Oral Thiocytic Acid (α-Lipoic Acid) and Gabapentin as Co-adjuvants in Paraneoplastic Neuropathic Pain

ABEER H. EL-KHOULY, M.D.
The Department of Anesthesia and Pain Relief, National Cancer Institute, Faculty of Medicine, Cairo University.

Abstract

Thiocytic acid is a powerful antioxidant. Several studies indicate that oxidative stress play important role in nerve damage and neuropathy. Thiocytic acid also controls NMDA receptors activity which are involved in hyperalgesia and allodynia in neuropathic pain. Gabapentin is a potent anticonvulsant, which was considered as a first choice drug in management of secondary neuropathic pain. This study was designed aiming to evaluate the role of oral thiocytic acid or gabapentin or their combination as co-adjuvant to oral morphine in neuropathic cancer pain therapy. Forty five patients were randomized to one of three groups (n=15). The gabapentin group received oral gabapentin 1200 mg/day; the thiocytic acid group received oral thiocytic acid 600 mg 3 times daily and the combined group received both thiocytic acid and gabapentin in the same prescribed doses in the previous two groups but together. Pain intensity was measured by Visual Analog Scale of pain (VAS) 10-cm line, alldynia area (in cm²) and severity of alldynia by VAS. Total oral morphine rescue analgesic per day and side effects were recorded. The decrease in VAS pain scores and severity of alldynia were more significant in the combined group than the other two groups at any measurement time (p<0.05). The reduction in alldynia area was up to 40% in the gabapentin group, 25% in thiocytic acid group and 45% in the combined group. Patients of the combined group showed less daily consumption of morphine on days 14 and 28 (p=0.012, p=0.005) respectively. The incidence of headache and sedation was higher in the thiocytic acid group, while the incidence of somnolence was higher in the gabapentin group. Side effects were tolerable in the combined group. We can conclude that thiocytic acid and gabapentin as co-adjuvant to oral morphine significantly improved pain scores and alldynia in neuropathic pain.

Key Words: Thiocytic acid – α-lipoic acid – Antioxidant – Neuropathic pain.

Introduction

NEUROPATHIC pain originates from neural tissue injury [1]. In cancer patients it may result either from tumor invasion into neural tissues or from surgery, radiotherapy, or chemotherapy [2].

Neuropathic pain is often severe, persistent, and can be evoked by non-noxious stimuli, such as light touch in the affected area (alldynia). It appears to be less responsive to opioid drugs than nociceptive pain. However, antidepressants and anticonvulsants are known to have clinical efficacy, but complete pain control is rarely achievable [3]. Substantial evidence has been recently accumulated; indicating that oxidative stress was shown to induce nerve damage leads to programmed cell death of nerves [4]. Oxidative processes can trigger production of excitatory amino acids, increase ca++ influx. This increased intracellular calcium leads to activation of the N-methyl-D-aspartate (NMDA) receptors. These excitatory amino acid receptors are involved in hyperalgesia and alldynia in neuropathic pain [5].

The therapeutic effect of lipoic acid has been reported to improve motor nerve and sensory nerve conduction velocity in experimental diabetic neuropathy and diabetic patients [6,7].

α-Lipoic acid (LA) and its reduced form, dihydrolipoic acid, are powerful antioxidants. Continuous oxidative and excitotoxic stress may play a role in chronic neurological disease and neuropathic pain [8]. Thiocytic acid is now proved to be effective in treatment of painful diabetic neuropathy [9].

Gabapentin is a structural analogue of gamma-amino butyric acid (GABA). It was found to be promising in treating neuropathic pain associated with post-herpetic neuralgia [10], reflex sympathetic dystrophy and diabetic neuropathy. It was also found, in an uncontrolled clinical study, to be effective in neuropathic cancer pain [11].

Hong and others found that the thiocytic acid has a modulatory effect on redox binding site of NMDA and glutamate receptors and protection against oxidant induced perturbation of intracellular...
calcium homeostasis together with increased intracellular reduced form of glutathione (GSH) level by 30-70%  [12,13].

The aim of this work was to evaluate the potential role of oral α-lipoic acid (thioctic acid), gabapentin or the combination of both drugs as coadjuvants to oral morphine in neuropathic pain therapy.

