Pregabalin vs. Naltrexone in alcohol dependence: a multicenter, randomized, double-blind, comparison trial

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BACKGROUND AND AIM: Pregabalin, a structural analogue of γ-aminobutyric acid, is a novel compound with broad-spectrum efficacy in the treatment of diverse medical conditions. Evidence from different double-blind, placebo controlled studies suggests that Pregabalin may have efficacy in general anxiety disorders (Montgomery, 2006; Fink, 2008).

Pregabalin, in hyperexcited neurons, acts as a presynaptic inhibitor of the release of excessive levels of excitatory neurotransmitters, including glutamate, substance P, calcitonin gene-related peptide, and monoaminergic neurotransmitters (Field, 2001). It selectively binds to the δ-5 subunit protein of voltage-gated calcium channels, as does gabapentin, although its binding is at least 3 times as potent as that of gabapentin (Bryans and Wustrow, 1999). Pregabalin binding rapidly reduces the influx of calcium, reducing the exocytosis of synaptic vesicles in the synaptic cleft. Pregabalin has relatively the same range of efficacy of naltrexone, one of the approved drugs used in alcohol relapse prevention. Those significant points in favour of the employment of pregabalin were represented by its well-documented efficacy in alcohol dependent subjects (Sirisupram and Janssensain, 2003), both in the treatment of craving and in the relapse prevention.

METHODS: A total of 102 patients were screened, of whom 31 were excluded. The most common reason for exclusion was failure to meet eligibility criteria. All the patients were evaluated by attending psychiatrists using the Structured Clinical Interview for DSM-IV (SCID I; SCID II). Excluded from participation were subjects regularly taking alcohol, abstinence from alcohol was confirmed both at the start and end of the study by determining blood alcohol concentration at each outpatient control, and by measuring alcohol specific urinary biomarkers.

RESULTS: There were no statistically significant differences between PRE and NAL groups in the proportion of subjects who relapsed (PRE=15; NAL=7) or who completed the study: 27 in the PRE group, 21 in the NAL group. The number of subjects remaining alcohol free for the entire study period (PRE=15; NAL=11) and the proportion of patients who completed the study: 27 in the PRE group, 21 in the NAL group. The number of patients in the PRE group (F= 25.8; p < 0.001) and in the NAL group (F= 5.2; p < 0.05). Post-hoc analysis showed that for the PRE group this reduction was already significant after 15 days (T1). A significant difference between groups (p<0.05) was found in favour of the PRE group. The SCL-90-R general index of “Positive Symptom Total” significantly reduced between times in the two groups considered (PRE: F= 3.33; p<0.05; NAL: F=3.38; p<0.05) whereas the subscales for “phobic anxiety”, “hostility”, and “psychoticism” only reduced in the pregabalin treated subjects (F=2.44; p=0.05; F=2.56; p=0.05; F=3.02; p<0.05) [Fig. 3]. The number of patients in diagnosis reporting a condition of total abstinence from alcohol at the end of the study was significantly higher (p= 0.01) in the PRE group (8/18; 50%) with respect to the NAL group (2/13; 15%).

CONCLUSIONS: To our knowledge, this is the first randomized, parallel group trial to evaluate the efficacy of pregabalin for alcohol dependence. Results from this study globally place pregabalin at the same range of efficacy of naltrexone, one of the approved drugs used in alcohol relapse prevention. Those significant points in favour of the employment of pregabalin were represented by the improvement of specific symptoms in the area of anxiety, hostility and psychosocial, a survival time remaining abstinent superior than naltrexone, and a better outcome in those patients reporting a comorbid psychiatric disorder. The mechanism involved in the efficacy of pregabalin in relapse prevention could be less related to craving for alcohol and more connected to the treatment of the comorbidity psychiatric symptomatology, as rated by the SCL-90-R. If it could be confirmed in placebo controlled trials that pregabalin is efficacious in decreasing alcohol use, decreasing craving, and attenuating psychopathological symptom severity, we will have gained a valuable agent for the treatment of alcohol dependent subjects.

Fig. 1: Pregabalin: recently defined mechanism of action

Fig. 2: Diagram of subject flow by treatment group (N=27)

Fig. 3: Survival remaining abstinent (Z= -2.27; P<0.05).

Methods of Detoxification

Fig. 4: Mean change from baseline at the last assessment (T3) of the Obsessive Compulsive Drinking Scale (OCDS), and of the Phobic Anxiety, Hostility and Psychoticism subscales of the Symptom Check List (SCL-90-R) * p<0.05

Fig. 5: Graph showing cumulative survival among patients remaining abstinent (Z= -2.27; P<0.05).

CONCLUSIONS:

The study was designed as a 16 week multicenter, randomized, double-blind comparison trial of pregabalin with naltrexone. We aimed to investigate the efficacy of pregabalin on alcohol drinking indices. Craving reduction, improvement of psychiatric symptoms and the evaluation of safety parameters in alcoholics were the secondary endpoints. Naltrexone, approved by the U.S. Food and Drug Administration for the treatment of alcohol dependence, was used as an active comparator for its well-documented efficacy in alcohol dependent subjects (Sirisupram and Janssensain, 2003), both in the treatment of craving and in the relapse prevention.

REFERENCES: