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Comparison of the pharmacological profiles of the hypnotic drugs, zaleplon and zolpidem

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Abstract

The BZ_1 (ω_1)-selective compound, zolpidem, is a clinically effective hypnotic drug with a pharmacological profile which differs from those of benzodiazepine anxiolytics and hypnotics. Zaleplon (CL 284,846) has recently been described as a hypnotic agent which also has BZ_1 (ω_1) receptor selectivity. The pharmacological effects of zolpidem and zaleplon were therefore compared in mice and rats. Both drugs blocked tonic convulsions induced in mice by pentylenetetrazole and electroconvulsive shock and clonic convulsions induced by isoniazid. Zaleplon was more potent than zolpidem but the maximal effect of zolpidem for increasing the latency to isoniazid-induced convulsions was greater than that of zaleplon. Little tolerance developed to the anticonvulsant effect of zaleplon against isoniazid-induced seizures following twice daily administration of 10 or 30 mg/kg for 10 days. Both compounds reduced locomotor activity and produced motor deficits in the rotarod and loaded grid tests in mice. However, while zaleplon produced all three effects at similar doses, zolpidem showed the greatest potency for reducing locomotion. Zaleplon and zolpidem also decreased locomotion and produced a rotarod deficit in rats. Again, the difference between the doses giving rise to these two effects was greater for zolpidem than for zaleplon. In a drug discrimination procedure using rats trained to discriminate a dose (5 mg/kg) of chlordiazepoxide, zaleplon produced partial substitution for chlordiazepoxide at doses which greatly reduced response rates. These results show that zaleplon and zolpidem have similar pharmacological profiles, presumably related to their BZ_1 (ω_1) receptor selectivity. However, the difference between doses producing motor deficits (rotarod, loaded grid) and those giving rise to other effects (anticonvulsant, decreased locomotion) was greater for zolpidem than for zaleplon. This difference may be related to a greater in vivo intrinsic activity of zolpidem as indicated by the different efficacies of the two drugs to antagonise isoniazid-induced convulsions.

Keywords: Zolpidem; Zaleplon; Hypnotic; BZ (ω) receptor

1. Introduction

Benzodiazepines have been used effectively as hypnotics for many years. However, potential problems, such as the development of dependence (Woods et al., 1992) and rebound insomnia (Lader, 1992), have led to the development of novel drugs, such as zopiclone and zolpidem (Goa and Heel, 1986; Langtry and Benfield, 1990), with similar, but not identical, mechanisms of action.

Zolpidem is an imidazopyridine derivative which acts at BZ (ω) sites associated with $GABA_A$ receptors but which has marked selectivity for the BZ_1 (ω_1) receptor subtype which corresponds with $GABA_A$ receptors containing α_1 subunits (Arbilla et al., 1985; Benavides et al., 1988; Faure-Halley et al., 1993; Pritchett and Seeburg, 1990). The pharmacological profile of zolpidem in experimental animals differs from the profiles of benzodiazepines in that it shows sleep-induction and decreases in locomotor activity at doses lower than those which produce other effects, such as motor incoordination and muscle relaxation (Depoortere et al., 1986; Perrault et al., 1990). It has thus been suggested that receptor subtype selectivity may be of importance in determining the specificity of pharmacological profiles and that BZ_1 (ω_1) selectivity may be particularly important for hypnotic action (Sanger et al., 1994; Zivkovic et al., 1988).

Recently, another novel non-benzodiazepine hypnotic drug, zaleplon (CL 284,846), has been described (Allen et al., 1993; Beer et al., 1994) which also has selectivity for the BZ_1 (ω_1) receptor subtype (Day et al., 1992). Few details of the pre-clinical pharmacology of zaleplon have been described but it has been found to have discriminative stimulus effects in rats distinct from those of benzodiazepines (Vanover and Barrett, 1994) and to show less

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marked anxiolytic-like effects than benzodiazepines (Sanger, 1995; Griebel et al., 1996). Similar properties have previously been described for zolpidem (Sanger and Zivkovic, 1986, 1988). The present study was therefore carried out in order to make direct comparisons between zaleplon and zolpidem in several behavioural tests in mice and rats.