**Patients and Methods**

The study protocol was approved by the Ethical Committee in the National Cancer Institute, Cairo University. After giving informed written consent, 45 patients who came to our pain clinic regularly and suffering from neuropathic pain related to their neoplastic condition were randomized to one of three groups:

1- Thioctic acid group (n=15): received oral thioctic acid 600 mg 3 times (1800 mg) daily (Thiotacid, 600mg/tablet, EVA PHARMA, Egypt).

2- Gabapentin group (n=15): received gabapentin in a dose of 1200 mg/day (Neurontin, 400 mg/capsule, PFIZER, Egypt).

3- Combined group (n=15): received oral thioctic acid 600 mg 3 times daily, and gabapentin 1200mg/day.

Screening Visual Analog Scale VAS consisted of a 10-cm line with 0 representing “no pain at all” and 10 representing “the worst possible pain”. Patients were enrolled in the study only if pain intensity was at least 4 cm or more on a 10 cm (VAS), inspite of taking their usual analgesics, such as nonsteroidal anti inflammatory drugs, acetaminophen, and opioids. Other drugs e.g. tricyclic antidepressants, anticonvulsants, mexiletine and benzodiazepine were not allowed to be used.

The area of alldynia was determined by gently stroking the skin outside the painful area with a cotton-wool tip which was slowly advanced 1 cm closer to the area of alldynia while asking the subject to report when the sensation changed to become unpleasant or painful. Each area of alldynia was measured in cm².

The severity of alldynia was determined by the amount of pain evoked on a 10 cm VAS. Each evening, the patients were asked to record their pain intensity on a 10-cm VAS, and also record any side effects of the drug they received e.g. hallucination, dizziness, somnolence, nausea/ vomiting, headache, sedation and allergic reaction.

If VAS score was more than 3, patients were given a rescue analgesic in the form of morphine sulphate tablets 10 mg and can be repeated every 10 minutes if VAS score was still above 3 with a maximum dose of 90 mg per 8 hours and were asked to report the number of tablets taken per day. Patients were asked to come to the pain clinic every week for one month, where pain intensity, area, severity of alldynia, side effects and total morphine rescue analgesic were recorded at 0,7,14 and 28 days after treatment.

**Statistical analyses:**

Statistical analysis carried out using stat view for windows software package version 4.57 (APACUS Concept, Berkeley, CA, USA). The normality of distributions was assessed using the Shapiro-Wilk test.

Groups were compared for demographic data using one-way analyses of variance (ANOVA). The incidence of adverse events, patient gender and the site of primary disease were compared among groups using Chi-Square analyses corrected for multiple comparisons. VAS scores, the area of alldynia and daily morphine consumption on days 0,7,14 and 28 were compared using two-way analyses of variance for repeated measures. \( p<0.05 \) is considered significant.

**Results**

The groups showed no significant difference regarding age, gender or distribution of cancer primary site. The clinical diagnosis, the duration of the condition, the initial VAS and area of alldynia are shown in (Table 1). The VAS pain scores in the three groups showed a significant decrease from baseline at days 7,14 and 28 (\( p<0.05 \)). The decrease in VAS pain score was more in the combined group (thioctic acid + gabapentin) than the other two groups at any measurement time (\( p<0.05 \)) (Fig. 1).

There was a decrease in the area of alldynia from baseline in the three groups at day 14 (\( p=0.016, p=0.003, p=0.0001 \)) and day 28 (\( p=0.01, p=0.006, p=0.015 \)). The observed decrease was in the gabapentin group more than the thioctic acid group at days 14 and 28 (\( p=0.013, p=0.005 \)) respectively. The greatest decrease was in the combined group at day 28 (\( p=0.002 \)). The reduction in alldynia area was up to 40% in gabapentin group, 25% in thioctic acid group and 45% in the combined group at day 28 [Table (2) and Fig. (2)].
A similar observation was noted for the severity of allodynia as measured by the VAS pain scores, the combined group showed the greatest reduction in VAS for allodynia at day 14 (p=0.002) and day 28 (p=0.001) (Fig. 3).

There was no significant difference of the daily consumption doses of morphine rescue analgesic between the thiocitic acid and the gabapentin groups on days 7, 14 and 28 (p>0.05). The combined group showed less daily consumption of oral morphine than the other two groups on days 14 and 28 (p = 0.012 and p= 0.005 respectively) (Table 3).

