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Short communication

Gastrointestinal adverse effects of antiepileptic drugs in intractable epileptic patients

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ABSTRACT

Gastrointestinal (GI) discomforts are among the most common side effects of antiepileptic drugs (AEDs) that might lead to discontinuation or irregular consumption of the drugs. This study was conducted to evaluate the frequency of GI side effects of different AEDs in intractable epileptic patients treated with single or multiple drugs. GI discomfort of 100 epileptic patients (aged 35–76 years) treated with one or multiple AEDs was assessed. Seventy six patients (76%) were treated with two or more AEDs, and 24 (24%) were on monotherapy. The most common prescribed drug for monotherapy was carbamazepine and the most frequent combination was phenytoin and carbamazepine. Patients were suffering from different GI side effects including heartburn (34.6%), nausea (33.7%), constipation (26%), vomiting (22.1%), diarrhea (21.2%) and dysphagia (19.2%). Nausea and vomiting were significantly higher in patients receiving monotherapy with carbamazepine and valproic acid, respectively. When phenytoin, gabapentine, or valproic acid was added to the other AEDs, the risk of the occurrence of diarrhea, dysphagia, or heartburn was significantly increased, respectively. Addition of gabapentine to the other AEDs in multiple drug therapy was accompanied with the highest frequency of GI complications. This study indicated that GI side effects, which can affect drug absorption and utilization, were common in intractable epileptic patients with long-term AEDs treatment. This may influence the efficacy of the therapy with AEDs and enhance the probability of further attacks.

1. Introduction

Antiepileptic drugs (AEDs) are among the most commonly prescribed centrally active agents[1] not only for treatment of epilepsy but in patients suffering from different types of pain as well as psychiatric disorders. All classical AEDs including carbamazepine (CBZ), phenobarbital (PB), oxcarbazepine (OXC), phenytoin (PHT), valproate (VPA), and primidone (PRM) were reported to be accompanied with various gastrointestinal (GI) side effects including heartburn, nausea, constipation, vomiting, diarrhea, etc.[2–4] Although new AEDs such as levetiracetam (LEV) and topiramate (TOP) are accompanied with lower incidence of side effects, they still have been reported to cause some GI disturbance.[3,5] GI complications influence the AEDs absorption and subsequently reduced the drug efficacy. In addition, GI discomfort may lead to irregular consumption of the AEDs.[6] Therefore, choosing proper single or combination AEDs therapy with less GI effects is of great importance in epileptic patients, especially those with drug-resistant attacks.

This study was conducted to assess the GI side effects of long-term AEDs therapy in a group of patients with intractable post-traumatic epilepsy. These patients were receiving either classical and/or new AEDs in form of mono or multiple therapies. This study may be helpful to recognize GI complications of each drug alone and in combination with other medications in refractory epileptic patients.

2. Patients and methods

GI complications were studied in 100 epileptic patients with post-traumatic intractable epilepsy who referred to the Epilepsy Clinic of Khatam-Alanbia Hospital in Tehran between January and April 2009. These patients were all veterans with cranial injury during Iraq–Iran war (1980–1988). Four neurologists assessed the patients' eligibility to enter the study. The participants who had

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Table 1
Diagnostic criteria for gastrointestinal discomforts.

Diarrhea	More than three loose stool in a day for more than two consecutive days of most of the weeks
Constipation	Abnormal stool form (at least 25% lumpy or hard stools), abnormal stool passage (at least 25% defecations with straining and feeling of incomplete evacuation, manual maneuvers to facilitate more than 25% defecations) and/or abnormal stool frequency (less than 3 bowel movements per week)
Vomiting	Episodes of vomiting for at least three separate days in a week, in the absence of eating disorders, rumination, and major psychiatric disorders in accordance with DSM-IV, self induction of vomiting, as well as metabolic disturbances that can explain vomiting
Dysphagia	Material may split from the mouth. Increase in the secretion of phlegm. Biting the tongue. Experiencing difficulty in the beginning of the swallow. Sticking of food in a mouth. Choking or coughing during eating or drinking with or without regurgitation of food. Meals are taking much longer time. Liquid or food coming through the nose. Drinking extra fluids with meal to wash food down.
Nausea	Queasy, sick to the stomach discomfort that may progress to the sense of a need to vomit
Heartburn (pyrosis)	Burning retrosternal sensation that can move up and down the chest like a wave. In more severe cases it may radiate to the sides of the chest, the neck, and even the angles of the jaw[18]