2. Materials and methods

2.1. Subjects

The subjects were male CD1 and OF1 (for electroshock experiments) mice (18–24 g) supplied by Charles River and Iffa Credo, respectively, and male Wistar rats (180–200 g) also supplied by Iffa Credo. They were housed in groups of 30 (mice) or five (rats) under standard laboratory conditions with food and water continuously available except for the rats used in the drug discrimination experiment which were housed singly under conditions of food deprivation. These animals were given a standard daily quantity of 20 g of food at the end of each day and over the weekends. The housing rooms were temperature- and humidity-controlled with lights on between 07:00 and 19:00 h. The experiments described below were carried out during the light period (morning and afternoon), the two drugs being tested under identical conditions. Housing conditions and experimental protocols were in accordance with current French Legislation.

2.2. Pentylenetetrazole-induced convulsions

At 30 min after i.p. injection of zaleplon, zolpidem or the vehicle, mice were given an s.c. injection of 125 mg/kg, of pentylenetetrazole. The occurrence of tonic extension of the hindlimbs was noted during the 30-min period which followed.

2.3. Electroshock-induced convulsions

Following injection of zaleplon or zolpidem electroshock seizures were produced by an electric current (60 mA, 50 Hz, 0.4 s) delivered through a pair of corneal electrodes. The occurrence of tonic extension of the hindlimbs was noted.

2.4. Isoniazid-induced convulsions

Isoniazid (800 mg/kg s.c.) was administered simultaneously with zaleplon or zolpidem. The latency to the first clonic convulsion was noted.

In a separate experiment, mice were given orally twice daily (at approximately 08:00 and 16:00 h) zaleplon 10 or 30 mg/kg or vehicle for 10 days. At 42 h after the last administration, they were injected with one of a range of doses of zaleplon (i.p.) simultaneously with isoniazid (800 mg/kg) and the latency to the first convulsion was noted. The purpose of this experiment was to investigate the possible development of tolerance to the anticonvulsant effect of zaleplon.

2.5. Locomotor activity

At 30 min after i.p. injection of zaleplon or zolpidem, the mice and the rats were placed individually in Plexiglass activity cages (circular cages, 20-cm diameter for mice, and square cages with 39-cm sides for rats) in a sound-attenuating cupboard. Each cage was fitted with two intersecting photobeams and photocells which recorded beam breaks. Activity was recorded during a 20-min period for rats and for 10-min in mice.

2.6. Rotarod performance

Mice were pre-tested on the rotarod (turning at 10 turns/min, diameter 3 cm), and animals which stayed on the apparatus for 2 min were selected for drug testing. Each animal was given a maximum of two trials during the pre-test. Approximately 2 h later each animal was injected i.p. with zaleplon or zolpidem and was placed 30 min later on the rotarod. The time each mouse stayed on the rotarod was recorded up to a maximum of 2 min.

Rats were trained to stay on a rotarod turning at a speed of 5 turns/min (diameter 6 cm) for at least 1 min. It was not necessary to eliminate any animals. Approximately 3 h later a second pre-test was given during which the apparatus first turned at the same constant speed for 1 min and then turned at an accelerating speed (5–42 turns/min in 10 min).

24 h later, each rat was injected i.p. with zaleplon or zolpidem and, 30 min later, was replaced on the rotarod. The length of time each animal stayed on the apparatus at accelerating speed was recorded.

2.7. Loaded grid test

During the pre-test, mice were held by their tails and allowed to grip with their front paws a metal grid to which increasing weights were attached. Animals which continued to grip 30 g for 10 s were selected for the experiment. Several hours later, each mouse was given a second pre-test and was then injected with zaleplon, zolpidem or vehicle. 30 min later, each animal was retested and the maximum weight tolerated was recorded.

2.8. Drug discrimination

A group of 12 rats was trained to discriminate between a dose of 5 mg/kg i.p. of chlordiazepoxide and saline using a standard, two-lever, fixed ratio 10 (FR10), food-rewarded operant procedure. Thus, rats obtained a food pellet (45 mg) each time they pressed 10 times on the appropriate lever in the 2-lever operant test chamber.

Responses on one lever were rewarded in sessions which followed chlordiazepoxide injection and responses on the other lever were rewarded during the session following saline injection (see Sanger and Zivkovic, 1986, for further details of the procedure). Daily sessions were 15 min in duration. When the animals had acquired the generalisation, they were given substitution tests with a range of doses of chlordiazepoxide. Eight of the rats were then tested with several doses of zaleplon. The zolpidem results presented had been obtained in a group of 10 rats several years earlier using an identical procedure (Sanger and Zivkovic, 1987). The results were recorded as the number of rats choosing the chlordiazepoxide-associated lever during the substitution tests and the number of lever presses emitted during these tests (expressed as a percentage of the number of lever presses following saline injection).

