EFFECTS OF ZOPICLONE AND LORAZEPAM ON ECT SEIZURE DURATION: CLINICAL IMPLICATIONS OF FINDINGS FROM AN ANIMAL MODEL

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ABSTRACT

Lorazepam is commonly prescribed to treat insomnia in depressed patients who receive electroconvulsive therapy (ECT); however, lorazepam may interfere with ECT seizure parameters, and may thereby compromise the efficacy of the treatment. This study therefore sought to assess whether zopiclone, a hypnotic agent, interferes less with the ECT seizure. For ethical reasons, the study utilized an animal model. Sprague-Dawley rats (n=10/group) received either zopiclone (1.5 mg/kg), lorazepam (0.2 mg/kg), or a placebo equivalent. After 30 minutes, an electroconvulsive shock was administered to the rats. It was observed that the motor seizure duration but not the total motoric phase was significantly attenuated by zopiclone. Lorazepam did not impact significantly upon either seizure measure. It is concluded that zopiclone may be a suitable hypnotic for patients receiving ECT only if sufficient time is allowed for the drug to be substantially washed out of the body.

Key words: Electroconvulsive therapy, electroconvulsive shocks, seizure duration, zopiclone, lorazepam, rats

Depressed patients who receive electroconvulsive therapy (ECT) are frequently prescribed lorazepam to treat insomnia; doses used range from 1-3 mg nightly (Sackeim et al., 1993). The preference for lorazepam is possibly due to its relatively short mean half-life of 12 hrs, in comparison with 25 hrs for nitrazepam and 30 hrs for diazepam (Psychotropic Drug Guidelines Subcommittee, 1995). Since benzodiazepine drugs have anticonvulsant properties, a valid concern is that the co-prescription of such hypnotic drugs may compromise the therapeutic effects of ECT; this concern is particularly relevant to ECT with unilateral electrode placement (Pettinati et al., 1990). There is no consensus on the co-prescription of other agents with sedative properties, such as the tricyclic antidepressant drugs. On the one hand, the tricyclic drugs may augment the antidepressant action of ECT; on the other hand, these drugs may unfavourably prolong the ECT seizure duration and predispose to increased cognitive adverse affects through this mechanism and through central anticholinergic actions (Andrade, 1990; Pritchett et al., 1993).

Zopiclone is a cyclopyrrolone hypnotic agent which acts on the benzodiazepine-GABA receptor complex but not at the same site as the benzodiazepine drugs (Byrnes et al., 1992); therefore, zopiclone may conceivably have a lesser impact on the ECT seizure. Furthermore, zopiclone has a short mean half-life of 5 hours (Psychotropic Drug Guidelines Subcommittee, 1995). Therefore, at the time ECT is administered, the drug would have been substantially washed out of the body; this could further reduce its effects upon the ECT seizure.
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In view of these conjectures, the present study sought to examine the effect of zopiclone on one aspect of the ECT seizure, motor seizure duration. For ethical reasons, an animal model was utilized.

MATERIAL AND METHOD

Adult, male, Sprague-Dawley rats were housed 3/cage and were provided free access to tap water and standard laboratory diet. In each cage, rats received zopiclone in solution, lorazepam in solution, or distilled water alone. Zopiclone was administered in the dose of 1.5 mg/kg, while lorazepam was administered in the dose of 0.2 mg/kg. These doses were selected after careful preliminary studies on rats demonstrated satisfactory and comparable sedation approximately 40 minutes after drug administration. These doses also maintained the proportion of 7.5 mg (zopiclone) to 1 mg (lorazepam); these are the conventional doses at which the drugs are prescribed, to the average patient, for hypnosis. Both drugs were administered by slow, intra-oral syringing, and volumes of administration were comparable.

A single electroconvulsive shock (ECS) was administered to each rat using earclip electrodes coated with electrode jelly. ECS was given 30 minutes after drug administration, using the Malar Medisystems (Cochin) constant current, unipolar brief-pulse (ECT) device. The administered charge was 30 mC, with stimulus settings of 0.5A for current intensity, 1 msec for pulse width, 60 Hz for pulse frequency, and 1 sec for stimulus train duration.

