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ORIGINAL REPORT

Safety of valproic acid in patients with chronic obstructive pulmonary disease: a population-based cohort study

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ABSTRACT

Purpose Valproic acid is an anticonvulsant that also inhibits histone deacetylase (HDAC), a property that could worsen pulmonary function in patients with chronic obstructive pulmonary disease (COPD). The clinical significance of this property is unknown. We therefore compared the risk of COPD exacerbation in older patients with COPD commencing treatment with either valproic acid or phenytoin, an anticonvulsant that does not affect HDAC.

Methods We conducted a population-based retrospective cohort study of Ontario residents with COPD aged 66 years or older who started treatment with valproic acid or phenytoin between 1 April 1993 and 30 November 2012. The primary outcome was a hospital admission or emergency department visit for a COPD exacerbation within 240 days of drug initiation. A secondary outcome examined initiation of oral corticosteroids in the outpatient setting.

Results During the study period, we identified 4596 COPD patients who commenced valproic acid and 8478 who commenced phenytoin. Following multivariable adjustment, valproic acid did not increase the risk of the primary outcome (adjusted hazard ratio 1.00, 95% confidence interval 0.79 to 1.26). Although valproic acid was associated with a lower risk of initiating oral corticosteroids in the first thirty days following commencement of anticonvulsant therapy (adjusted hazard ratio 0.32; 95% confidence interval 0.21 to 0.49), no difference was observed during subsequent follow-up.

Conclusion Among older patients with COPD, treatment with valproic acid does not increase the risk of adverse pulmonary outcomes relative to phenytoin. These findings suggest that valproate-induced HDAC inhibition is of little clinical relevance in this context. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—chronic obstructive pulmonary disease; valproic acid; histone deacetylase; propensity score; pharmacoepidemiology

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a debilitating illness that affects approximately 65 million people worldwide and is projected to become the third leading global cause of death by 2020.[1,2] Several lines of evidence suggest that the progressive inflammatory course of COPD is related to reduced activity of histone deacetylase (HDAC) enzymes, particularly HDAC2, in the alveolar macrophages and lungs of these patients.[3,4] Because these regulatory proteins suppress inflammatory gene expression and pro-inflammatory cytokine production in alveolar macrophages, reduced HDAC activity is correlated with disease severity and corticosteroid insensitivity in patients with COPD.[5–10] Drugs that impair HDAC expression or function could therefore conceivably worsen pulmonary function in patients with COPD or provoke disease exacerbations by further amplifying inflammation and corticosteroid resistance.

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Valproic acid is a broad spectrum anticonvulsant that is also used in patients with mood disorders and headache.[11] At therapeutic concentrations, valproic acid is a selective inhibitor of HDAC activity and inducer of HDAC2 degradation, effects which would be expected to worsen pulmonary function in patients with COPD.[12–15] However, no studies have examined whether valproic acid is associated with adverse pulmonary events in patients with COPD. This is important because COPD is commonly accompanied by stroke and malignancy, both of which are associated with seizures, valproic acid is a commonly used anticonvulsant drug in the elderly and exacerbations of COPD account for a substantial portion of the burden of the illness.[1,2,16–19] We therefore compared the risk of COPD exacerbation in older patients with COPD commencing treatment with either valproic acid or phenytoin, a commonly used anticonvulsant that does not affect HDAC activity.[15] We speculated that, by virtue of HDAC inhibition, valproic acid would be associated with a heightened risk of disease exacerbation in patients with COPD relative to phenytoin.

METHODS

Study design

We conducted a population-based retrospective cohort study of Ontario residents with COPD aged 66 years or older who started treatment with valproic acid or phenytoin between 1 April 1993 and 30 November 2012. This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre, Toronto.

Data sources

We determined medication exposure using the Ontario Drug Benefit (ODB) Database, which contains comprehensive records of prescription drugs dispensed to Ontario residents aged 65 years or older. We excluded the first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records. We obtained hospitalization and emergency department data from the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System, respectively. These databases contain detailed clinical information regarding all hospital admissions and emergency department visits in Ontario. We used the Ontario Health Insurance Plan database to identify claims for physician services, and validated disease registries to define the presence of diabetes, asthma and congestive heart failure.[20–22] Finally, we obtained basic demographic data and date of death from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encrypted health card numbers, and are regularly used for population-based drug research.[23–26]

Identification of cohort

We identified patients with COPD using the Ontario COPD database, a validated registry of Ontario residents diagnosed with COPD.[27] From within this cohort, we identified individuals who were newly prescribed valproic acid or phenytoin using the ODB database, and defined the index date as the date of first prescription for either drug during the study period. To restrict our analysis to new users of these drugs, we excluded individuals who received a prescription for either of these drugs in the year before the index date. To avoid the confounding effects of severe COPD, we excluded all individuals who had been hospitalized or visited the emergency department with an exacerbation of COPD in the year preceding the index date, as well as those individuals who had filled a prescription for oral corticosteroids during this period. We censored patients who switched between study drugs, after 240 days of observation time, at death, or at the end of follow-up (31 March 2013), whichever occurred first.

