Clinical Implication of the Antidiuretic Hormone (ADH) Receptor Antagonist Mozavaptan Hydrochloride in Patients with Ectopic ADH Syndrome

Ectopic ADH Syndrome Therapeutic Research Group, Ken Yamaguchi1,*, Noriharu Shijubo2, Tetsuro Kodama3, Kiyoshi Mori3, Takahiko Sugiura4, Takayuki Kuriyama5, Masaaki Kawahara6, Tetsu Shinkai7, Haruo Iguchi7 and Masanori Sakurai8

1Shizuoka Cancer Center, Shizuoka, 2Department of Respiratory Medicine, JR Sapporo Hospital, Sapporo, 3Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center Hospital, Tochigi, 4Department of Medical Oncology, Daido Hospital, Nagoya, 5Department of Internal Medicine, Kuriyama Clinic, Tanabe, 6Department of Respiratory Diseases, Otemae Hospital, Osaka, 7Shikoku Cancer Center, Matsuyama and 8Department of Internal Medicine, Mizuno Hospital, Tokyo, Japan

*For reprints and all correspondence: Ken Yamaguchi, Office of the President, Shizuoka Cancer Center, Shimonagakubo 1007, Nagaizumi-cho, Suntogun, Shizuoka 411-8777, Japan. E-mail: k.yamaguchi@scchr.jp

Received June 22, 2010; accepted August 11, 2010

Ectopic antidiuretic hormone syndrome is a medical emergency characterized by dilutional hyponatremia. Clinical effectiveness of the vasopressin V2 receptor antagonist mozavaptan was evaluated in 16 patients. In short-term (7-day) treatment with the drug, serum sodium concentration (mean ± standard deviation) significantly (P = 0.002) increased from 122.8 ± 6.7 to 133.3 ± 8.3 mEq/l, and symptoms due to hyponatremia were improved. On the basis of these results, mozavaptan (Physuline®) was approved as an orphan drug for the treatment of the syndrome in 2006 in Japan. During the 43 months following its launch, 100 patients have been treated with the drug; overall clinical effects of the drug were found similar to those of this clinical trial. Clinically, mozavaptan may allow hyponatremic patients to be treated by aggressive cancer chemotherapy with platinum-containing drugs. Moreover, the drug may free patients from strict fluid-intake restrictions and thereby improve their quality of life.

Key words: SIADH – ectopic ADH syndrome – small cell lung carcinoma – hyponatremia – antagonist

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is divided into two categories; one is the ectopic ADH syndrome induced by abnormally secreted ADH (arginine vasopressin) from cancer cells, and another is the morbidity caused by inappropriately secreted ADH from the pituitary gland in various benign diseases. In both situations of SIADH, ADH binds to vasopressin V2 receptors (V2Rs) in renal tubules and thereby increasing water reabsorption. Clinically, SIADH is characterized by elevated fluid retention in the body, resulting in dilutional hyponatremia and subsequent manifestations of various central nervous system (CNS) symptoms.

In the present study, clinical effectiveness of a newly developed vasopressin V2R antagonist was evaluated in patients with ectopic ADH syndrome. This morbidity is frequently observed in patients with small cell lung carcinoma (SCLC) and makes it to be difficult to aggressive cancer chemotherapy with platinum-containing drugs. Patients with SIADH often require severe water restriction, worsening their quality of life.

Mozavaptan, the world’s first non-peptide V2R antagonist with aquaretic action, was developed by Otsuka Pharmaceutical, Japan, in 1989 (1). Its potent effect was first demonstrated by clinical pharmacological trials involving healthy adult male subjects in 1992 (2). To understand
whether mozavaptan might play an important role in the
treatment of ectopic ADH syndrome, the Ectopic ADH
Syndrome Therapeutic Research Group conducted an open-
label multicenter clinical trial at Japanese hospitals from
December 1994 to December 1997. This paper describes the
study results and their implication for mozavaptan’s potential
usefulness in the treatment of cancer-related ectopic ADH
syndrome.

PATIENTS AND METHODS
This open-label, multicenter study protocol was approved by
the Institutional Review Board of each participating medical
institution prior to its inception; written informed consent
was obtained from all patients.
Recruited were inpatients aged 20 to <75 years who had
malignant tumors that might cause ectopic ADH syndrome
as well as the diagnostic criteria of ectopic ADH syndrome
as defined by Bartter and Schwartz (3) such as serum
sodium concentration ≤124 mEq/l, persistent urinary sodium
excretion, normal renal, adrenal, and thyroid function, and
no evidence of edema or dehydration.
Following a ≤2-day placebo administration period during
which baseline data were collected, patients were given
orally mozavaptan (single 30 mg tablet) once daily for 7
days, or where this was difficult, 3 days was allowed. Fluid
restriction was used throughout the study period only for
patients in whom it had already begun. Treatment of hypona-
tremia with demeclocycline, lithium chloride, or urea was
not permitted.

