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Clinical short communication

Treatment with antiepileptic drugs in patients with stroke. A change in clinical practice may be required

Ali Jabareen[a], Ronen R. Leker[b], Sara Eyal[c], Dana Ekstein[b,*]

[a] Rambam Medical Center, Haifa, Israel
[b] Department of Neurology, The Agnes Ginges Center of Neurogenetics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[c] Institute for Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel

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ABSTRACT

Background: Stroke prevention is an important socio-economic aim. Epilepsy and antiepileptic drugs (AEDs), roughly divided into enzyme-inducers and non-enzyme-inducers, have been associated with increased risk of stroke.

Methods: A retrospective review of patients admitted with a diagnosis of anytime stroke and taking at least one AED was performed. A subgroup of subjects admitted for acute strokes was separately studied. Potential interactions between AEDs and other consumed medications were identified using MicroMedex and Lexi-Interact.

Results: The study included 827 patients, 59% of them using 5–10 medications. Two thirds of the patients received at least one enzyme-inducer AED, with phenytoin being the most commonly used AED (38% of the patients). Among the subgroup of 82 patients admitted for stroke, 61% were prescribed AEDs after the stroke. More patients had large vessel and embolic strokes among these than among the patients that had strokes while on AEDs. Statins, antiplatelet drugs, antidiabetics and calcium channel blockers (CCBs) were the most frequently used non-AED drugs, by 56, 55, 30 and 28%, respectively. The most common combinations between AEDs and non-AED medications bearing risk for potential major interactions were those of AEDs with statins, warfarin, calcium channel blockers and anti-depressants.

Conclusions: A change in the AEDs prescription practice in stroke patients should be implemented, to avoid interactions with major groups of other medications prescribed to these patients.

1. Introduction

Stroke is an important cause of mortality worldwide and a major cause of neurological morbidity. Therefore, stroke prevention is of major social and economic importance. Chronic administration of antiepileptic drugs (AEDs) is the mainstream of epilepsy treatment, including in 2–15% of stroke patients who develop epilepsy. [1] These drugs are also widely utilized for the treatment of other medical conditions. [2] Some of the older AEDs, namely phenobarbital, primidone, phenytoin and carbamazepine, are inducers of drug metabolizing enzymes (enzyme-inducing AEDs; EIAEDs), while most newer AEDs are non-enzyme-inducers (NEIAEDs). Valproic acid and felbamate are enzyme inhibitors.

The risk of stroke and myocardial infarction is increased in epilepsy patients compared with people without epilepsy, particularly in those being treated with high doses of AEDs. The risk is highest in patients treated with EIAEDs, and especially with phenytoin. [3] Furthermore, people treated with EIAEDs are at increased risk for myocardial infarction. [3] The increased risk of vascular events associated with the use of AEDs could be attributed to the direct contribution of EIAEDs to hyperlipidemia and to hyperhomocycteinemia [4], as well as to interactions between these drugs and cardiovascular medications. [5]

In this study we assessed the use of AEDs in combination with other medications in a large population of hospitalized patients with stroke, and analyzed the potential drug-drug interactions (DDIs) between AEDs and other drugs taken by the patients.

2. Methods

Patients' files were retrospectively reviewed, and database were

Abbreviations: AED, antiepileptic drug; EIAED, enzyme-inducer AED; NEIAED, non-EIAED; CCB, calcium-channel blocker; NOAC, non-vitamin K antagonist oral anticoagulant; DDI, drug-drug interaction

* Corresponding author at: Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem 91120, Israel.
E-mail address: dekstein@hadassah.org.il (D. Ekstein).

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searched for potential DDIs. The research was approved by the Hadassah Medical Organization Institutional Review Board (0262-15-HMO), and the need for patient consent was waived.

The institutional electronic database was searched for patients who were hospitalized between 2007 and 2011, had any type of stroke (ICD-9 430-438), at any time, and received at least one of 14 AEDs: carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, and vigabatrin. Felbamate and zonisamide were not included, because they are not approved for use by the Israeli Ministry of Health. Lacosamide, perampanel and brivaracetam were not available in Israel during the period of the study. The AEDs were divided into EIAEDs (phenobarbital, primidone, phenytoin and carbamazepine) and NEIAEDs (all other drugs). Last hospitalization was included for patients hospitalized more than once. All medications in the admission and the discharge lists were considered.

A subset of patients whose main reason for hospitalization was acute stroke was identified out of the whole cohort. In depth demographic and clinical information was obtained for these patients.

Potential DDIs were identified by the online versions of the databases MicroMedex and Lexi-Interact and were classified according to the labels available in the databases (Supplementary Material).

Chi-square analysis was performed for comparison of proportions.

3. Results

A total of 827 patients had a diagnosis of stroke. Other common diagnoses were hypertension (65%) and epilepsy (44%) (Fig. 1A). Each patient took 5.3 medications on average, 59% of patients used 5–10 medications, and 3% used > 10 different drugs.