Outcome measures

The primary outcome of the study was a hospital admission or emergency room visit for COPD (International Classifications of Diseases, 9th and 10th edition codes 491,492, 496 and J41 to J44, respectively) within 240 days of drug initiation. We reasoned that a 240-day follow-up period would be sufficient for capturing acute and durable effects of valproic acid-mediated inhibition of HDAC. We considered only the first hospital admission or emergency department visit as a study outcome in patients who had multiple admissions during the study period. As a secondary outcome, we examined receipt of prescriptions for oral corticosteroids during follow-up as an indicator of COPD exacerbations managed in the outpatient setting. To test the specificity of our findings, we used hospital visits for cataract surgery as a tracer outcome, since there is no plausible reason why the use of valproic acid or phenytoin would differentially influence this outcome.

Statistical analysis

We calculated descriptive statistics for patients' baseline demographic and clinical characteristics, and

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computed standardized differences to test for intergroup differences. Standardized differences of less than 0.1 indicate good balance between groups for a given covariate.[28]

We conducted time-to-event analyses using Cox proportional hazards regression to examine the association of valproic acid with our primary and secondary outcomes, using phenytoin-treated patients as the reference group. We verified the proportional hazards assumption by testing the statistical significance of a time-dependent treatment variable and by visually inspecting the estimated log(−log) survival curves. All analyses were conducted using an intention-to-treat approach in which follow-up was not terminated on treatment cessation but was instead only terminated by the occurrence of a primary event or the end of the follow-up interval. To prevent model overfitting, we adjusted our analyses for an extensive list of covariates associated with the probability of receiving either valproic acid or phenytoin using propensity scores generated by a high dimensional propensity score algorithm.[29] The seven data dimensions included in the algorithm reflect those used in previously published studies and included the number of prescription drug claims in the previous year (one dimension), hospitalization and emergency department diagnoses and procedures in the past 3 years (four dimensions) and physician claims in the past 3 years (two dimensions). The algorithm selects the top 200 most prevalent codes in each data dimension to test the potential for confounding. These covariates are then sorted in descending order of confounding potential, from which we selected the top 500 empirical variables for propensity score estimation. In addition to adjustment for the propensity score, we adjusted all models for baseline characteristics for which the standardized difference between groups exceeded 0.10. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

We identified 13 074 patients with COPD who initiated treatment with a study drug during the twenty-one year study period. Of these, 4596 (35.2%) started valproic acid and 8478 (64.8%) started phenytoin. The two groups of patients were similar with respect to medication use, socioeconomic status and chronic illness prior to cohort entry (Table 1). However, new users of phenytoin had a higher prevalence of stroke or transient ischemic attack [(1712 (20.2%) versus 275 (6.0%)], seizure disorder [843 (9.9%) versus 80 (1.7%)] and lung malignancy [138 (1.6%) versus 14 (0.3%)] in the two years prior to starting treatment (Table 1). Patients in both groups were followed for a median of 240 days.

Overall, 175 (3.8%) patients receiving valproic acid and 373 (4.4%) patients receiving phenytoin reached the primary outcome of a hospital admission or emergency room visit for COPD. Following multivariable adjustment, we found no difference in the risk of the primary outcome in patients treated with valproic acid relative to phenytoin (adjusted hazard ratio 1.00, 95% confidence interval 0.79 to 1.26) (Table 2). In the secondary analysis, 188 (4.1%) patients treated with valproic acid received a prescription for oral corticosteroids during follow-up, compared with 517 (6.1%) patients treated with phenytoin. Because the assumption of proportionality was violated for the secondary outcome, we were unable to estimate a single hazard ratio denoting the effect of the exposure drugs on subsequent receipt of oral corticosteroid therapy. Instead, we included an interaction term between treatment and follow-up time to estimate the instantaneous effect of valproic acid relative to phenytoin at 30-day intervals (Table 3). Apart from the first 30-days of treatment, where valproic acid was associated with a reduced risk of initiating oral corticosteroids (adjusted hazard ratio 0.32; 95% confidence interval 0.21 to 0.49), there was no difference between valproic acid- and phenytoin-treated patients in the risk of this outcome (Table 3). As expected, we found no difference in the risk of cataract surgery between the two groups (adjusted hazard ratio 0.79; 95% confidence interval 0.57 to 1.09) (Table 2).