Table 2
Characteristics features of epileptic attacks in 100 patients suffering from intractable traumatic epilepsy. Data are presented as mean ± SEM. AEDs; antiepileptic drugs.

Characteristics of the patients	Number (%)
Seizure type	
Tonic–clonic seizures	34 (34%)
Multifocal complex partial seizure	21 (21%)
Focal simple partial seizure	34 (34%)
Partial seizures evolving to secondarily generalized seizures	11 (11%)
Age (year)	42.9 ± 8.26
Age at onset of seizures	25.2 ± 6.83
Time interval between brain trauma and onset of seizures (year)	1.44 ± 0.28
Seizure frequency (attacks per month)	3 ± 2.73
Seizure duration (year)	18.03 ± 7.1
Duration of AEDs therapy	17.32 ± 6.3

primary GI problems, received toxic dose or had irregular use of drugs would not be recruited. The basic characteristics (age, age of seizure onset, duration of AEDs therapy, the interval between brain trauma and seizure onset, seizure type, frequency and duration) were obtained. GI discomforts were assessed according to the diagnostic criteria which are summarized in Table 1. Prescribed daily doses (PDDs) of AEDs (N03A ATC group) were recorded for drugs used in monotherapy or in combination therapy. The PDD is the average daily amount of the drug that is actually prescribed by a specified group of physicians for a given time period. PDDs were compared with the defined daily doses (DDDs) suggested by WHO in the ATC/DDD index.

The study was approved by the Ethic Committee of Shefa Neuroscience Center and informed consent was obtained from each patients.

Statistical values were presented as percent or mean ± SD. Because of the exploratory character of this study, when analyzing the responses to the side effects checklist, we dichotomized complaints as not present or present. Data were analyzed using SPSS, with standard parametric (descriptive) statistics. For testing the differences between the several drugs non-parametric analysis of variance was used, based on the Kruskal Wallis test. In addition correlational analysis was performed to reveal the relation between PDDs and GI complications, using Spearman test. Significance was established when the probability values were less than 0.05.

3. Results

The mean age of participants was 42.9 ± 8.26 years (ranged: 35–76). These patients were treated for intractable epilepsy for 17.2 ± 5.6 years. The characteristic features of seizure attacks in these patients are shown in Table 2. Seventy six patients (76%) were treated with two or more AEDs and 24 (24%) patients were on monotherapy. AEDs included gabapentine (GBP), lamotrigine (LTG), OXC, TOP, VPA, PB, PHT, and CBZ. The most common prescribed drug for monotherapy was CBZ (9.6%) and the most frequent combination therapies were PHT and CBZ (14.5%), PB and PHT (9.6%), as well as PB, PHT, and VPA (5.8%; Table 4).

CBZ (41.7%) had the highest GI adverse effects in patients treated with single drug. This follows by VPA (20.8%), PB (12.5%), PHT (8.3%), and TOP (4.2%). GI adverse effects were at highest rate when GBP (39%) was included in the combination-therapy. CBZ (26.3%), PB (6.6%), PHT (3.9%), LTG (3.9%), VPA (1.3%), and OXC (1.3%) were also associated with GI side effects in patients receiving multiple AEDs for treatment of their epileptic attacks.

The most common GI complications observed either with mono or multiple AEDs therapy were heartburn (35%), nausea (33%), constipation (27.3%), vomiting (23%), diarrhea (22.2%), and dysphagia (20%).

