CHOLINESTERASE INHIBITORS AND THE RISK OF PULMONARY DISORDERS IN HOSPITALIZED DEMENTIA PATIENTS

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ABSTRACT

Objective
To evaluate whether Cholinesterase inhibitors (ChEI) are associated with an increased risk of pulmonary disorders (PD) in hospitalized dementia patients.

Methods
We conducted an observational cross-sectional study by examining the medical records of all the dementia patients hospitalized in the acute geriatric ward at the Bertinot Juel Hospital between January 1, 2005 and June 30, 2009. First, we examined whether there were any differences between the patients receiving ChEIs and those who were not. Second, we measured whether the patients had any type of PD outcome, including pneumonia, persistent cough, bronchitis, and asthma. Finally, we studied the association between ChEIs and PD. We used a logistic regression analysis preceded by a univariate analysis to adjust for other variables, such as age, weight, severity of dementia, length of stay in hospital, and history of asthma.

Results
The study included 183 patients with a mean age of 83 years. There were 131 females and 52 males. There were 55 patients with PD, including 37 with pneumonia, 11 with bronchitis, 4 with asthma, 2 with acute respiratory failure and 1 with a persistent cough. In 38 of these cases, the PD was present before hospitalization and was considered the cause of hospitalization. In 17 cases, the PD was not present at admission but occurred during hospitalization. Only ChEI treatment and age (> 80 years) were associated with an increased risk of pulmonary disorders. The adjusted relative risk was 1.98 [1.21, 3.23] for ChEI and 1.30 [1.10, 1.54] for age.

Conclusion
When prescribing ChEIs, physicians should be aware about the risk of PD. As well, withdrawing ChEIs in patients who present repeated PD should be discussed. Prospective studies need to be conducted to confirm our findings.

Key Words: *Cholinesterase inhibitor, pulmonary disorders, dementia, Alzheimer*

The acute geriatric unit in the Bertinot Juel Hospital is a 20-bed ward where approximately 400 elderly patients are admitted per year. Approximately 10% of the patients are diagnosed with dementia. Additionally, pulmonary disorders (PD) are a common pathology in our practice. Physicians at our unit have questioned whether there is an association between cholinesterase inhibitor (ChEI) treatment and the risk of PD. For example, one patient was admitted three times for pneumonia while being treated with ChEIs. Following withdrawal of the ChEI, the patient did not present pneumonia again for over two years. Other similar cases concerned us about this possible association; although, there was no documented risk in the medical literature.

Therefore, we conducted this study to evaluate whether there was an association between ChEIs and the risk of being hospitalized for PD or developing a PD when hospitalized.

METHODS

We conducted an observational, cross-sectional study (II.C.1 in the classification by Bailar, et al.[1]) by examining the medical records of all dementia patients hospitalized in 20-bed acute geriatric ward at the Bertinot Juel Hospital between January 1, 2005 and June 30, 2009. The inclusion criterion for the study was a diagnosis of dementia prior to admission. When a patient was hospitalized multiple times during the study period, we only considered the first admission following the dementia diagnosis in order to ensure independence between the data. Patients were excluded from the study if they were prescribed ChEIs during their hospitalization in our acute ward because the possible delays between the exposures and outcomes were not excluded.

First, we measured whether there were any differences between patients receiving ChEIs and those who were not. To do so, we studied the following variables: age, sex, dementia stage, dementia type, history of asthma or chronic pulmonary disease (CPD), number of medications, weight, body mass index (BMI), undernutrition (defined as BMI < 21), serum creatinine, creatinine clearance, long-term oral cortisone treatment prior to admission, diabetes, current malignancy (not in remission), length of stay in the hospital (LOS), and whether hospitalization occurred during the winter or not.

Second, we measured the outcomes, including any PD, such as pneumonia, persistent cough, bronchitis, and asthma. Pneumonia was defined as: fever, dyspnea, cough productive of purulent sputum, clinical and /or radiological signs of pulmonary consolidation. Bronchitis was defined as: Fever, acute cough and sputum production with no radiological abnormality; and improvement in bronchitis symptoms within 2 weeks. Persistent cough was defined as a cough that persists, as only symptom, more than 2 weeks after any upper respiratory infection.

Finally, we studied association between exposure to ChEIs and PD outcomes, adjusting for other variables cited above. The adjustment was performed using a logistic regression analysis preceded by a univariate analysis. The forward elimination method was used to select variables in the logistic regression because this method provided the best management for missing values. Each time we tested a new variable, data with missing values for the variable were excluded; however, if the variable was not retained, then the excluded data were re-entered during further steps to test other variables.