2.9. Drugs

Zolpidem hemitartrate (Synthélabo Recherche) and zaleplon (base) (American Cyanamid) were prepared in physiological saline to give injection volumes of 20 ml/kg for mice and 2 or 5 ml/kg for rats. Doses are expressed as the bases.

In each procedure, each drug was tested at several doses and the test animals were compared with vehicle-treated animals. However, with the exception of the drug discrimination experiment with zolpidem, all experiments were carried out during the same 3-month period and the control values were similar, so direct comparisons between the two drugs seemed appropriate. Except for electroshock and pentylenetetrazole convulsions, the effects of the different doses of each drug were compared with the appropriate control values using analysis of variance (ANOVA) and Dunnett's test. ED_{50} values were calculated using probit analysis except for isoniazid-induced convulsions where doses which produced a half-maximal effect were estimated from the dose-response curves. For pentylenetetrazole and electroshock-induced seizures the ED_{50} values refer to doses which protected 50% of the animals against seizures. For locomotor activity and rotarod and loaded grid performance, ED_{50} values are the doses which produced levels of activity 50% of those shown by the control animals. For the drug discrimination experiment, the ED_{50} discrimination is the dose at which 50% of the rats responded on the chlordiazepoxide-associated lever and the ED_{50} rate is the dose at which rates of lever pressing were decreased to 50% of those occurring after saline administration.

3. Results

3.1. Anticonvulsant effects in mice

Both zaleplon and zolpidem showed anticonvulsant activity in mice, producing dose-related antagonism of tonic convulsions induced by pentylenetetrazole and electroshock and clonic convulsions produced by injection of isoniazid (Figs. 1 and 2). The maximum increase in the latencies to isoniazid-induced convulsions was considerably greater with zolpidem than with zaleplon. Statistical analysis of the isoniazid convulsions data showed highly significant effects of zolpidem ($F(5,114) = 125$, $P < 0.001$) and of zaleplon ($F(5,133) = 80$, $P < 0.001$). Zaleplon was 3–6 times more potent than zolpidem in antagonising convulsions (Fig. 1, Table 1).

The effects of acute administration of zaleplon following chronic treatment with this drug on latencies to isoniazid-induced convulsions are shown in the lower panel of Fig. 2. After chronic treatment with the vehicle, zaleplon produced a dose-related anticonvulsant effect similar to that found in the preceding experiment, the results of which are shown in the upper panel of Fig. 2. The figure indicates that chronic treatment (10 days) with zaleplon at twice-daily doses of 10 or 30 mg/kg produced little alteration of the effect of the drug. There were statistically significant effects of dose ($F(4,135) = 245$, $P < 0.001$) and of pre-treatment ($F(2,135) = 3.5$, $P < 0.05$) but the interaction was not significant. Individual comparisons

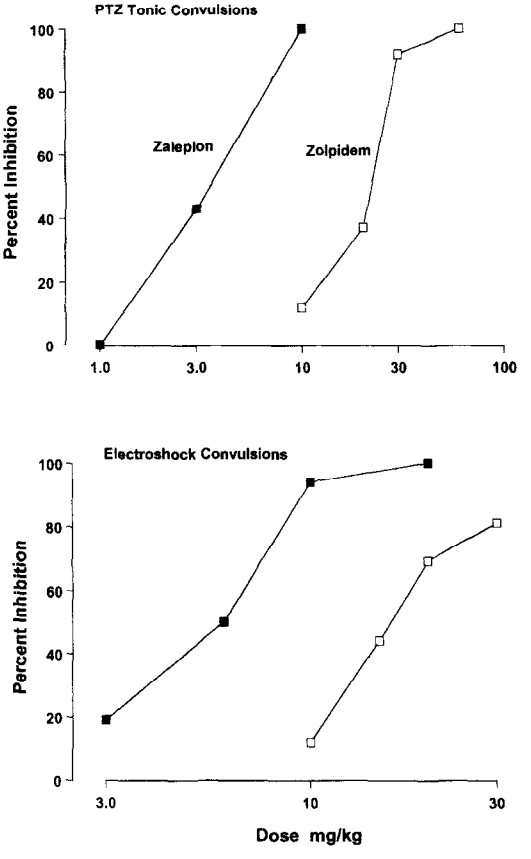

Fig. 1. The anticonvulsant effects of zaleplon and zolpidem against tonic convulsions provoked in mice by pentylenetetrazole (125 mg/kg s.c.) and electroshock ($n = 16$–24 mice/group). Results are shown as the percentage inhibition of the convulsions (i.e. number of mice not convulsing/number of animals tested $\times 100$).

