AUTONOMIC NEUROPATHY AND GALLBLADDER MOTILITY DISORDERS IN PATIENTS WITH DIABETES MELLITUS

ABSTRACT: Assessment of the partial relief of symptoms are related to improvement of gallbladder motility disorders in patients with diabetes mellitus and autonomic neuropathy after treatment with Gabapentin. 30 patients with type II diabetes mellitus displaying various symptoms of autonomic neuropathy undertook this clinical study. Patients had one or more of these symptoms: sinus rest tachycardia, orthostatic hypotension, urinary disorders with no kidney functional impairment, gastric and bowel disorders. They have no previous gastric surgery, vagal denervation, or gallstones. Sex ratio was: M/W=19/11, mean age=65.32±9.78 years, body mass index=33.44±5.51kg/m². They also didn’t receive associated treatment with prokinetic agents. According to a scale of evaluation of symptoms marked with 0- absence, 1-mild, 2-moderate, 3-severe, we made a scoring of dyspepsia before and after therapy. Patients undertook a clinical trial consisting of treatment with gabapentinum with initial dose of 3x300 mg/day, with increasing doses till 3600 mg/day for 6 months. Patients were examined by transabdominal ultrasonography with a 3.5-7 MHz convex array probe, before and after the treatment. We calculated the gallbladder initial and residual volume with ellipsoid method and gallbladder ejection fraction. Before therapy the group of diabetic patients with neuropathy had a mean gallbladder ejection fraction=31.10%±3.98, showing a constant low rate of gallbladder emptying. After therapy the mean gallbladder ejection fraction was 49.59%±5.11, representing an elevation of gallbladder ejection fraction with 18.49%±1.13% and an improving of gallbladder motility. Patients treated with Gabapentin experienced a partial relief of dyspeptic complains. Best results were seen in improvement of bloating, bitter taste and abdominal pain. Even if there was a significant improvement of gallbladder motility, ejection fraction remained below 60%. This aspect raised the possibility of other mechanisms involved in mitigation of dyspeptic symptoms in diabetic patients treated with Gabapentin.

Keywords: autonomic neuropathy, gallbladder motility, dyspepsia

NEUROPATIA AUTONOMĂ ŞI TULBURĂRI DE MOTILITATE ALE VEZICULEI BILIARE LA PACIENȚII CU DIABET ZAHARAT

Rezumat: Scopul studiului a fost stabilirea unei legături între ameliorarea manifestărilor dispeptice la pacienții diabetici tratați cu Gabapentin și îmbunătățirea paramețrilor motilității veziculei biliare. Pacienții și metode: 30 pacienți cu diabet zaharat tip II cu obezitate, raportul: B/F=19/11, vârsta medie=65.32±9.78 ani, index masă corporal IMC=33.44±5.51kg/m² tratați cu antidiabetice orale, prezentând variate simptome de neuropatie autonomă (tachicardie sinusală de repaus, hipotensiune arterială ortostatică, tulburări urinare fără afectare funcțională renală, tulburări digestive) au fost inclusi în acest studiu. Pacienții nu aveau istoric de intervenții chirurgicale gastrice, denervare vagală, litiază biliară sau tratament cu prokinetică.
INTRODUCTION

It has been demonstrated that the biliary discharge functions were damaged in patients who developed autonomic neuropathy or underwent vagotomy. [1][2]

As it is well known, regulation of gallbladder function is under the control of neuroendocrine hormones. Normally, gallbladder emptying is regulated by both neural and hormonal controls. For biliary flow, gallbladder contraction is accompanied by the relaxation of the Oddi sphincter, and gallbladder emptying can be damaged in autonomic neuropathy [3]

Cholecystokinin is a physiological mediator providing relaxation of the Oddi sphincter and contraction of the gallbladder.[4]

Gabapentin has been shown to be useful in reducing chemotherapy- induced nausea in an open label preliminary study. Mitigation of tachykinin neurotransmitter activity by gabapentin has been a postulated mechanism [5].

The potential anti-emetic effect of gabapentin was also evaluated in the perioperative setting [6].

AIM

Assessment if the partial relief of symptoms are related to improvement of gallbladder motility disorders in patients with diabetes mellitus and autonomic neuropathy after treatment with gabapentin.

PATIENTS AND METHODS

Patients

30 patients with type II diabetes mellitus, treated with oral medication, sex ratio M/W = 19/11, mean age = 65.32±9.78 years, body mass index = 33.44±5.51 kg/m², displaying various symptoms of peripheral and autonomic neuropathy undertook this clinical study. Patients had one or more of these conditions: chronic pain associated to peripheral neuropathy, sinus rest tachycardia, orthostatic hypotension, urinary disorders, with no kidney functional impairment, gastric and bowel disorders: dyspepsia, delaying of gastric emptying, nocturnal diarrhea.

They had no previous gastric surgery, vagal denervation, or gallstones and didn’t receive associated treatment with prokinetic agents.

Methods

Patients undertook a clinical trial consisting of treatment with gabapentin with initial dose of 3x300 mg/day, with increasing doses till 3600 mg/day for 6 months. A thorough history was taken focused on dyspeptic complains: anorexia, nausea, vomiting, bitter taste, postprandial bloating, upper abdominal pain. According to a scale of evaluation of symptoms marked with 0- absence, 1-mild, 2-moderate, 3-severe, we made a scoring before and after therapy. Patients were examined by transabdominal ultrasonography with a 3.5-7 MHz multifrequency convex array probe, before and after the treatment.

Biliary sonograms have included transverse and longitudinal views of the gallbladder with clear anatomical relationship to the liver, kidney, and portal vein for a clearly identification.