The work was conducted in compliance with the requirements of the site's Institutional Review Board/Human Subjects Research Committee. Formal ethical approval was not needed for this analysis of anonymised, routinely collected data. *Software:* Epi Info™ (Center for Disease Control and Prevention, Atlanta, GA, USA).

RESULTS

The study included 183 patients, and 84% of the patients had Alzheimer's disease or mixed dementia. The mean age of the patients was 83 years, and there were 131 females and 52 males. One hundred patients were receiving ChEIs. Treatment duration was < 6 months for 13 patients, between 6 and 12 months for 26 patients, more than 1 year for 20 patients, and unknown for 41 patients.

Table 1 shows that the ChEI+ and ChEI- groups only differed in terms of the type of dementia suffered (Alzheimer and mixed dementia vs. vascular and other dementia). This difference was predictable, since ChEIs have only been approved to treat Alzheimer's disease and their usefulness in treating other forms of dementia is still being discussed.

Table 2 shows that there was no difference in the reason for admission between the ChEI+ and ChEI- groups. However, the result of the chi-square test in Table 2 is difficult to interpret, since we have six categories and five degrees of freedom, which decreases the power of the test. To remedy this problem, we compared each reason for admission against all other reasons for admission. The only significant difference between the ChEI+ and ChEI- groups was whether the patient was admitted for PD.

As shown in Table 3, being treated by ChEIs was associated with a significant risk of hospitalization for PD.

In total, there were 55 PD cases (37 pneumonia, 11 bronchitis, 4 asthma, 2 acute respiratory failures and 1 persistent cough). In 38 of the PD cases, the PD occurred before hospitalization and was the cause of hospitalization. In the other 17 PD cases, the PD was not present at the admission but occurred during the hospitalization. Antibiotics were required in 47/55 cases (85%), oxygen was needed in 43/55 cases (78%), and aerosolized $beta_2$ agonists were needed in 28/55 cases (51%).

From Table 4 (qualitative variables) and Table 5 (quantitative variables), we selected the variables associated with a $p < 0.20$ to perform a logistic regression analysis with forward elimination. These variables were ChEI treatment, age, severity of dementia, weight, and LOS. We also tested the "history of asthma or CPD" variable because of its close relationship to the outcome, although, it had a p value of 0.40.

The final model retained only age (≥ 80 years old vs. < 80 years old) and ChEI treatment. All of the other variables were dropped during the multivariate process. Since we conducted a cross-sectional study, and there were not matched controls, we present the adjusted Mantel-Haenszel relative risk in addition to the odds ratio provided by the regression method in Table 6. For readers who are familiar with logistic regression, we present all of our regression steps in Appendix 1. It is important to note that the severity of dementia was no longer a significant PD factor, after being adjusted for age and ChEI treatment. As shown in Table 7, there is no difference between the three types of ChEI in terms of the associated PD risk.

TABLE 1 Characteristics of patients receiving ChEI at the admission (ChEI+) and those who were not (ChEI-), showing no difference between the 2 groups, except in the type of dementia.

	ChEI+ **100 patients**	**ChEI-** **83 patients**	**test**	**p**	**missing**
Age	Mean ± SD 82.9±6.0	Mean ± SD 82.8±6.7	Anova	0.93	0
Sex ♀/♂	72/28	59/24	Chi2	0.89	0
Weight (Ibs)	Mean ± SD 130 ± 31	Mean ± SD 128 ± 26	Anova	0.68	16
Severe dementia MMSE ≤ 10	43	30	Chi2	0.40	65
History of asthma or CPD	10	8	Chi2	0.93	0
Serum Creatinine (mg/dL)	Mean ± SD 1.02 ± 0.63	Mean ± SD 0.92 ± 0.52	Anova	0.58	6
Estimated Creatinine clearance (cockcroft and Gault formula)	Mean ± SD 51±23	Mean ± SD 50±22	Anova	0.77	23
Severe CKD (MDRD estimated GFR is <30 mL/min/1.73 m^2)	10	4	Fisher	0.27	6
BMI	Mean ± SD 23±5	Mean ± SD 22±5	Anova	0.57	80
Undernutrition (BMI < 21)	20	15	Chi2	0.90	80
Diabetes	19	10	Chi2	0.20	0
Admission occurred in winter	31	22	Chi2	0.50	0

Current malignancy	8	9	Fisher	0.34	0
LOS (days)	Mean ± SD 10.5±5.9	Mean ± SD 11.4±6.6	Wilcoxon	0.33	0
Oral Corticoids prior to admission	1	0	-	-	0
Alzheimer and mixed dementia / vascular and others dementia	89 11	64 19	Chi2	0.03	0

BMI: Body mass index, CKD: chronic kidney disease, CPD: chronic pulmonary disease, GFR: glomerular filtration rate, MMSE: mini mental state examination.

