RESIDUAL EFFECTS OF FLURAZEPAM AND BROtizOLAM ON PSYCHOMOTOR PERFORMANCE

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- 1 Residual effects of brotizolam (0.25 mg) and flurazepam (30 mg) were studied in healthy young adults. Performance and subjective assessments were observed from 7 to 8 h after overnight ingestion, and effects were compared with that of placebo.
- 2 Visuo-motor coordination, visuo-mental processing time, visuo-motor reaction time and reading errors were not impaired with brotizolam.
- 3 There were residual effects with 30 mg flurazepam. Visuo-motor coordination, visuo-mental processing time, visuo-motor reaction time, and reading errors were impaired compared with placebo and 0.25 mg brotizolam.
- 4 Subjective assessments of performance correlated with measured performance. There was a decrease with flurazepam (visuo-motor coordination and visuo-mental processing time) compared with placebo.

Keywords flurazepam brotizolam residual effects psychomotor performance

Introduction

Present-day requirements imposed on man are increasingly directed towards the intellectual-mental component of their make-up thanks to advances in technology and systematized organisation. Even leisure activities, such as driving an automobile or the practice of a hobby, require alertness and concentration. The residual impairment of performance following overnight ingestion of hypnotics is therefore of particular interest. Hypnotics free of residual effects would be of considerable value. Many of the currently available hypnotics have residual effects on performance when administered in doses within the normally accepted therapeutic range. However, it is evident that such effects are not inevitably the sequel of using such drugs. Our work has been concerned mainly with the effect of brotizolam (a triazolothienodiazepine) on visuo-motor coordination, visuo-mental processing time for the central visual field and visuo-motor reaction time for the peripheral visual field compared with that of placebo and flurazepam. These measures of performance are important for most working places. For example, Stephens & Michaels (1963) have described driving as essentially a time-sharing activity between a task of visual search and recognition and one of compensatory tracking.

Methods

Twenty-four healthy male students with ages varying from 21 to 26 years (mean age 23.7 years) and weights ranging from 60 to 95 kg (mean weight 69.8 kg) were included. They were required to avoid alcohol during the 3 days of the study, and were not involved in taking any other form of drug therapy. Subjects had normal visual acuity at 1 m distance and no defects of convergence or accommodation. There were no restrictions apart from the request that they should eat a light breakfast without tea or coffee on the morning of the performance studies, and observations were carried out in an air-conditioned room.

Subjects were required to reach a steady level of performance before drug studies were carried out. Steady performance was reached by the completion of three 'training' sessions of 30 min each. Subjects were randomly distributed into three groups. Eight males ingested placebo and 0.25 mg brotizolam, eight placebo and 30 mg flurazepam and eight 0.25 mg brotizolam and 30 mg flurazepam. All medication was identical in appearance. The study was double-blind and treatments were presented in random order. At least 7 days separated each assessment from the next. Each run was preceded

by 3 days medication ingested at 23.00 h–24.00 h. Measurement of performance began early in the morning, 7 h after the third drug dose.

The main task was one of compensatory tracking. The subject was required to compensate, by using a hand-held stick, an unknown, computer generated, sinusoidal signal of randomly changing (every 4–10 s) frequency (0.02–0.05 Hz). The error-signal was displayed on a horizontal array of red light emitting diodes (length 14.25° visual angle) on a white surround (60 cd/m²). The subject was required to position a randomly moving light spot in the centre of a horizontal line. The error-signal, i.e. the distance between the light spot and centre of the line, was recorded. The mean over the final 5 min of the test was computed, and this constituted the performance measure.

In the first additional task the subject was required to read a random array of four numerals displayed tachistoscopically (exposure time 250 ms) and random in time, above the main tracking task in the central visual field. The subject was required to read aloud the number as quickly and as accurately as possible ('enforced choice'). Reaction time was measured starting with the exposure time and ending at the beginning of reading. This time provides a fairly good measure of the mental processing time, which comprises essentially perception of the visual pattern, abstraction of features, recognition of the numerals and actuating of the verbal identification. It thus represents a procedure far more complicated than a simple motor reaction. Reading errors were recorded simultaneously by the test director.

In the second additional task the subject was required to respond to a blinking light presented in the peripheral visual field at randomly varying positions (eight positions, 7.5° viewing angle distance) by pressing a foot pedal. Motor reaction time was recorded. The additional tasks followed each other randomly every 2 to 4 s.