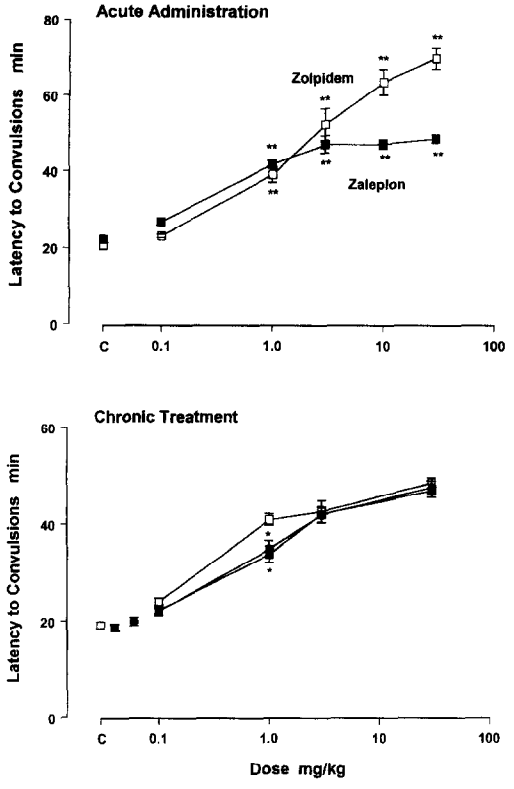

Fig. 2. The effects of zaleplon and zolpidem on the latency to clonic convulsions induced by injection of isoniazid (800 mg/kg s.c.). The upper panel shows dose-related increases in latencies produced by acute administration of zaleplon and zolpidem. Doses of zaleplon and zolpidem of 1.0 mg/kg and above produced statistically significant increases in latency ($P < 0.01$). The lower panel shows the effects of acute i.p. administration of zaleplon 42 h after the last of a series of 10 days twice-daily oral administration of the drug: □, chronic vehicle; ■, chronic zaleplon 10 mg/kg; ●, chronic zaleplon 30 mg/kg. * $P < 0.05$ difference between vehicle and drug pretreated groups: $n = 10$–30 mice/group.

Table 1
Potencies of zaleplon and zolpidem

Test	ED_{50} mg/kg i.p.	
	Zaleplon	Zolpidem
Mice		
PTZ tonic seizures	3.0 (N.D.)	18.6 (15.5–22.2)
Electroshock seizures	5.0 (3.8–6.4)	17.6 (14.0–21.3)
Isoniazid seizures	0.3	1.8
Locomotor activity	4.8 (1.3–15.8)	9.1 (6.5–12.4)
Rotarod	5.6 (4.8–6.9)	23.0 (20.0–26.2)
Loaded grid	7.9 (4.9–12.4)	38.8 (N.D.)
Rats		
Locomotor activity	0.7 (0.2–3.9)	1.0 (0.8–1.2)
Rotarod	1.3 (1.1–1.5)	4.3 (3.9–4.7)
DDiscrimination, substitution	0.9 (0.4–2.6)	1.3 (N.D.)
Discrimination. rate	1.3 (1.0–1.7)	2.1 (1.4–5.9)

ED_{50} values were determined by probit analysis except for isoniazid-induced convulsions where doses which produced a half-maximal effect were estimated from the dose-response curves (figures in brackets represent the 95% confidence limits).
N.D., not determined (because dose-response curves did not fit the regression analysis within 95% confidence limits).

showed statistical significance for the differences between pre-treatments only after acute administration of the 1.0-mg/kg dose. It is interesting to note that following withdrawal of chronic zaleplon treatment the sensitivity of the animals to isoniazid was not increased (points at C in lower part of Fig. 2).

