

Prolactogenic effects of etizolam

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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-treated patients tended to be higher than that for the patients without etizolam.

Table 1
Demographic characteristics of subjects

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

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 γ -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 mammotropes 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 DArgic 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.

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