EIAEDs and valproic acid constituted the main epilepsy treatment, with phenytoin being the most commonly prescribed (38% of the patients; Fig. 1B). Only 15% of the patients used the established newer AEDs - gabapentin (7%), lamotrigine (5%), or levetiracetam (3%). Most patients (82%) received AEDs as monotherapy. Overall, 66% of the patients used at least one EIAED.

Demographic and clinical data of 82 patients who were admitted for acute stroke (qualifying stroke) out of the 827 patients cohort are presented in Table 1. We presume that the rest of the patients had strokes before 2007 or were admitted in other institutions for the acute event.

Table 1
Demographic and clinical data.

	All n = 82	AED before stroke[a] n = 32 (39%)	AED after stroke[a] n = 50 (61%)
Age: average (range)	74 (44–98)	72 (47–92)	75 (44–98)
Sex: female – n (%)	36 (45%)	15 (47)	21 (42)
Type of stroke[a] - n (%)			
ICH	13 (16)	5 (16)	8 (16)
TIA	8 (10)	6 (19)	2 (4)
Large vessel ischemic	41 (50)	10 (31)	31 (62)
Small vessel ischemic	19 (23)	11 (34)	8 (16)
Unknown ischemic	1 (1)	0 (0)	1 (2)
Mechanism of ischemic stroke[a] - n (%)			
Embolic	32 (53)	7 (33)	25 (63)
Thrombotic	27 (44)	14 (67)	13 (33)
Unknown	2 (3)	0 (0)	2 (5)
Indication for AED – n (%)[b]			
Epilepsy	65 (79)	20 (62)	45 (90)
Pain	12 (15)	7 (22)	5 (10)
Psychiatric	6 (7)	6 (19)	0 (0)

AED – antiepileptic drug; ICH – intracerebral hemorrhage; TIA – transient ischemic attack.

[a] stroke – qualifying stroke, for which information was available in the subgroup defined in the Methods.

[b] one subject in "AED before stroke" group had both epilepsy and psychiatric indication for AED.

Most of the patients (61%) in this subset of subjects started treatment with AED after the qualifying stroke. As expected, most of these patients had embolic and large vessel ischemic strokes. Out of the 8 patients who had lacunar strokes, 5 received AEDs for treatment of pain, and one for subsequently developed epilepsy due to a brain tumor.

Among the 32 patients who had a stroke while already receiving AEDs, there was a more even distribution between small and large vessel events, and most of the ischemic strokes were thrombotic. Of note, none of the patients with intracerebral hemorrhage had been treated with warfarin. Only 62% among these patients received AEDs for treatment of epilepsy, while others were prescribed these

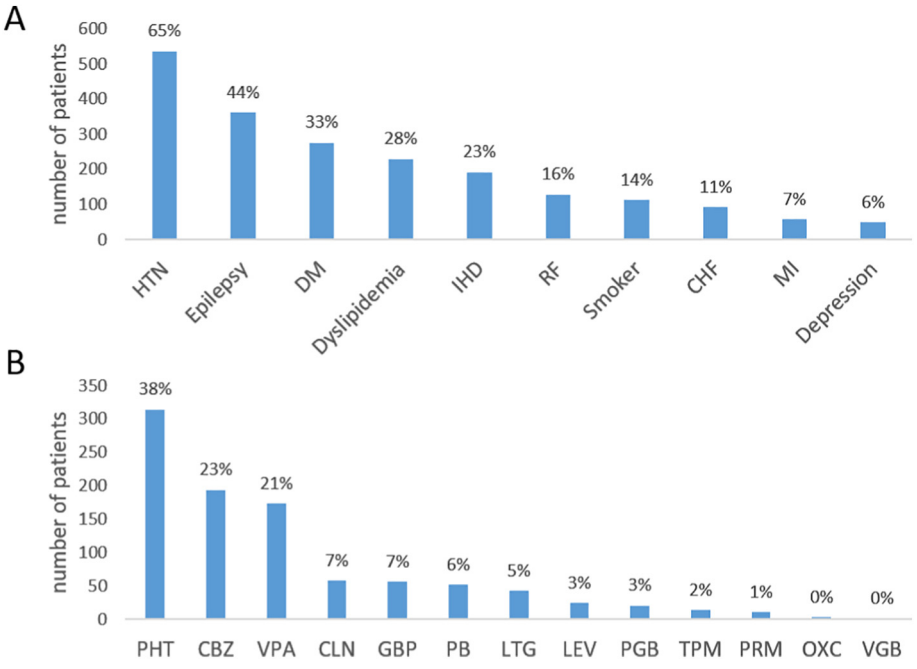

Fig. 1. Distributions of medical diagnoses and type of AED. A. Medical diagnoses. HTN – hypertension, DM – diabetes mellitus, IHD – ischemic heart disease, RF – renal failure, CHF – congestive heart failure, MI – myocardial infarction. B. AED types. PHT – phenytoin, CBZ - carbamazepine, VPA - valproic acid, CLN - clonazepam, GBP - gabapentin, PB - phenobarbital, LTG - lamotrigine, LEV - levetiracetam, PGB - pregabalin, TPM – topiramate, PRM - primidone, OXC - oxcarbazepine, VGB - vigabatrin.