADRs) caused by pharmacodynamic (PD) and/or pharmacokinetic (PK) interactions in spontaneous reports including cholinesterase inhibitors recorded in the French Pharmacovigilance Database up to 31 March 2006.

probable dementia were more likely to use anticholinergic drugs (33%) than matched comparison group patients (23.4%). Moreover, of treatment group patients receiving anticholinergics, 26.1% used multiple anticholinergic medications. Finally, PD mechanisms could explain approximately 60–70% of DDIs with donepezil and galantamine versus 100% with rivastigmine (since this ChEI is not metabolised by the CYP system).

Comparison of different presentations of ChEIs registered in two references showed that *Vidal* was more informative than *BNF* for all the ChEIs. We found approximately 80% of DDIs with ChEIs in *Vidal*; this rate was only 34% for *BNF*. *Vidal* seems more faithful to the summary of product characteristics (SPC) submitted by pharmaceutical firms compared with *BNF*. Galantamine had the most complete data in the two references (in contrast to rivastigmine in *Vidal* and donepezil in *BNF*). However, we did not notice less potential DDIs with galantamine.

SPC presentations of ChEIs in *BNF* are devoid of interactions with bradycardic, TDP-inducer, cholinergic and CYP enzyme-inducer drugs. We note the absence of interactions with bradycardic drugs and TDP inducers in SPC presentations of donepezil and rivastigmine in *Vidal*. However, our data show that interactions with bradycardic drugs caused 73 ADRs (47 with donepezil, 13 with rivastigmine and 13 with galantamine), which led to death in five cases due to syncope, bradycardia, arrhythmia or cardiac arrest. These data are consistent with those previously described in the literature. In two trials lasting 2 years and involving >2000 patients with moderately altered cognitive function, galantamine was associated with increased mortality (mainly due to cardiovascular events).[36] A comparative randomised trial lasting 3 years compared donepezil with placebo. There were more deaths in patients receiving donepezil than in those receiving placebo (63 deaths with donepezil, 50 with placebo; $p = 0.08$).[37]

There are some limitations to our study. Each case report registered in the French Pharmacovigilance Database can contain a maximum of six asso-

Table III. Drug-drug interactions (DDIs) with cholinesterase inhibitors and adverse drug reactions (ADRs) related to these DDIs by different pharmacological classes in spontaneous reports recorded in the French Pharmacovigilance Database up to 31 March 2006

Drug Interactions	Donepezil		Rivastigmine		Galantamine		Total	
	DDIs	ADRs	DDIs	ADRs	DDIs	ADRs	DDIs	ADRs
Anticholinergic drugs	70	17	31	5	17	2	118	24
Cholinergic drugs	9	6	1	1	1	1	11	8
Bradycardic drugs	122	47	50	13	33	13	205	73
β-Adrenoceptor antagonists	55	18	9	3	19	12	83	33
Digoxin	32	13	12	3	5	3	49	19
Amiodarone	25	9	14	2	6	0	45	11
Calcium channel antagonists	19	8	16	7	5	0	40	15
CYP inhibitors	98	37	0	0	20	6	118	43
CYP inducers	9	0	0	0	0	0	9	0
Muscle relaxants	0	0	0	0	1	0	1	0

CYP = cytochrome P450.

ciated drugs. We could not identify DDIs for patients taking more than six drugs or for whom the case reports are not well informed (when all the drugs are not reported). So our data could present an underestimation of cases with DDIs.

Conclusion

In conclusion, this study shows that DDIs with ChEIs are involved in more than one-third of ChEIs prescriptions in the French Pharmacovigilance Database and lead to ADRs in nearly one-third of cases; furthermore, these ADRs are frequently serious. PD mechanism could explain 85% of the DDIs found in the present study. The most frequent PD interaction was the interaction between ChEIs and bradycardic drugs followed by the unexpected association with anticholinergic drugs. Informativity of British and French dictionaries differs largely and *Vidal* is more informative than *BNF* for all the ChEIs. *BNF* is devoid of interactions between ChEIs and bradycardic, TDP inducer, cholinergic and CYP enzyme-inducer drugs.

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