The primary endpoint was serum sodium concentration.
Blood samples were collected immediately before dosing on
each test day. Clinical symptoms associated with hypona-
tremia such as anorexia, nausea/vomiting, headache and CNS
symptoms were recorded. Urine volume, urinary osmolality,
urinary electrolyte (sodium, potassium, chloride) excretion,
serum electrolyte (potassium, chloride) concentration, serum
osmolality, and plasma ADH concentration were measured.
New medical problems or exacerbations of those already
existing were reported as adverse events.

In each case, the serum sodium level after the final admin-
istration of the study drug was compared with baseline
value. The patients are divided into three groups: (i) the
serum sodium level is improved to normal range; (ii) the
level is still low, but increase is ≥6 mEq/l and (iii) the level
is still low, and increase is <6 mEq/l. And mean sodium
concentration after the final administration of the study drug
was compared with that of baseline value by paired t-test.

RESULTS
Sixteen patients [M/F: 10/6; mean age: 63.9 (range: 48–78)
years] who received at least one dose of the study drug were
included in the efficacy and safety evaluation. All patients
received mozavaptan 30 mg once daily for 7 days, except
two individuals who received treatment for 3 days.
Underlying diseases were SCLC (n = 14), thymic small
cell carcinoma (n = 1) and cervical cancer (n = 1). Fluid
intake was restricted in 5 of the 16 patients (Table 1).
Serum sodium concentration (mean ± SD) at the time of
diagnosis of the ectopic ADH syndrome was 117.3 ± 4.3
(range: 110–124) mEq/l. Plasma ADH concentration was
4.9 ± 5.8 (median: 2.3; range: 0.4–18.9) pg/ml immediately
before treatment.

At baseline and at the end of study, mean serum sodium
concentration was 122.8 ± 6.7 and 133.3 ± 8.3 mEq/l,
respectively, a statistically significant difference (P = 0.002; Fig. 1). Serum sodium concentration increased at 24 h after
the first administration of mozavaptan and remained elevated
≤24 h after administration for 7 days. Serum osmolality
gradually increased starting from 24 h after first adminis-
tration till the study end. Cumulative urine volume over 24 h
increased on the first treatment day, whereas urine osmolality
decreased in the first two treatment days.

A total of 16 patients were evaluated for the serum
sodium level. The serum sodium level was improved to
normal range in eight patients, still below normal range but
increased by at least 6 mEq/l in four patients and increased by <6 mEq/l in four patients (Table 1).

Symptoms associated with ectopic ADH syndrome such
as anorexia, nausea/vomiting, headache and CNS symptoms
improved or disappeared in seven of eight patients who had
at least one of these symptoms at baseline. By symptom,
anorexia disappeared in three and improved in two among
eight patients who had the symptom at baseline, whereas
nausea/vomiting, headache and CNS symptoms disappeared
by the completion of treatment in all patients who had at
least one of the symptoms at baseline. On the other hand,
however, new anorexia and headache developed in one
patient each.

Although some patients showed slight increases or
decreases of plasma ADH concentration after receiving
mozavaptan, overall there were no obvious changes.

There were 35 adverse events in 11 of the 16 patients;
none was serious. The most common adverse event was dry
mouth developing in five patients. Fifteen adverse drug reac-
tions occurred in six patients (dry mouth, n = 5; increased
blood potassium, n = 2; malaise, increased AST, increased
ALT, decreased blood calcium, increased blood lactate dehy-
drogenase, increased blood urea, decreased appetite and noc-
turia, n = 1 each).