Patients in the thiocitic acid group reported more headache and sedation significantly in the combined group compared to the other two groups (p=0.0001, p=0.012 respectively). Somnolence was more in the gabapentin group compared to the other two groups (p=0.002). Dizziness was mild and showed no significant difference between the three groups. There was only one patient in each group that complained of nausea, vomiting and hallucinations. Also, there was no significant difference in allergic reaction between the three groups. (Table 4).

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**Table (1): Patient characteristics and clinical data.**

<table>
<thead>
<tr>
<th>Data</th>
<th>Gabapentin group (n=15)</th>
<th>Thiocitic acid group (n=15)</th>
<th>Combined group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>9/6</td>
<td>8/7</td>
<td>7/8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.1±8.2</td>
<td>50.5±9.3</td>
<td>55.1±7.8</td>
</tr>
<tr>
<td>Pain duration (months)</td>
<td>30.4±7.7</td>
<td>33.6±6.1</td>
<td>30.2±8.2</td>
</tr>
<tr>
<td>Cancer type</td>
<td>Breast 6</td>
<td>Breast 5</td>
<td>Breast 6</td>
</tr>
<tr>
<td></td>
<td>Bladder 4</td>
<td>Bladder 4</td>
<td>Bladder 3</td>
</tr>
<tr>
<td></td>
<td>Lung 5</td>
<td>Lung 4</td>
<td>Lung 4</td>
</tr>
<tr>
<td>Total n=45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial VAS for pain (cm)</td>
<td>6.4±2.2</td>
<td>6.7±3.3</td>
<td>6.5±1.3</td>
</tr>
<tr>
<td>Initial VAS for allodynia (cm)</td>
<td>7.1±2.3</td>
<td>6.8±3.1</td>
<td>7.5±2.1</td>
</tr>
<tr>
<td>Area of alldynia (cm²)</td>
<td>34.5±7.1</td>
<td>35.3±8.2</td>
<td>35.1±7.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD
M: male  F: female

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**Table (2): Area of allodynia (cm²) during the treatment period.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Gabapentin group (cm²)</th>
<th>Thiocitic acid group (cm²)</th>
<th>Combined group (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>34.5±7.1</td>
<td>35.3±8.2</td>
<td>35.1±7.8</td>
</tr>
<tr>
<td>7 days</td>
<td>30.9±8.2</td>
<td>34±8.1</td>
<td>31±7.2</td>
</tr>
<tr>
<td>14 days</td>
<td>23.5±5.3 *</td>
<td>30.1±7.2 *</td>
<td>22.6±5.3 *</td>
</tr>
<tr>
<td>28 days</td>
<td>18.6±3.9 *</td>
<td>28.2±6.2 *</td>
<td>14.7±3.4 *</td>
</tr>
</tbody>
</table>

Values are mean ± SD
* Significant versus baseline, wsignificant versus the other two groups

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**Table (3): Mean Total daily morphine consumption (mg) in three groups.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Gabapentin group (mg)</th>
<th>Thiocitic acid group (mg)</th>
<th>Combined group (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>59.1±10.2</td>
<td>60.2±11.2</td>
<td>57.3±9.5</td>
</tr>
<tr>
<td>7th day</td>
<td>50.2±9.1</td>
<td>51.1±10.1</td>
<td>49.5±8.1</td>
</tr>
<tr>
<td>14th day</td>
<td>38.3±8.5</td>
<td>39.4±9.6</td>
<td>25.6±9.2 *</td>
</tr>
<tr>
<td>28th day</td>
<td>30.5±9.3</td>
<td>31.1±8.9</td>
<td>15.9±10.1 *</td>
</tr>
</tbody>
</table>

Values are mean ± SD
* Significant difference versus the other two groups (p<0.05)

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**Table (4): Incidence of adverse events.**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Gabapentin group (n=15)</th>
<th>Thiocitic acid group (n=15)</th>
<th>Combined group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>6 (40%) *</td>
<td>1 (6.7%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (6.7%)</td>
<td>1 (6.7%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>1 (6.7%)</td>
<td>1 (6.7%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>8 (53.3%) *</td>
<td>2 (13.3%) w</td>
</tr>
<tr>
<td>Sedation</td>
<td>1 (6.7%)</td>
<td>8 (53.3%) *</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>0</td>
<td>2 (13.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are number patient (%)
* Statistically significant from the other two groups (p<0.05)
w Statistically significant versus thiocitic acid group (p<0.05)