Motor seizure duration was assessed by an experienced observer who used a stopwatch. The beginning of the seizure was defined as the cessation of all movements; this includes a post-ictal phase of random motor activity, sometimes termed as the ‘running phase’ (Fochtman, 1999; personal communication). While the theoretical significance of the running phase remains to be clarified, it is emphasized that the rat is unconscious until long after both these endpoints are attained.

RESULTS

Seizure duration and motoric phase data are presented in the table. Nonparametric statistical testing was employed because of heteroscedasticity of data. The Kruskall-Wallis One-Way Analysis of variance found a significant difference in mean (ranked) seizure duration \( (X^2=6.67, \text{ d.f.}=2, \ p=0.036) \) but not in motoric phase duration \( (X^2=0.90, \text{ d.f.}=2, \ NS) \). Zopiclone significantly attenuated seizure duration but not the duration of the motoric phase, while lorazepam did not impact upon either measure.

| Materials                  | Seizure duration | Motoric duration |
|----------------------------|------------------|------------------|
|                            | Range            | Mean (s.d.)      | Range            | Mean (s.d.)      |
| Zopiclone (n=10)           | 11-25            | 14.0 (4.2)       | 25-36            |
| Lorazepam (n=10)           | 11-47            | 18.9 (10.9)      | 30.4 (3.7)       |
| Distilled water (n=10)     | 14-38            | 20.2 (7.8)       | 24-64            |

DISCUSSION

Agents that abbreviate the ECT seizure may impact negatively on the efficacy of ECT; a seminal observation was that lidocaine-abbreviated seizures are subtherapeutic (Cronholm & Ottosson, 1960). Although it is currently realized that seizure duration is not an ideal measure of ECT, it is nonetheless the measure that is most readily accessible to clinicians (Andrade, 1997). Bedside recommendations for ECT seizure adequacy therefore continue to prescribe minimum
durations for the motor and/or electroencephalog- 
graphic seizures (American Psychiatric 
Association, 1990; Scott & Lock, 1995).
This study was conducted with the 
expectation that zopiclone might have a lesser 
impact on ECT seizure duration because it does 
not act upon the same site as do the 
benzodiazepine drugs, and because it has not 
been reported to have clinically significant 
anticonvulsant properties (Goa & Heel, 1986). 
However, it was observed that while attenuation 
of seizure duration by lorazepam did not attain 
statistical significance, that with zopiclone did. 
Thus, zopiclone may be even more detrimental 
to ECT efficacy than benzodiazepines. 
These findings were not totally 
unexpected. In animal models, zopiclone was 
shown to inhibit seizures induced by 
electroconvulsive shocks and by 
pentylenetetrazol; the anticonvulsant potency of 
zopiclone in these studies was greater than that 
of chlordiazepoxide and nitrazepam (Julou et 
al., 1983; Goa & Heel, 1986). However, no 
literature was available on a direct comparison 
between zopiclone and lorazepam, with 
reference to the seizure duration measures 
addressed in the present investigation. The 
present study was therefore heuristic and 
necessary.
Neither zopiclone nor lorazepam 
attenuated the total motoric duration. However, 
this phase includes a post-ictal period of random 
motoric movements that bear uncertain 
relevance to the intensity of the ECS seizure 
(Fochtman, 1999; personal communication), 
therefore, the absence of impact on the motoric 
phase is of uncertain theoretical importance, but 
nonetheless merits scrutiny in future research. 
From simple, linear, mathematical 
modelling based on drug half-lives, some 
additional considerations are warranted. If ECT 
is scheduled 12 hrs after hypnotic drug treatment, 
approximately 75-85% of the previous night's 
zopiclone dose, and 50% of the previous night's 
lorazepam dose, would have been washed out 
of the body. These considerations apply to 
zopiclone in both single and daily dosing 
situations. With lorazepam, after 2-3 nights of 
treatment, attainment of steady-state levels 
would result in only 35% of the drug being 
washed out by the time the morning's ECT is 
scheduled. It therefore makes sense to prefer 
zopiclone if the scheduling of ECT is such that 
sufficient time has elapsed for zopiclone to have 
been substantially washed out of the body; 
otherwise, lorazepam may remain the hypnotic 
of choice until better alternatives, such as 
zolpidem, become available in India.

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