One patient was withdrawn after administration of the
study drug for 3 days because of anorexia. After completion
of administration of moazvaptan, one cancer-related death
occurred 30 days post-treatment (ID 1 in Table 1); the patient
had small cell lung cancer, and had myasthenia gravis, dia-
betes, pneumonia and hypertension. Chemotherapy (carbopla-
tin and etoposide) was given from 146 to 144 days before
treatment with mozavaptan, which reduced the tumor size and
improved SIADH. However, the chemotherapy was
Table 1. Clinical characteristics of each patient at baseline and changes in serum sodium concentration/clinical symptoms

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Disease</th>
<th>Tx duration (days)</th>
<th>Fluid-intake restriction</th>
<th>Data at baseline</th>
<th>Changes in serum sodium concentration (mEq/l)</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At the time of diagnosis</td>
<td>At baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma ADH concentration (pg/ml)</td>
<td>Serum osmolality (mOsm/kg)</td>
<td>Urine osmolality (mOsm/kg)</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>64</td>
<td>SCLC</td>
<td>7</td>
<td>Yes</td>
<td>12.5</td>
<td>274</td>
<td>712</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>64</td>
<td>Thymic SCC</td>
<td>3</td>
<td>Yes</td>
<td>3.3</td>
<td>256</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>SCLC</td>
<td>7</td>
<td>Yes</td>
<td>0.8</td>
<td>254</td>
<td>754</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>2.1</td>
<td>254</td>
<td>657</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>65</td>
<td>SCLC</td>
<td>3</td>
<td>Yes</td>
<td>2.4</td>
<td>300</td>
<td>753</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>66</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>18.9</td>
<td>256</td>
<td>461</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>78</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>0.5</td>
<td>279</td>
<td>590</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>75</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>0.4</td>
<td>254</td>
<td>465</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>66</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>7.8</td>
<td>261</td>
<td>492</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>48</td>
<td>SCLC</td>
<td>7</td>
<td>Yes</td>
<td>2.1</td>
<td>283</td>
<td>730</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>66</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>1.4</td>
<td>241</td>
<td>450</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>53</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>1.5</td>
<td>241</td>
<td>465</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>60</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>2.8</td>
<td>245</td>
<td>406</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>65</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>5.2</td>
<td>263</td>
<td>370</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>63</td>
<td>SCLC</td>
<td>7</td>
<td>No</td>
<td>15.7</td>
<td>275</td>
<td>755</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>60</td>
<td>Cervical cancer</td>
<td>7</td>
<td>No</td>
<td>1.0</td>
<td>268</td>
<td>349</td>
</tr>
</tbody>
</table>

SCLC, small cell lung carcinoma; Thymic SCC, thymic small cell carcinoma; ANRX, anorexia; NV, nausea/vomiting; HA, headache; CNSS, central nervous system symptom; n/a, not available.
CNS symptoms before treatment. Anorexia (last dose, 7 had anorexia, nausea/vomiting, headache and/or anorexia and headache developed in one patient each. Of the four patients disappeared following therapy. However, new vomiting in five, headache in five and CNS symptom in unchanged in two patients; all other symptoms (nausea/concentration of/C21 serum sodium concentration from baseline. Value was 133.3 + 8.3 mEq/l.

Figure 1. Time-course of serum sodium concentration (mean ± SD) in 16 cancer patients with ectopic ADH syndrome. Baseline serum sodium concentration was 122.8 ± 6.7 mEq/l. At 24 h after the first dose, serum sodium increased to 129.1 ± 5.7 mEq/l; at 24 h after completion of treatment, the value was 133.3 ± 8.3 mEq/l.

terminated due to marked myelosuppression, and then this led to marked tumor growth. The serum sodium concentration was 132 mEq/l 29 days before the mozavaptan treatment, but gradually decreased to 119 mEq/l 14 days before treatment. At that time, the patient’s condition did not permit chemotherapy, and mozavaptan therapy was performed. Although mozavaptan was effective, the condition became worse due to rapid tumor progression. The patient died 30 days after completion of the mozavaptan therapy, and the autopsy demonstrated direct invasion to heart and thoracic vertebra, indicating that the patient had died of cancer. No other serious adverse events were reported.

DISCUSSION

Since the ectopic ADH syndrome is the morbidity induced by inappropriately secreted ADH from cancer cells, V2R antagonist rationally might be expected to exert pharmacological effects in the syndrome. During Phase I pharmacological evaluation, mozavaptan 30 mg/day exerted potent V2R antagonistic activity. Therefore, we plan to evaluate the clinical efficacy and safety of this agent at a dose of 30 mg/day in cancer patients with ectopic ADH syndrome defined by Bartter and Schwartz (3).

We found that the drug increased the mean serum sodium level; 10 patients at 24 h after the first dose and 12 patients at 24 h after the last dose showed a ≥6 mEq/l increase in serum sodium concentration from baseline.

Of 12 patients who showed an increase in serum sodium concentration of ≥6 mEq/l from baseline at 24 h after the last dose, 7 had anorexia, nausea/vomiting, headache and/or CNS symptoms before treatment. Anorexia (n = 7) disappeared in three, was alleviated in two and remained unchanged in two patients; all other symptoms (nausea/vomiting in five, headache in five and CNS symptoms in four patients) disappeared following therapy. However, new anorexia and headache developed in one patient each. Of the remaining four subjects who showed an increase in serum sodium concentration of <6 mEq/l, three had no symptoms and one complained of anorexia that remained unchanged 24 h after the last dose.