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**Fig. (1): The VAS pain scores of the three groups.**

Columns are means with SD bars

**Fig. (2): Mean area of allodynia in cm².**

Columns are means with SD bars

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Discussion

Excitotoxicity has been involved in neuronal death of chronic degenerative disorders [14]. Excessive activation of N-methyl-D-Aspartate (NMDA) receptors leads to mitochondrial dysfunction through increase of nitric oxide and other free radicals resulting in disturbance of intracellular calcium homeostasis. The reduced form of glutathione (GSH) is a very important free radical scavenger; it protects neurons from excitotoxicity. A naturally occurring α-lipoic acid and its reduced form (dihydrolipoic acid) are inter-convertable forms that are proved to be essential cofactors for mitochondrial bioenergetic enzymes [15]. α-lipoic acid modulates redox-binding site of NMDA and glutamate receptors, so it helps to maintain calcium homeostasis and protects neurons from excitotoxins together with increase (GSH) level by 30-70% [16]. Thioctic acid also chelates transition of metal ions (copper, iron) in heavy metal poisoning [15].

It is proved that thioctic acid restores nitric oxide (NO) level in the endothelial wall of vasa nervosum resulting in increase endoneureal blood flow and allows sprouting of nerve ending and formation of new nerve fiber in neuritis through its antioxidant properties which lead to increase production of nerve growth factor (NGF) [17]. In vivo studies on rats indicated that thioctic acid protects neurons against excitotoxic death mediated by NMDA receptor agonists and mitochondrial toxins [14]. Now, in vivo studies, it had proved that α-lipoic acid was effective in treatment of painful diabetic neuropathy and other diabetic complications and neuropathy of cranial nerves [18]. Other in vivo studies on animals demonstrated that α-lipoic acid is taken up by all areas of the CNS including the brain as it crosses blood brain barrier and peripheral nerves making it effective in numerous neurodegenerative disorders as Parkinson’s disease, Huntington's disease and Amyotrophic lateral sclerosis [19].

Preliminary human studies indicate that α-lipoic acid may play an effective role in control of neuropathic post-herpetic pain, trigeminal neuralgia and sciatica. This is expected to be mediated through its metabolic role inter-relationship with its antioxidant properties; it manages pain, burning, numbness and paraesthesia [7,13,14,20].

From all these previous studies, α-lipoic acid is considered an ideal therapeutic thiol to treat and prevent brain and nervous system disorders involving free radical processes [8]. This makes thioctic acid a promising therapeutic co-factor, can be tried in cancer related neuropathic pain. To our knowledge, this is the first trial in which thioctic acid has been studied in neuropathic cancer pain patients.

A gabapentin specific binding site was identified as the alpha 2 delta subunit of voltage gated calcium channels which may be responsible for the gabapentin anti-allodynic effects [21].

In this current study, the combined group (thioctic acid + gabapentin) showed the greatest decrease in pain intensity, area and severity of allodynia and the lowest daily morphine consumption than the other two groups. It seems that thioctic acid and gabapentin have additive effect to each other.

There was a significant decrease in pain scores and allodynia in both gabapentin group and thioctic acid group. This comes in agreement with Amyre and colleagues in their study that supports the idea that α-lipoic acid plays an important role in control of neuro-degenerative disorders and also has neuro-protective action in many acute and chronic neuropathic diseases [9,14,17].

In this study, it is observed that large proportion of patients experienced headache and sedation in the thioctic group (40%, 33.3% respectively). However, these adverse effects significantly decreased in the combined group (thioctic acid+ gabapentin).

In conclusion, the combined thioctic acid and the gabapentin as co-adjuvant to oral morphine significantly improved pain scores and allodynia in neuropathic cancer pain and the side effects were tolerable during the treatment period.

Thioctic acid is an attractive drug for further plans to investigate its effect on the future treatment of cancer related neuropathic pain. It is a logical choice as co-adjuvant in the treatment of neuropathic pain.
References