DISCUSSION

In our population based study of older patients with COPD, we found no increase in the risk of hospital admissions or emergency department room visits for COPD exacerbation among those treated with valproic acid relative to phenytoin. In addition, apart from a decreased risk of initiating oral corticosteroids among valproic acid-treated patients during the first 30 days of treatment, we found no difference in this outcome at remaining 30-day follow-up intervals. We reason that the initial decrease in risk reflects unmeasured confounding related to severity of underlying COPD, given that patients receiving phenytoin appeared to be systematically less well at baseline relative to patients prescribed valproic acid.

The finding that valproic acid did not increase the risk of adverse pulmonary events was unexpected in light of evidence that this drug inhibits HDAC, the reduced activity and expression of which is associated

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Table 1. Baseline characteristics

Variable	Valproic acid users ($n = 4596$)	Phenytoin users ($n = 8478$)	Standardized difference
Age (median, IQR)	76 (71–82)	78 (72–83)	0.12
66 – 74	1971 (42.9%)	3177 (37.5%)	0.12
75 – 84	1871 (40.7%)	3700 (43.6%)	0.06
85+	754 (16.4%)	1601 (18.9%)	0.06
Female, no. (%)	2480 (54.0%)	4030 (47.5%)	0.13
Charlson Co-morbidity Index, No. (%)			
No hospitalization	2110 (45.9%)	2998 (35.4%)	0.22
0	732 (15.9%)	1101 (13.0%)	0.08
1	722 (15.7%)	1465 (17.3%)	0.04
2 +	1032 (22.5%)	2914 (34.4%)	0.26
Number of prescription medications in previous year (median, IQR)	12.0 (8.0–17.0)	10.0 (6.0–15.0)	0.29
Residence in a long-term care facility, no. (%)	1701 (37.0%)	2417 (28.5%)	0.18
Medication use in previous 365 days, no. (%)			
Inhaled corticosteroid	813 (17.7%)	1453 (17.1%)	0.01
Inhaled anticholinergic	621 (13.5%)	1176 (13.9%)	0.01
Long-acting bronchodilator	75 (1.6%)	94 (1.1%)	0.05
Short-acting bronchodilator	1018 (22.2%)	1984 (23.4%)	0.03
Inhaled bronchodilator/corticosteroid combination	338 (7.4%)	462 (5.5%)	0.08
Inhaled bronchodilator/anticholinergic combination	260 (5.7%)	409 (4.8%)	0.04
Xanthine	71 (1.5%)	330 (3.9%)	0.14
Respiratory antibiotic	1756 (38.2%)	3150 (37.2%)	0.02
Previous diagnoses			
Myocardial infarction	363 (7.9%)	600 (7.1%)	0.03
Diabetes	1305 (28.4%)	2368 (27.9%)	0.01
Asthma	1115 (24.3%)	1900 (22.4%)	0.04
Congestive heart failure	1090 (23.7%)	2284 (26.9%)	0.07
Medical conditions in previous 2 years			
Aspiration pneumonia	77 (1.7%)	195 (2.3%)	0.04
Pneumonia	326 (7.1%)	808 (9.5%)	0.09
Influenza	8 (0.2%)	23 (0.3%)	0.02
Seizure disorder	80 (1.7%)	843 (9.9%)	0.3
Alcohol abuse	147 (3.2%)	465 (5.5%)	0.11
Pneumothorax	10 (0.2%)	17 (0.2%)	0.00
Stroke or transient ischemic attack	275 (6.0%)	1712 (20.2%)	0.40
Pulmonary embolism	26 (0.6%)	53 (0.6%)	0.01
Lung malignancy	14 (0.3%)	138 (1.6%)	0.12
Income quintile, no. (%)			
1 (lowest)	1085 (23.6%)	2061 (24.3%)	0.02
2	985 (21.4%)	1920 (22.7%)	0.03
3	920 (20.0%)	1684 (19.9%)	0.00
4	807 (17.6%)	1432 (16.9%)	0.02
5 (highest)	782 (17.0%)	1313 (15.5%)	0.04
Missing	17 (0.4%)	68 (0.8%)	0.05

Table 2. Risk of adverse pulmonary events among patients treated with valproic acid or phenytoin

	Number (%) of events in valproic acid treated patients	Number (%) of events in phenytoin treated patients	Unadjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)*
Primary outcome				
Hospital admission or emergency room visit for COPD	175 (3.8%)	373 (4.4%)	0.81 (0.68 – 0.98)	1.00 (0.79 – 1.27)
Tracer outcome				
Cataract surgery	91 (2.0%)	188 (2.2%)	0.83 (0.64 – 1.07)	0.79 (0.57 – 1.09)