TABLE 2 Reasons of admission of patients, gathered in six categories

	Cardio Vascular disorders	**falls**	**Neuro or Psychiatric disorders**	**Medico-social problems**	**Pulmonary disorders**	**others**	**Chi2**
AChE+	9	13	22	9	27	20	P=0.30
AChE-	9	10	20	11	11	22	

TABLE 3 Pulmonary disorders, as reason of admission, compared to others reasons

	Pulmonary disorders	**Others reasons**	**RR**	**IC**	**Chi2**
AChE+	27	73	2.04	1.08-3.86	P=0.02
AChE-	11	72	-	-	

TABLE 4 Univariate analysis of categorical variables that could be associated with the risk of pulmonary disorders

		Number	**PD+/PD-**	**CRR**	**CI**	**p**	**test**	**missing**
Treatment by	Yes	100	40/60	2.21	1.32-3.71	**0.001**	Chi2	0
ChEI	No	83	15/68	-	-			
Age ≤ 80 years	Old	61	10/51	-	-			
>80 years	Too Old	122	45/77	2.25	1.22-4.15	**0.004**	Chi2	0
History of Asthma	Yes	18	7/11	1.16	0.79-1.70	0.40	Chi2	0
or CPD:	No	165	48/117	-	-			
Sex	Males	52	16/36	1.03	0.64-1.68	0.89	Chi2	0
	Females	131	39/92	-	-			

Diabetes:	Yes	29	6/23	0.65	0.31-1.38	0.23	Chi2	0
	No	154	49/105	-	-			
Corticoids	Yes	1	0/1	-	-			0
	No	182	55/127	-	-			
Under nutrition	Yes	35	12/23	1.30	0.71-2.37	0.40	Chi2	80
(BMI<21)	No	68	18/50	-	-			
Severe CKD:	Yes	14	4/10	0.95	0.40-2.25	0.58	Fisher	6
GFR <30	No	163	49/114	-	-		1tailled	
(MDRD)								
Malignancies	Yes	17	4/13	0.77	0.32-1.86	0.74	Yates	0
	No	166	51/115	-	-			
Admission in	Yes	53	17/36	1.10	0.68-1.76	0.70	Chi2	0
winter	No	130	38/92	-	-			
LOS <10 days	Short	89	31/58	1.36	0.87-2.13	**0.17**	Chi2	0
≥ 10 days	Long	94	24/70	-	-			
Severe stage of	Yes	73	24/49	2.11	0.99-4.50	**0.04**	Chi2	65
disease	No	45	7/38	-	-			
(MMSE≤10)								
ChEI duration	<6 months	13	4/9	-	-	0.27	Chi2	41
	6-12 months	26	11/15					
	>12 months	20	4/16					
Alzheimer and mixed dementia		153	48/105	1.34	0.67-2.7	0.38	Chi2	0
Vascular and others dementia		30	7/23	-	-			

TABLE 5 Univariate analysis of continuous variables that could be associated with the risk of pulmonary disease (PD).

	PD+ Mean ± SD	PD- Mean ± SD	p	test	missing
Age	84.3 ± 6.6	82.2 ± 6.1	**0.05**	Anova	0
Weight (Ibs)	123 ± 27	130 ± 29	**0.15**	Anova	16
LOS (days)	9.7 ± 4.6	11.5 ± 6.8	**0.17**	Wilcoxon[1]	0
Serum Creatinine (mg/dL)	0.97 ± 0.54	1.01 ± 0.61	0.75	Anova	6
Estimated Creatinine clearance	47±20	52±23	0.25	Anova	23
Number of drugs prior to admission	5.04±2.75	5.12±2.73	0.86	Anova	0

[1] LOS distribution is not Normal. It's why we used Wilcoxon instead of Anova.

