BROTIZOLAM AND CHRONIC INSOMNIA: A MULTI-CENTRE STUDY

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- 1 A double-blind, crossover study was carried out on the acceptability of three doses of brotizolam (0.125, 0.25 and 0.5 mg) in chronic insomniacs aged between 21 and 75 years (33 men: 42 women).
- 2 Patients reported a shorter time to fall asleep and less nocturnal awakenings. Improvement in sleep was evident during the first week of the study when each patient received 0.25 mg.
- 3 There were no dose-related side-effects, and on withdrawal from the medication there was no evidence of disturbed sleep which would have suggested a rebound effect.

Keywords brotizolam chronic insomnia

A double-blind crossover study on the usefulness of three doses (0.125, 0.25 and 0.5 mg) of brotizolam in chronic insomnia was carried out in 75 patients (33 men: 42 women) aged between 21 and 75 (mean 41) years in five hospitals. A complaint of difficulty in getting to sleep within 30 min, more than three awakenings during the night or a sleep period of less than 6 h was required for admission to the study. Patients whose insomnia was due to pain, nocturia or diarrhoea were excluded as well as those pregnant or lactating. There were no restrictions concerning diet, smoking or alcohol.

The patients, of whom 44 had a primary complaint of insomnia, were informed of the nature of the study and verbal consent was obtained. They were divided randomly into two groups and after a period of 3 days without medication they received therapy for a period of 4 weeks followed by 3 days of placebo ingestion. For periods of 7 days within the 4-week medication period the first group received 0.25, 0.5, 0.25 and 0.125 mg brotizolam respectively, and the second group received 0.25, 0.125, 0.25 and 0.5 mg brotizolam respectively. The medication was ingested before going to bed.

The patients were seen by the physician on days 3, 10, 17 and 24 immediately before the commencement of each 7-day period of therapy, and on day 31 at the end of therapy and on day 34 at the end of the 3-day placebo period. At these times daily and nightly assessments, compliance, side-effects and overall efficacy were assessed and weekly assessments completed. The data were analysed using analysis of variance with the 3 days preceding medication as the control period.

The study did not establish any consistent differences between the efficacy and side-effects of the various doses of the drug. With all doses the patients reported a shorter time to fall asleep ($P < 0.001$), prolonged ($P < 0.001$) and deeper sleep ($P < 0.001$), and the number of times they reported waking during the night decreased ($P < 0.001$). Improvement in sleep was reported during the first week of the study (0.25 mg brotizolam) in both groups ($P < 0.001$), and they felt more rested in the morning. There were no dose-related side-effects, and one patient withdrew from the study because of headaches. After the 4-week period of medication assessments of sleep tended to return to those of the control period.

This study together with related investigations (Sánchez-Martínez & Landa-Palos, 1982; Rodríguez *et al.*, 1981; Velasco *et al.*, 1981) has demonstrated in a clinical setting the usefulness of brotizolam as an hypnotic, although it did not establish any consistent dose-related differences. However, although there was no evidence of untoward effects with the highest dose (0.5 mg), the efficacy of the lower doses, together with other experimental (Nicholson *et al.*, 1980; Roehrs *et al.*, 1983) and clinical (von Delbrück *et al.*, 1983; Lohmann *et al.*, 1983) studies, would suggest the dose range 0.125–0.25 mg as appropriate in the treatment of insomnia. Further, brotizolam was found to be effective over a 4-week period of ingestion, and on withdrawal there was no evidence of an adverse effect on sleep which would suggest a rebound phenomenon.

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Brotizolam und chronische Schlaflosigkeit.

Eine multizentrische Studie

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- 1 Zur Ermittlung der Akzeptanz von Brotizolam in drei unterschiedlichen Dosierungen (0,125, 0,25 und 0,5 mg) wurde eine doppelblinde Crossover-Studie an chronisch schlafgestörten Patienten im Alter zwischen 21 und 75 Jahren durchgeführt (33 Männer, 42 Frauen).
- 2 Die Patienten berichteten, schneller einzuschlafen und während der Nacht weniger häufig auf-

gewacht zu sein. Die Verbesserung des Schlafes war in der ersten Woche der Studie feststellbar, als jeder Patient 0,25 mg erhielt.

- 3 Dosisabhängige Nebenwirkungen traten nicht auf, und nach Absetzen der Medikation gab es keine Anzeichen von Schlafstörungen, die auf einen Rebound-Effekt hingewiesen hätten.

Le brotizolam et l'insomnie chronique. Etude multicentrique

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- 1 Une étude crossover en double aveugle a été réalisée pour examiner l'acceptabilité de trois doses de brotizolam (0,125, 0,25 et 0,50 mg) chez des patients souffrants d'insomnie âgés de 21 à 75 ans (33 hommes, 42 femmes).
- 2 Les patients ont reporté que le délai avant l'arrivée du sommeil avait été plus bref et que le nombre

d'éveils nocturnes avait été inférieur. L'amélioration du sommeil a été observée durant la première semaine de l'étude lorsque chaque patient a reçu 0,25 mg.

- 3 Aucun effet secondaire dépendant de la dose n'a été observé. L'arrêt de l'application de la médication n'a pas entraîné de trouble du sommeil, lequel aurait pu signifier l'existence d'un effet rebound.

Brotizolam e insomnio crónico—Estudio multicéntrico

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- 1 Se ha realizado un estudio doble-ciego cruzado para evaluar la aceptación de 3 dosis de brotizolam (0,125, 0,25 y 0,5 mg) en pacientes con insomnio crónico y edades comprendidas entre 21 y 75 años (33 hombres, 42 mujeres).
- 2 Los pacientes comunicaron que el período de inducción del sueño fue más breve y el número de

despertares nocturnos menor. La mejoría del sueño se manifestó durante la primera semana del estudio cuando cada uno de los pacientes recibió 0,25 mg.

- 3 No se produjeron efectos secundarios en relación con las dosis y al interrumpir la medicación no se advirtieron manifestaciones de sueño alterado que pudiesen sugerir un efecto rebote.