With the patient in the supine position, the probe was placed in the right upper quadrant. Once the gallbladder was identified, longitudinal oblique and transverse axial views of the gallbladder were obtained.

We calculated the gallbladder initial and residual volume with ellipsoid method and gallbladder ejection fraction of 0- 100%.

About chemotherapy-induced nausea, patients were also evaluated in the perioperative setting. Mitigation of tachykinin neurotransmitter activity by gabapentin has been a postulated mechanism [5].

Rezumat (continuare): Pacienții li s-a administrat tratament cu Gabapentin în doze progresiv crescătoare de la 3x300mg/zi la 3600mg/zi, timp de 6 luni. S-au urmărit parametri de motilitate ai veziculei biliare înainte și după tratament. Am evaluat severitatea disprișei pacienților înainte și după tratament conform unei scale marcând cu 0- simptom absent, 1- ușor, 2- moderat, 3- sever, calculându-se un scor dispetic. Evaluarea funcțională a veziculei biliare s-a realizat utilizând ultrasonografia abdominală cu calculea indicatorilor de volum și fracția de ejeție a veziculei biliare după metoda elipsoidului, la jenum și la 30 minute după administrarea unui prânz colecistokinetic. O fracție de ejeție sub 60% a fost considerată patologică. Rezultate: Ameliorarea simptomelor dispetic le a fost observată la 20% din pacienți pentru anorexia, 46,66% pentru greață, 40% pentru vârstă, 70% pentru gust amar, 93,33% pentru balonări, 80% pentru dureri abdominale. Înaintea tratamentului fracție de ejeție medie a veziculei biliare era 31,10%;±3,98, demonstrând o rată constantă scăzută de evacuare biliară. După tratament fracția de ejeție medie a veziculei biliare a devenit 49,59%;±5,11, ceea ce a reprezentat o ameliorare funcțională veziculară cu 18,49%;±1,13%. Concluzii: Pacienții tratați cu Gabapentin au prezentat o ameliorare parțială a simptomelor dispetic. Cele mai bune rezultate s-au obținut cu simptomele de balonare, gust amar și dureri abdominale. Chiar dacă s-a constatat o ameliorare semnificativă a parametrilor funcționali ai veziculei biliare, totuși fracția de ejeție s-a menținut constant sub limita de 60%. Aceste rezultate implică posibilitatea existenței unor mecanisme complementare de îmbunătățire a acizelor dispetic le la diabeticii tratați cu Gabapentin.
fraction in fasting state and 30 minutes after a cholecystokininetic meal.

For gallbladder volume (V) calculations for the ellipsoid formula used were \( V = \frac{Q}{6} \times \text{width} \times \text{height} \times \text{depth} \)

The formula for gallbladder ejection fraction (EF): \( \text{EF} = \frac{(\text{initial volume} - \text{maximum residual volume})}{\text{initial volume}} \times 100 \). An ejection fraction below 60% was considered pathological.

**Statistical analysis**

Quantitative values expressed as mean ± SD or median ranges were compared with 2-sample. Significant differences were determined by impaired Student T-test. Statistical significance was set at \( p < 0.05 \).

**RESULTS**

Improvement of dyspeptic symptoms was noted (compared to previous assessment of symptoms scale, table 1 and figure 1 below) in 20% for anorexia, 46.66% for nausea, 40% for vomiting, 70% for bitter taste, 93.33% for bloating, 80% for abdominal pain. (Table 1)

Before therapy the group of diabetic patients with neuropathy had a mean gallbladder ejection fraction = 31.10% ± 3.98, showing a constant low rate of gallbladder emptying.

After treatment the mean gallbladder ejection fraction was 49.59% ± 5.11, representing an elevation of gallbladder ejection fraction with 18.49% ± 1.13% \( (p < 0.05) \), and an improvement of gallbladder motility.

**DISCUSSIONS**

- According to our results after treatment with gabapentin diabetic patients showed a slightly but visible improvement of gallbladder motility. This condition was represented by improving of gallbladder tonus and emptying. The gallbladder ejection fraction increased with promising clinical outcome. However improvement of the dyspeptic symptoms could not be entirely explained only by minor regulation of GB motility (EF being still below 60%).

- It’s possible that other local or distant regulatory pathways are involved. We could speculate that also the motility of the stomach with possible improvement of delayed gastric emptying is another track to investigate. These aspects should be analyzed in further studies.

**Table 1.** Scoring before and after treatment with Gabapentin

<table>
<thead>
<tr>
<th></th>
<th>ANOREXIA</th>
<th>NAUSEA</th>
<th>VOMITING</th>
<th>BITTER TASTE</th>
<th>BLOATING</th>
<th>PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median scoring before treatment</td>
<td>0.74</td>
<td>1.46</td>
<td>1.26</td>
<td>1.6</td>
<td>2.13</td>
<td>1.33</td>
</tr>
<tr>
<td>Median scoring after treatment</td>
<td>0.46</td>
<td>0.93</td>
<td>1</td>
<td>0.93</td>
<td>1.2</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**Fig. 1** Improvement of scoring for dyspepsia after treatment with gabapentin
CONCLUSIONS

- Patients treated with Gabapentin experienced a partial relief of dyspeptic complains. Best results were seen in improvement of bloating, bitter taste and abdominal pain.
- Even if there was a significant improvement of gallbladder motility, ejection fraction remained below 60%. This aspect raised the possibility of other mechanisms involved in mitigation of dyspeptic symptoms in diabetic patients treated with Gabapentin.

REFERENCE