Nausea was significantly higher in monotherapy with CBZ ($p = 0.026$) as well as vomiting in monotherapy with VPA ($p = 0.047$; Table 3). PHT ($p = 0.02$) and CBZ ($p = 0.042$) in combination with other AEDs had significant correlation with occurrence of heartburn. In addition, administration of GBP and VPA in combination with the other antiepileptic medications significantly increased the occurrence of diarrhea ($p = 0.007$) and

Table 3
Gastrointestinal side effects of antiepileptic drugs (AEDs) in patients treated with a single drug.

GI disorders	AEDs					
	Carbamazepine (9 patients)	Phenobarbital (3 patients)	Phenytoin (3 patients)	Valproate (5 patients)	Gabapantine (3 patients)	Topiramate (1 patient)
Nausea	8 (72.2%)*,§	2 (50%)	1(33.3%)	3 (50%)	0	0
Vomiting	4 (36.4%)	2 (50%)	0	4 (66.7%)*	1 (25%)	0
Dysphagia	5 (45.5%)	1 (25%)	1(33.3%)	2(33.3%)	0	0
Constipation	3 (27.3%)	1 (25%)	2(66.7%)	2(33.3%)	1(25%)	1
Heartburn	7 (63.6%)	3 (75%)	1(33.3%)	2(33.3%)	0(0%)	0
Diarrhea	4 (36.4%)	2 (50%)	1(33.3%)	2(33.3%)	0	0

§ Number (percent).
* $P < 0.05$.

Table 4
Gastrointestinal side effects of antiepileptic drugs (AEDs) in patients treated with multiple drugs.

GI disorders	AEDs							
	Carbamazepine	Phenobarbital	Phenytoin	Valproate	Lamotrigine	Oxcarbazepine	Gabapantine	Topiramate
Nausea	15 (31.2%)[§]	11 (23.4%)	11 (26.8%)	7 (31.8%)	3 (27.3%)	0	3 (42.9%)	1 (16.1%)
Vomiting	9 (18.8%)	7 (14.9%)	7 (17.1%)	4 (18.2%)	1 (9.1%)	1 (25%)	2 (28.6%)	0
Dysphagia	8 (16.7%)	7 (14.9%)	4 (9.8%)	3 (13.6%)	1 (9.1%)	0	3 (42.9%)*	1 (16.1%)
Constipation	15 (31.2%)	10 (21.3%)	11 (26.8%)	2 (9.1%)*	3 (27.3%)	2 (50%)	3 (42.9%)	2 (33.3%)
Heartburn	17 (35.4%)*	18 (38.4%)*	10 (24.4%)	11 (50%)*	3 (27.3%)	2 (50%)	0	1 (16.1%)
Diarrhea	9 (18.8%)	8 (17%)	3 (7.3%)*	2 (9.1%)	2(18.2%)	0	2 (28.6%)	1 (16.1%)

§ Number (percent).
* $P < 0.05$.

dysphagia ($p = 0.002$), respectively (Table 4). The highest rate of GI complications including nausea, vomiting, dysphagia, constipation, and diarrhea in patients on polytherapy has been observed when GBP was included.

Mean PDDs (in mg) in mono-/combination-therapy in these patients were as follows (DDDs in mg; in parenthesis): CBZ 600 and 800 (1.0), PHT 300 and 400 (0.3), GBP 0.6 and 1.2 (1,800), LTG 200 and 350 (0.3), PB 100 and 150 (0.1), VPA 1 and 1.2 (1.5). The assumed average maintenance daily dose of CBZ in monotherapy was significantly correlated to nausea ($p = 0.002$). The average drug load of PHT was also significantly correlated to diarrhea in patients treated by multiple AEDs ($p = 0.03$). After changing of AEDs, GI adverse effects in abovementioned patients resolved.

