Prolactogenic effects of etizolam

Yasuhiro Kaneda1,2
1. Department of Neuropsychiatry, The University of Tokushima School of Medicine, Tokushima 770-8503, Japan.
2. Life-jiyukan, Komatsushima 773-0021, Japan.

Correspondence to: Yasuhiro Kaneda, M.D., Ph.D., Department of Neuropsychiatry, The University of Tokushima School of Medicine, 3-18-15 Kuramoto-Cho, Tokushima, Tokushima 770-8503, Japan, TEL: +81-88-633-7130 FAX: +81-88-632-3214 E-MAIL: kaneday@clin.med.tokushima-u.ac.jp
Submitted: October 6, 2000
Accepted: November 16, 2000

Key words: dopamine etizolam female γ-aminobutyric acid prolactin

Introduction

The benzodiazepines (BZs) are the most widely used hypnotics. The thienobenzodiazepine derivative etizolam, 6-(o-chlorophenyl)-8-ethyl-1-methyl-4H-s-triazolo[3,4-c]thieno[2,3-e][1,4]diazepine, is a comparatively new potent anxiolytic and/or hypnotic [1]. The BZs have been considered largely free of neuro-endocrine effect [2]. However, hyperprolactinemia and galactorrhea have been suggested to be induced by etizolam [3]. A small study was conducted on female patients with dementia to evaluate the prolactogenic effects of etizolam.

Patients and methods

The original sample of this study was 11 female elderly inpatients with dementia (nine patients with vascular dementia and two with Alzheimer’s disease). All of the patients had been successfully treated with etizolam as a hypnotic. A tablet (5 mg) or tablets had been administered orally at 2100 h. Eleven age-matched dementia patients did not receive etizolam. Table 1 shows the demographic characteristics of the subjects. The study was approved by the relevant ethics committees and was performed in accordance with the Declaration of Helsinki II. Informed consent was obtained from all subjects and their families for the research involved in this study.

Blood samples for hormone estimation were drawn once from all subjects between 1100 and 1130 h. The sera were prepared and stored at –20 centigrade until the time of analysis. Serum prolactin (PRL) was assayed by a radioimmunoassay.

Statistical analyses were done using nonparametric tests.

Results

The serum PRL concentrations for the patients with etizolam and those without it were 6.80 ng/ml (SD = 4.09, range 2.8–15.5) and 4.36 ng/ml (SD = 1.80, range 1.8–6.6), respectively (Table 1). Nine out of 11 patients with etizolam (82%) showed higher PRL than age-matched patients without etizolam. Although there was no significant difference in the mean level of serum PRL between the groups, the mean level of serum PRL for the etizolam-treat-
Discussion

The result showed a greater but non-significant prolactogenic effect of etizolam.

Most of the pharmacological actions of BZs are considered to be mediated via binding to BZ receptors, and the consequent increase in the effects of $\gamma$-aminobutyric acid (GABA) [4]. Moreover, BZs are suggested to affect the monoamine transmitters, such as serotonin (5-HT) [5], noradrenaline [6], and dopamine (DA) [7], directly or by enhancing the GABA system.

Meanwhile, a wide variety of neurotransmitters are involved in regulation of PRL secretion. Above all, DA plays an important role in the regulation of PRL: DA inhibits PRL secretion from anterior pituitary mammmotropes via $D_2$-DA receptors [8]. 5-HT pathways are known to facilitate the release of PRL [8], and GABA has been suggested to exert an inhibitory control on PRL secretion in humans [9].

Therefore, we suggest that the mechanism by which etizolam stimulates the secretion of PRL may be explained by a GABAergic inhibitory effect on tubero-infundibular D Argic neurons, and/or by an inhibitory effect of etizolam directly on DA. In addition, since enkephalins are known to raise PRL [10] and BZs are indicated to have an opiate agonistic effect [11], etizolam may stimulate PRL via an opiate agonistic effect.

Acknowledgments

The author is grateful for the comments of Professor Tetsuro Ohmori (Tokushima, Japan) and Dr. Shigeo Iwasa (Komatsushima, Japan) and appreciates the cooperation of the staffs in the faculties. Some of these results were presented at the International Symposium on Dementia, Kobe, Japan, September, 1999.

---

Table 1
Demographic characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients without etizolam</th>
<th>Patients with etizolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>83.5 (6.7)</td>
<td>84.7 (7.5)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>39.8 (6.9)</td>
<td>47.8 (7.8)</td>
</tr>
<tr>
<td>Dosages (mg/day)</td>
<td>-</td>
<td>0.55 (0.15)</td>
</tr>
<tr>
<td>Administration periods (mos)</td>
<td>-</td>
<td>28.5 (22.9)</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>4.36 (1.80)</td>
<td>6.80 (4.09)</td>
</tr>
</tbody>
</table>

REFERENCES