



Use of antiepileptic drugs and risk of infection in Taiwan and Denmark: A collaborative cross-national sequence symmetry analysis

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Conflict of interest

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Background and objectives

Antiepileptic drugs (AED) have been reported associated with infectious disorders; however, the association is potentially mediated by subjects using AED due to other chronic conditions that are related to frailty and thus risk of infection, such as stroke.

We aimed to investigate the risk of infectious disorders associated with the use of AED, using nationwide registries from Taiwan and Denmark.

Methods

Data were extracted from the Taiwan National Health Insurance Research Database (NHIRD) and the Danish Patient Registry and the Danish Prescription Register (DPR). New AED users from 2006-2010 without a history of cerebral palsy, stroke, dementia and disability after head trauma were included.

We performed a sequence symmetry analysis (SSA). In brief, this entails testing whether there is a disproportionate amount of subjects initiating drug A following drug B, as opposed to the other way around (denoted as the sequence ratio, SR), thereby indicating that drug B causes a need for drug A. In this case, the index drug was AED while we used both prescriptions for antibiotics (ATC J01) or hospital diagnoses as markers for infection.

Results

A total of 1,376,220 and 198,925 AED users were identified in the NHIRD and DPR, respectively; 192,291 and 20,984 of which also redeemed an antibiotic. The baseline characteristics between Taiwanese and Danish samples were similar in terms of age and gender. Clonazepam was the most prevalently used AED in Taiwan compared to gabapentin in Denmark. Overall, the use of AED was not associated with

the use of antibiotics in Taiwan, showing adjusted SRs of 0.79 (95% CI, 0.78-0.79). In Denmark, some AED and some antibiotics classes showed an association, including cephalosporins and other beta-lactam (1.39; 1.14-1.68), sulphonamides/trimethoprim (1.10; 1.05-1.15) and miscellaneous antibiotics defined by ATC code J01X (1.07; 1.05-1.08). In addition, AED were associated with admission due to infectious respiratory (1.25; 1.15-1.37) and cardiovascular (1.23; 1.16-1.30) events in Denmark.

Only few individual AED were indicated to be associated with infection with relatively small effect sizes in Taiwan. In Denmark, several AED were associated with sulphonamides/trimethoprim use including carbamazepine, phenytoin, oxcarbazepine and gabapentin.

Interpretations/Conclusions

Overall, our study does not support the hypothesis that the use of AED is associated with infectious disorders. While no associations were observed in the Taiwanese setting, some AED were associated with infections in Denmark.

Table 1
Prescribing Order in Recipients of Both Antiepileptic Drugs and Marker Drug/Diagnoses

Marker drug / diagnosis	Taiwan		Denmark	
	Casual Group / Non-casual group	Adjusted SR (95%CI)	Casual Group / Non-casual group	Adjusted SR (95%CI)
Prescription symmetry analysis				
Antibacterials(composite)	71,737 / 120,554	0.79 (0.78 - 0.79)	8,885 / 12,099	0.93 (0.90 - 0.95)
Tetracyclines	48,577 / 52,763	0.96 (0.95 - 0.96)	1,494 / 1,606	0.99 (0.93 - 1.07)
Amphenicols	21,128 / 22,608	0.99 (0.97 - 1.01)	0 / 0	-
Beta-lactam	117,532 / 148,516	0.90 (0.90 - 0.91)	9,694 / 12,574	0.94 (0.92 - 0.97)
Other beta-lactama	115,439 / 159,032	0.85 (0.84 - 0.85)	242 / 176	1.39 (1.14 - 1.68)
TMP-SMXb	49,049 / 50,810	1.02 (1.01 - 1.03)	3,897 / 3,940	1.10 (1.05 - 1.15)
Macrolides	82,843 / 93,193	0.95 (0.94 - 0.96)	6,078 / 7,252	0.92 (0.89 - 0.95)
Aminoglycoside	60,184 / 67,743	0.94 (0.93 - 0.95)	2 / 2	-
Quinolone	65,490 / 66,706	0.98 (0.97 - 0.99)	3,675 / 3,325	1.11 (1.06 - 1.17)
Miscellaneous	34,470 / 30,998	1.07 (1.05 - 1.08)	1,676 / 1,396	1.24 (1.15 - 1.33)
Infectious event symmetry analysis				
Respiratory	16,886 / 17,803	0.91 (0.90 - 0.93)	1,077 / 810	1.25 (1.15 - 1.37)
Skin & Soft Tissue	5,615 / 6,486	0.85 (0.82 - 0.88)	23 / 50	0.47 (0.28 - 0.76)
Urinary system	14,039 / 14,276	0.96 (0.94 - 0.99)	604 / 596	1.00 (0.89 - 1.12)
Skeleton& Joints	5,615 / 6,486	1.03 (0.94 - 1.13)	749 / 732	0.97 (0.87 - 1.07)
Central Nervous System	84 / 234	0.36 (0.28 - 0.46)	76 / 86	0.88 (0.65 - 1.20)
Cardiovascular	8,577 / 8,764	0.90 (0.87 - 0.93)	2,884 / 2,331	1.23 (1.16 - 1.30)
Gastrointestinal tract	1,717 / 1,885	0.89 (0.83 - 0.95)	504 / 525	0.98 (0.87 - 1.11)

a. Other beta-lactam including cephalosporins, monobactams, and carbapenems
b. Sulphonamides / trimethoprim