4. Discussion

This study revealed that GI adverse effects are common in patients suffering from intractable epilepsy and treated with different AEDs for several years. In our investigation, patients treated with GBP and CBZ tended to have the highest rate of GI problems. GBP and CBZ were followed by VPA, and PB. An analysis on Italy antiepileptic drug therapy showed a different toxicity profile related to each AED with common GI complications. This study reported a high rate of GI adverse reactions correlated to GBP (21%), LTG (13%), OXC (12%), CBZ (8%), and PB (1%).[7] The result of the 16 trials on a total of 1140 patients showed that PRM was related to a moderate risk of GI complications. The small risk was observed in VPA, CBZ, ethosuximide, felbamate, GBP and OXC. The risk of GI complications was negligible in PHT, PB, LTG and TPM.[8] In line with our results, they showed that the probability of having GI complications was higher in patients receiving GBP and CBZ than those treating with PHT, PB and LTG.[8]

Our results revealed that 22.1% and 33.7% of patients treated with single or multiple AEDs had vomiting and nausea, respectively. Nausea and vomiting have been reported in patients treating with CBZ, OXC, VPA, PHT, and TPM.[9–12] However, the rate of nausea and vomiting in these studies was less than our findings. Herranz et al., in a study on 35 children treated with CBZ monotherapy, found that 14% had GI disturbances including nausea and vomiting.[13] Nausea has been reported in 10.2% and 11.2% and vomiting was observed in 8.6% and 11.6% of the patients treated with OXC or VPA, respectively.[10] In another study, nausea was reported in 13.2 and 15.5% and vomiting in 9.6 and 11.3% of patients treated OXC and PHT, respectively.[9] Bootsma et al. reported that GI complaints including nausea, vomiting, and stomachache was accounted for discontinuation of TPM treatment in 10.1% of 470 epileptic patients.[11]

We observed diarrhea in 22.2% of our patients. The average drug load of PHT was correlated to diarrhea in patients treated by multiple AEDs in these patients. In line with our results, other studies indicate a higher incidence of diarrhea accompanied by PHT therapy.[10,14] Constipation was also common among our patients (27.3%). In one study, constipation reported in 5% and 1% of patients receiving VPA and placebo, respectively.[15] Constipation can also give rise to nausea and vomiting.[14]

Our findings revealed that CBZ, PHT, PB, VPA, LTG, OXC, and GBP alone or in combination with other drugs can also cause heartburn and dysphagia. To the best of our knowledge, no studies have reported these complications in association with AEDs in epileptic patients. We noted a significant relationship between VPA therapy and heartburn as well as a significant correlation between GBP and dysphagia. These complications may be related to long-term therapy with AEDs in these patients. There are several general mechanisms by which neurological side effects of AEDs can cause or aggravate oropharyngeal dysphagia such as movement disorders, myopathy, and disturbance of salivation.[16] Dysphagia is a frequent symptom in patients with many different neurological disorders including brain trauma. The symptoms of neurogenic dysphagia may be relatively inapparent due to a variety of factors. A variety of medications including AEDs may cause or exacerbate neurogenic dysphagia.[16] However, in our patients dysphagia was due to AEDs adverse effect and not caused by a CNS lesion as withdrawal of the AEDs resolved the impairment in swallowing.

The most common prescribed drug for monotherapy was CBZ and the most frequent drugs used in combination therapies were PHT, CBZ, PB, and VPA. Some new AEDs (such as LTG and LEV) had become available only very recently in Iran at the time of this study. PHT was often prescribed with other AEDs in these patients. PHT has drawbacks of a therapeutic window, considerable inter-individual variation and non-linear saturable kinetics. PHT reduces the blood levels of other AEDs such as CBZ, LTG, and VPA.[17] These interactions may potentially contribute to therapeutic failure of AEDs in these patients.

Our study was limited to enrolling only men with post-traumatic epilepsy, as well as small number of patients on monotherapy. Considering the limitations to this study, larger scale trials which include men and women and recruiting not only post-traumatic epileptic patients, are warranted to investigate also the GI side effects of AEDs.

5. Conclusion

Our findings revealed that GI complaints including nausea, vomiting, diarrhea, constipation, heartburn, and dysphagia were highly common in post-traumatic epileptic patients treated with AEDs for a long-time. GI adverse effects can affect drug absorption and utilization in epileptic patients resistant to drug therapy. This may influence the efficacy of drug therapy and increases the probability of seizure attacks.

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