In addition to the above, pulse and pulse variability (Müller-Limmroth & Krueger, 1977) were recorded. Each experimental run lasted 60 min. It was preceded by a 10 min recording of base line pulse and variability and followed by another 10 min recording of recovery values. After each task the subject was asked 'How well did you perform?' and 'How is your feeling of stress?' (as assessed on a seven-point scale). Finally the subjects were required each morning to assess their sleep and well-being according to a questionnaire and a rating scale by von Zerssen *et al.* (1970).

Results

Effects of drugs on visuo-motor coordination,

visuo-mental processing time, visuo-mental reaction time and reading errors during 1 h runs are shown in Figures 1, 2 and 3. There were no residual effects in the first 5 min period, either with 0.25 mg brotizolam or with 30 mg flurazepam. Moreover, it

Figure 1 Error signal in a visuo-motor task (compensatory tracking). — placebo, ---- 0.25 mg brotizolam, 30 mg flurazepam.

was not possible to establish differences between placebo and 0.25 mg brotizolam during the 1 h run for visuo-motor coordination (Figure 1), visuo-motor reaction time (Figure 2), visuo-mental processing time (Figure 2) or reading errors (Figure 3). This means that there was no trend of impaired performance over the period of the study

Figure 2 Visuo-mental processing time and visuo-motor reaction time. — placebo, ---- 0.25 mg brotizolam, 30 mg flurazepam.

7–8 h after ingestion of 0.25 mg brotizolam. In contrast, significant decrements of performance were observed after ingestion of 30 mg flurazepam.

Whereas the error signal in the tracking task was constant in the visuo-motor coordination task with placebo and with brotizolam (Figure 1) it increased with flurazepam from 21.4 to 39.0 arbitrary units ($P < 0.01$).

Visuo-motor reaction time increased from 490 to 550 ms with placebo and brotizolam, whereas it increased to 620 ms with flurazepam (Figure 2).

Figure 3 Reading errors of numbers in the central visual field. — placebo, ---- 0.25 mg brotizolam, 30 mg flurazepam.

Values were significantly higher after the first 5 min with flurazepam (flurazepam-placebo $P < 0.05$, flurazepam-brotizolam $P < 0.01$). Visuo-mental processing time was constant over 60 min with placebo and brotizolam, but flurazepam led to a significant increase in processing time (flurazepam-placebo $P < 0.025$, flurazepam-brotizolam $P < 0.05$). Compared to placebo ($P < 0.10$) and brotizolam ($P < 0.05$), flurazepam increased the rate of reading errors during the 60 min run (Figure 3). No differences were found in pulse rate or pulse variability.

The subjects did not assess their performance as impaired after brotizolam, but did so after flurazepam (visuo-motor coordination $P < 0.01$, visuo-mental task $P < 0.02$). Their assessment of increased stress with flurazepam was however not found to be statistically significant.

There were no changes in assessments related to sleep. Better values in assessment of well-being were found in relation to placebo and brotizolam. The difference was most evident after the third ingestion. The von Zerssen self-rating scale (CIPS) supports this trend towards improved well-being with brotizolam and diminished well-being with flurazepam ($P < 0.01$).

Discussion

A dose of 0.3 mg brotizolam, i.e. nearly the optimum dose (Kubicki, 1979), seems to be equipotent with 30 mg flurazepam (Saletu *et al.*, 1979). Brotizolam and flurazepam showed significant psychoactivity, commencing in the second hour, which peaked in the fourth hour after

ingestion and decreased slowly thereafter. Duration of drug action is, however, dependent on the kinetics of distribution and elimination of the parent drug and its effective metabolites. In contrast to brotizolam, flurazepam has an active metabolite, *N*-desalkylflurazepam, with a long half-life of 24–48 h. Thus, significant accumulation of this metabolite occurs during continuous administration of flurazepam. It has psychopharmacological activity similar to that of flurazepam which itself has a very short half-life. Therefore, this metabolite might contribute to persistent hypnotic and sedative effects of flurazepam.

In sleep studies flurazepam did not reach peak effectiveness until the third drug night. One must remember also that the effect of the drug will be present during the day as well as at night. This may explain why we did not find any residual effects with 0.25 mg brotizolam at 7–8 h after ingestion in contrast to marked residual effects with 30 mg flurazepam on visuo-motor coordination, visuo-motor reaction, visuo-mental processing and reading errors. This result is in accordance with the findings of Nicholson *et al.* (1980) who measured the effects of 0.2 mg brotizolam in an adaptive tracking task without any additional secondary task.