*Reference group is individuals treated with phenytoin. Models adjusted for propensity score, age, sex, Charlson co-morbidity score, residence in long-term care facility, number of prescription drugs in previous year, xanthine use, stroke/transient ischemic attack, seizure disorder and lung malignancy.

with increased disease severity in patients with COPD. One possible explanation for this discordance is that valproic acid may be too weak an HDAC inhibitor to elicit adverse pulmonary events in patients with COPD.[30] This reasoning has also been offered as an explanation for the drug's inability to deplete latent

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Table 3. Risk of being prescribed oral corticosteroids over time among patients treated with valproic acid or phenytoin

	Unadjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)*
Secondary outcome: prescription for oral corticosteroid		
Day 0 to 30	0.26 (0.18 to 0.40)	0.32 (0.21 to 0.49)
Day 31 to 60	0.62 (0.42 to 0.92)	0.74 (0.48 to 1.12)
Day 61 to 90	0.86 (0.56 to 1.34)	1.02 (0.64 to 1.61)
Day 91 to 120	0.89 (0.56 to 1.44)	1.04 (0.64 to 1.71)
Day 121 to 150	0.70 (0.42 to 1.18)	0.81 (0.47 to 1.39)
Day 151 to 180	0.89 (0.5 to 1.57)	1.03 (0.57 to 1.85)
Day 181 to 210	1.32 (0.77 to 2.29)	1.53 (0.87 to 2.67)
Day 211 to 240	0.69 (0.35 to 1.35)	0.80 (0.40 to 1.58)

*Reference group is individuals treated with phenytoin. Models adjusted for propensity score, age, sex, Charlson co-morbidity score, residence in long-term care facility, number of prescription drugs in previous year, xanthine use, stroke/transient ischemic attack, seizure disorder and lung malignancy.

viral reservoirs in HIV-infected patients.[31,32] Similarly, it is unknown if clinically used doses of valproic acid result in pulmonary drug concentrations sufficient for inhibiting HDAC activity in the lung. Regardless, our findings demonstrate that valproic acid's effects on HDAC should not deter clinicians from prescribing the drug to older patients with COPD when clinically indicated, particularly since it is generally well tolerated and exhibits fewer drug interactions in relation to other commonly used anticonvulsants.[11]

Some limitations of our work merit emphasis. We used administrative data rather than pulmonary function testing to identify patients diagnosed with COPD. However, we used a previously validated case-finding algorithm for identifying patients with COPD that has a specificity of 95%.[27] Although we adjusted our analyses for a propensity score derived using 500 potential confounding variables, it is possible that our findings are biased by intergroup differences in the baseline risk of COPD exacerbation. In addition, we had no access to clinical information such as medication adherence, smoking history and intercurrent viral infections that may have precipitated disease exacerbations. However, these limitations apply equally to both valproic acid and phenytoin. We had no access to measures of disease severity, such as forced volume in 1 second (FEV_1), forced vital capacity, body mass index and presence of hypoxemia or hypercapnia. Finally, because we conducted our analyses in COPD patients aged 66 years and over with no evidence of a recent disease exacerbation, our findings may not be applicable to younger patients with COPD and those with a history of recent exacerbations.

In conclusion, we found no difference in the risk of hospital admissions or emergency room visits for COPD exacerbations in older patients with COPD treated with either valproic acid, an anticonvulsant which inhibits HDAC, or phenytoin, a drug which does not exhibit this property. These findings provide a measure of reassurance that valproic acid-mediated inhibition of HDAC is of limited clinical importance in the setting of COPD, and that this drug can be safely used in these patients.

CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURE

Tony Antoniou has no conflicts of interest. Zhan Yao has no conflicts of interest. Ximena Camacho has no conflicts of interest. During the past three years, Muhammad M. Mamdani has served on advisory boards and/or received honoraria from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk and Pfizer. David N. Juurlink has no conflicts of interest. Tara Gomes has no conflicts of interest. This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre, Toronto.

KEY POINTS

- Valproic acid inhibits histone deacetylase (HDAC), a property that could worsen pulmonary function in patients with COPD.
- There was no difference in the risk of adverse pulmonary outcomes in older patients with COPD treated with either valproic acid or phenytoin, a drug that does not inhibit HDAC.

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Tony Antoniou is the guarantor of this work, and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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AUTHOR CONTRIBUTIONS

TA, ZY, XC, MMM, DNJ and TG contributed substantially to the study design, data analysis and interpretation of the data. TA drafted the manuscript. ZY, XC, MMM, DNJ and TG critically revised the manuscript. All authors approved the final version of the manuscript submitted for publication.

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