TABLE 6 Final model of factors found to be associated with PD risk in recently hospitalized dementia patients

Method	**Logistic regression**	**Mantel-Haenszel**	
Association measure	AOR (95% CI)	ARR(95% CI)	P Value
ChEI treatment (adjusted to age)	3.01 (1.49-6.07)	1.98 (1.21-3.23)	< 0.01
Age>80 years versus Age < or = 80 (adjusted to ChEI)	2.97 (1.35-6.53)	1.30 (1.10-1.54)	< 0.01

AOR: Adjusted Odd Ratio, ARR: Adjusted Relative risk. ChEI: cholinesterase inhibitor

TABLE 7 Relation between PD and the type of AChE used

Molecule AChE	**PD-**	**PD+**	**TOTAL**
Aricept (Donepezil)	29	19	48
Row %	60,4	39,6	100
Exelon (Rivastigmine)	18	10	28
Row %	64,3	35,7	100
Reminyl (Galantamine)	13	11	24
Row %	54,2	45,8	100
TOTAL	60	40	100
Chi2: p=0.76			

DISCUSSION

This study demonstrates that there is a significant association between ChEI treatment and the risk of being hospitalized for PD or developing a PD after hospitalization. This association remained significant after adjusting for other variables in a multivariate analysis. Some cases- reports have already reported pulmonary adverse effects of ChEIs in the literature under conditions of toxicity.[2,3]

In reviewing the clinical trial (CT) literature, we observed a slight increase of PD in groups treated with ChEIs. Increased coughing was reported in 17% of patients receiving donepezil versus 14% in the placebo group during a 24-week trial.[4] Pneumonia was reported in 1.4% of patients receiving donepezil versus 0% in the placebo group during a one-year trial.[5] Additionally, pneumonia was reported in 2.6% of patients receiving galantamine versus 1.7% in the placebo group during an 18.5-month trial.[6] In some articles on galantamine safety, which did not have a placebo group, pneumonia was reported in 6% of patients during a 24-month study[7], 4.4% of patients during a 48-month study[8] and 3.7% of patients during a 36-month study.[9] In another report about galantamine[10], pneumonia was reported in 2.7% of patients, leading to drug discontinuation in 1.4% of the total patients.

We questioned why the CT literature did not indicate the significant association between ChEIs and the risk of PD. We present several possible reasons for this difference:

1) Some CTs[6,10,11,12] excluded patients with renal or hepatic disorders. These conditions facilitate drug toxicity and therefore, side effects. Renal or hepatic disorders were prevalent in the elderly patients in our study. For instance, the mean creatinine clearance as estimated by Cockcroft and Gault Formula (CG) was approximately 51 ml/min in our sample, which corresponds to moderate renal failure.

2) Some of the exclusion criteria in the CTs excluded sizable populations from the studies. For instance, the CT exclusion criteria removed patients with "any clinically significant coexisting medical condition"[7] or "any condition that, in the opinion of the investigator, would make the patient unsuitable for the study".[4]

3) The patients in the CTs were significantly healthier than the patients in our study. For example, the CTs that reported the mean weights of their patients ranged from 60 to 73 kg[4,7,10,13], while the mean weight in our study was 59 kg. Co-morbidity like diabetes was sometime an exclusion criterion in the CTs.[5,11,12] In contrast, 16% of the patients in our study were diabetics, and approximately half of these patients were receiving insulin. The patients in the CTs were healthier than the patients in our study and the mean number of comorbidities, when available, was 2.1[14] while it was 3.2 in our sample. The patients in the CTs were younger than the patients in our study. In most of the CTs[5-23], the mean patient age was less than 80. We only found one study[4] of patients with a mean age > 80, while the mean age of our patients was 83. The problem in representing dementia patients was studied by Gill et al[24], who found that fewer than half of the elderly patient's dispensed donepezil in Ontario would have been eligible to participate in the CTs that established the drug's efficacy.

4) Some investigators reported that all adverse events (AE) were recorded regardless of whether they were related to treatment.[18,25] In contrast, other investigators asked physicians to report the AE believed to be related to the treatment.[26] However, the majority of authors did not specify whether all AEs were reported or only those related to treatment.