Since SCLC is the chemo-sensitive tumor and SIADH is the condition of oncologic emergency, urgent treatment is always required. However, in the cases of SIADH, hyponatremia makes it difficult to perform chemotherapy; hydration is necessary for the therapy with cisplatin-based chemotherapy. Mozavaptan improved compliance to chemotherapy in patients with ectopic ADH syndrome.

The present study did not plan to give chemotherapy during the study period. Thus, information on chemotherapy was not designed to be collected from patients. However, we evaluated present cases whether they received chemotherapy after the mozavaptan treatment. Information was obtained from 14 patients of the 16 subjects, 9 were administered mozavaptan prior to scheduled chemotherapy, and 8 of these underwent chemotherapy with the regimen including cisplatin or carboplatin after successful correction of hyponatremia.

With regard to safety, the treatment was discontinued in one patient due to adverse drug reaction, and two patients required treatment for adverse effects but recovered after appropriate treatment. There was no excessively rapid increase in serum sodium concentration or central pontine myelinolysis, suggesting that mozavaptan can be safely used in the target patient population.

On the basis of these results, mozavaptan (Physuline®) was approved in Japan as an orphan drug for the treatment of ectopic ADH syndrome, in 2006. It is worth noting that until now demeclocycline, lithium chloride or urea was reported effective for the ectopic ADH syndrome, although clinical experiences revealed that the effects of these drugs are limited (4).

In the USA and EU, there are two V2R antagonists available on the market—conivaptan (oral tablet) (6). Conivaptan, a dual V1a receptor and V2R antagonist, is marketed in the USA with the indication of ‘treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients’. Tolvaptan, which by structural modification has a higher affinity for the V2R than does its parent drug, mozavaptan, is marketed in the USA with the indication of ‘treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure, cirrhosis and SIADH’ and in the EU with the indication of ‘treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)’. Mozavaptan is currently the only approved drug available for treatment of patients with ectopic ADH syndrome (7) in Japan but is neither approved nor under development outside Japan.

During the 43 months following its launch, 100 patients have been treated with the drug. On the basis of the post-marketing drug use results survey, overall clinical effects of the drug have been found similar to those of the
clinical trial. Mozavaptan provides two important contributions for the treatment of ectopic ADH syndrome. First, short-term treatment with mozavaptan may allow hyponatremic patients who might otherwise be contraindicated to receive aggressive cancer chemotherapy with platinum-containing drugs. Second, mozavaptan may free patients from strict fluid-intake restrictions and thereby improve their quality of life. Thus, mozavaptan provides new treatment options for aggressive chemotherapy as well as for palliative care in patients with ectopic ADH syndrome.

Acknowledgements

The authors thank Mr Yasuhito Ihara, Pharmaceutical Marketing Division, Otsuka Pharmaceutical Co. Ltd, Japan, for providing information on mozavaptan and other vasoressin antagonists.

Conflict of interest statement

None declared.

References


Appendix

Ectopic ADH Syndrome Therapeutic Research Group (continued).
Shosaku Abe: Sapporo Minamisanjo Hospital.
Yutaka Nishiwaki and Koichi Goto: Division of Thoracic Oncology, National Cancer Center Hospital East.
Kimihide Yoshida and Toyoaki Hida: Department of Thoracic Oncology, Aichi Cancer Center Hospital.
Hideki Muramatsu: Department of Respiratory Diseases, Kainan Hospital.
Kunihiko Gotoh: Gotoh Clinic of Internal Medicine.
Koichiro Tatsumi: Department of Respirology, Graduate School of Medicine, Chiba University.
Shinji Atagi: Department of Internal Medicine, National Hospital Organization Kinki, Chuo Chest Medical Center.
Toshihiko Nishian: Nishian Clinic.
Toshio Tabei: Division of Breast Surgery, Saitama Cancer Center.
Ichiro Kawase: Osaka Prefectural Medical Center for Respiratory and Allergic Disease.
Saburo Sone: Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School.
Eiji Shimizu: Division of Medical Oncology and Molecular Respirology, Faculty of Medicine, Tottori University.
Jiro Takahara: Department of Internal Medicine, Uchinomi Hospital.
Jiro Fujita: 1st Department of Internal Medicine, University of the Ryukyu Hospital.