Whereas adaptive tracking tasks such as that of Borland & Nicholson (1974) are suitable for testing the reserve in motor skill capacity, i.e. maximal performance over a 'short' time, the long lasting compensatory tracking task used in our experiments reflects the momentary unforced performance. Moskowitz (1973) has indicated the importance of secondary tasks. He has summarized evidence showing that alcohol does not produce a significant impairment in performance on a variety of tests of visual functioning or tracking. If, however, subjects are required to perform such tasks together, performance on both has been found to decline. Monotony and memory load are found to be more drug sensitive when working in combination rather than in isolation (Jones *et al.*, 1978). These facts may be the reasons why flurazepam did not influence significantly motor reaction time in the experiments of Grünberger *et al.* (1978).

In accordance with the results of Saletu *et al.* (1981) subjects felt no 'hangover' after brotizolam as compared with placebo.

In contrast to 30 mg flurazepam, none of the parameters tested in our experimental design gave any evidence of a significant 'hangover' effect of 0.25 mg brotizolam as compared with placebo for healthy young males.

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Nachwirkungen von Flurazepam und Brotizolam auf die psychomotorische Leistungsfähigkeit

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1 Die Nachwirkungen von Brotizolam (0,25 mg) und Flurazepam (30 mg) wurden bei gesunden, jungen Erwachsenen untersucht. Die Leistungsfähigkeit und die subjektiven Beurteilungen wurden 7–8 Stunden nach der abendlichen Einnahme beobachtet und die Wirkung mit der von Placebo verglichen.

2 Die visuomotorische Koordination, visuell-mentale Verarbeitungszeit, visuomotorische Reaktionszeit sowie die Anzahl von Lesefehlern wurden durch Brotizolam nicht negativ beeinflusst.

3 Flurazepam 30 mg verursachten Nachwirkungen. Die visuomotorische Koordination, visuell-mentale Verarbeitungszeit, visuomotorische Reaktionszeit sowie die Zahl der Lesefehler waren im Vergleich zu Placebo und zu 0,25 mg Brotizolam beeinträchtigt.

4 Die subjektive Beurteilung der Leistungsfähigkeit stimmte mit der gemessenen Leistung überein. Sie nahm nach Flurazepam hinsichtlich der visuomotorischen Koordination und der visuell-mentalen Verarbeitungszeit im Vergleich zu Placebo eindeutig ab.

Effets résiduels du flurazépam et du brotizolam sur les performances psychomotrices

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1 Les effets résiduels du brotizolam (0,25 mg) et du flurazépam (30 mg) ont été étudiés chez de jeunes adultes en bonne santé. Les performances et les appréciations subjectives ont été relevées de 7 à 8 heures après l'ingestion nocturne, et les effets comparés à ceux d'un placebo.

2 La coordination visuomotrice, le temps de traitement visuomental, le temps de réaction visuomotrice et l'épreuve des erreurs de lecture n'ont pas été affectés par le brotizolam.

3 La dose de 30 mg de flurazépam a entraîné des effets résiduels. La coordination visuomotrice, le temps de traitement visuomental, le temps de réaction visuomotrice et l'épreuve des erreurs de lecture ont été affectés par rapport au placebo et à 0,25 mg de brotizolam.

4 Les appréciations subjectives des performances ont concordé avec les mesures des performances. La coordination visuomotrice et le temps de traitement visuomental ont été diminués par le flurazépam par rapport au placebo.

Efectos residuales de flurazepam y brotizolam sobre el rendimiento psicomotor

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1 En adultos jóvenes sanos se han estudiado los efectos residuales de brotizolam (0,25 mg) y flurazepam (30 mg). El rendimiento y las evaluaciones subjetivas se registraron a partir de 7-8 horas después de la ingestión nocturna comparando los efectos con los de placebo.

2 Brotizolam no alteró la coordinación visual-motora, el tiempo de procesado visual-mental, el tiempo de reacción visual-motora ni los errores de lectura.

3 Con 30 mg de flurazepam sí hubo efectos residuales. La coordinación visual-motora, el tiempo de procesado visual-mental, el tiempo de reacción visual-motora y los errores de lectura se vieron afectados en comparación con placebo y 0,25 mg de brotizolam.

4 Las evaluaciones subjetivas del rendimiento guardaron relación con el rendimiento medido. Se produjo un decremento con flurazepam (coordinación visual-motora y tiempo de procesado visual-mental) en comparación con placebo.