5) Considering whether AE are related or unrelated to treatment is an important point, since physicians can examine AE carefully when they believe the event is related to treatment. One problem is that there is no agreement about the relationship between PD and ChEI treatment. For instance, in a study by Rogers et al.[12], bronchitis was considered to be related to ChEIs by the investigator, but was considered to be unrelated by the sponsor. Meanwhile, both believed that pneumonia was unrelated to ChEIs.[12]

6) Some CTs did not specify the type of AE recorded.[15,16,27]

7) In some of the CTs we studied, AEs were only recorded if they occurred in at least 5% of the patients. This threshold was apparently selected regardless of the length of the trial[5,13,18,20,21,25], which varied between three months[25] and two years.[18,20] In our opinion, the shorter the study, the lower the threshold should be when evaluating AE.

8) Considering the hypothesis of time-dependant toxicity, we should evaluate long-term safety trials. Nearly all long-term studies have an open-label extension phase preceded by a double-blind (DB) phase. In general, not all of the patients

who finish the DB phase are eligible for the extension phase because there is typically a second restrictive exclusion between the two phases. When we accounted for the patients withdrawn between phases, we found that some studies lost one-half[19], two-thirds[16], or even 90%[28] of their original sample. It is difficult to draw conclusions about long-term safety of ChEIs under these conditions.

Since our study was not a cohort study, its major limitation is the fact that the dementia diagnosis was obtained from the patients' medical files and was not supplied by our team. The patients included in our study generally arrived with medical documents in the form of a letter from their family doctor or with their hospitalization records from another unit. However, the declaration of a dementia diagnosis in France is a serious process. Since the diagnosis of dementia gives the patient the right to a total refund of their medical expenses, the protocol is signed by the National Health Insurance (Caisse d'assurance maladie) and the patient's family doctor. The family doctor should report the arguments supporting diagnosis, including the specialists' conclusions and imaging results. Additionally, in France, only geriatrics doctors, neurologists and psychiatrics can initiate treatment with ChEIs.

In our sample, there were 16 patients with mild to moderate Alzheimer's-type dementia who had not been treated with ChEI at admission. Of these patients, 2 had a history of asthma or CPD and 3 others had active malignancies. For the remaining 11 patients, there was no explanation as to why they were not receiving ChEIs. When we asked the physician responsible of our memory centre about this, he explained that treatment could have been initiated by a specialist and then stopped by a family doctor because of an adverse event like weight loss or gastrointestinal symptoms. We conclude that when prescribing ChEIs, the possible risk of PD should be considered. As well, withdrawing ChEIs in patients who present repeated PD should be discussed. Cohort studies are needed to reject or to confirm this risk.

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APPENDIX 1

Logistic Regression Steps with manual forward elimination:

Symbols:
↔: interaction term between two variables
-2L: - 2 Log likelihood ratio

Definition: The likelihood ratio test is a statistical test of the goodness-of-fit between two models. A relatively more complex model is compared to a simpler model to see if it fits a particular dataset significantly better.

Bold character: model retained at each step.

STEP A: "LOS" is tested and eliminated. In addition, interaction term is not significant.

ChEI (p>0.01)	ChEI (p<0.01)	ChEI (<0.01)
	LOS (p=0.24)	LOS (p=0.19)
		LOS↔ChEI (p=0.43)
-2L = 213	-2L = 211.7	-2L = 211

STEP B: "Asthma or CPD" is tested and eliminated. In addition, interaction term is not significant.

ChEI (p>0.01)	ChEI(<0.01)	ChEI (<0.01)
	Asthma or CPD (p=0.39)	Asthma or CPD (p=0.59)
		Asthma or CPD↔ChEI (p=0.99)
-2L = 213	-2L= 212.3	-2L=212.3

STEP C: "Weight" is tested and eliminated. In addition, interaction term is not significant.

ChEI (p>0.01)	ChEI (p<0.01)	ChEI (p=0.5)
	Weight (p=0.13)	Weight (p=0.07)
		Weight ↔CHEI (p=0.20)
-2L = 191.4	-2L=189.0	-2L=187.3

STEP D: "Severity of dementia" is tested and eliminated. In addition, interaction term is not significant.

ChEI (p<0.01)	ChEI(p<0.01)	ChEI (p=0.08)
	Severity of dementia (p=0.06)	Severity of dementia (p=0.21)
		Severity of dementia ↔CHEI (p=0.62)
-2L = 124.8	-2L=120.9	-2L=120.6

STEP E: "Age" is tested and retained, but interaction term was not significant.

ChEI (p>0.01)	**ChEI (p<0.01)**	ChEI (p=0.02)
	Age (Too old/old (p<0.01)	Age (oldold/old (p=0.03)
		Age↔ChEI (p=0.15)
-2L = 213	**-2L=204.9**	-2L=202.3

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