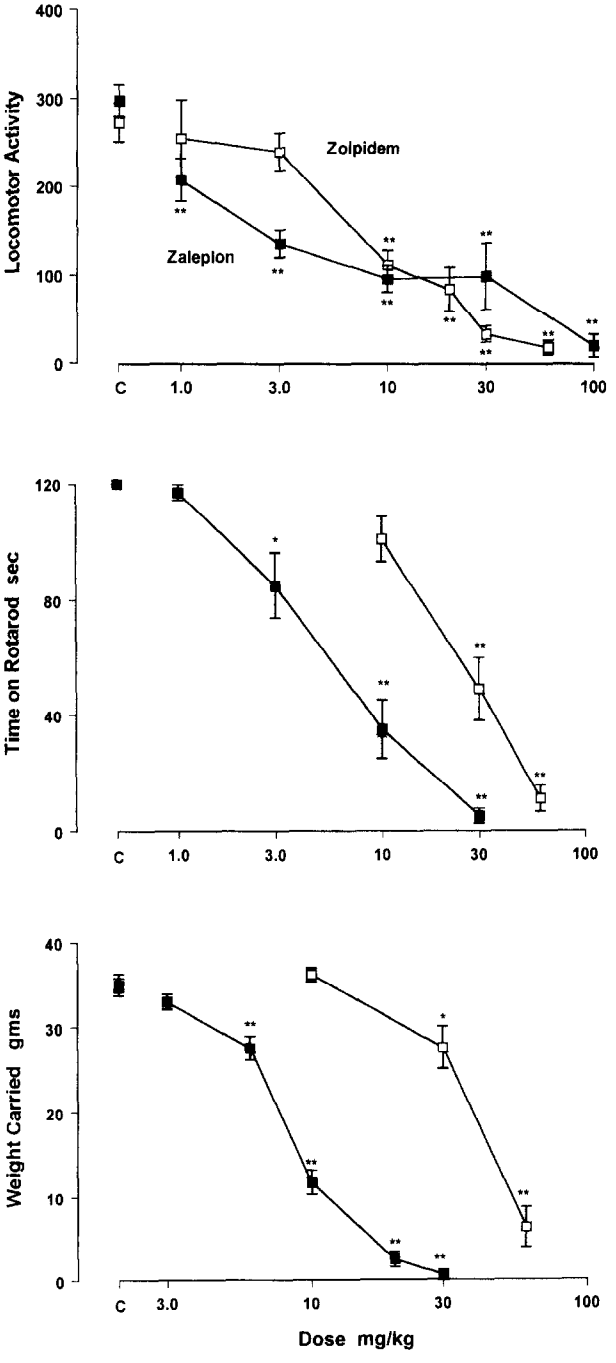

Fig. 3. Dose-related effects of zaleplon and zolpidem on locomotor activity, rotarod and loaded grid performance in mice. Results are expressed as the mean number of beam breaks in 10 min, the time on the rotarod and the mean maximum weight carried. * $P < 0.05$, * * $P < 0.01$ difference from the appropriate control group. $n = 8$–24 mice/group.

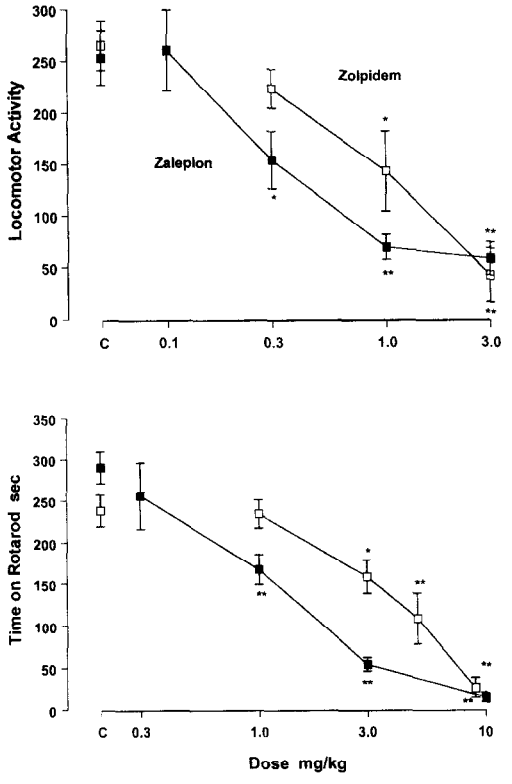

Fig. 4. Dose-related effects of zaleplon and zolpidem on locomotor activity and rotarod performance in rats. Results are expressed as the mean number of beam breaks in 20 min and the mean time spent on the rotarod. * $P < 0.05$, * * $P < 0.01$ difference from the appropriate control group. $n = 6$–15 rats/group.

3.2. Motor performance in mice

The effects of zaleplon and zolpidem on locomotor activity and motor performance in the rotarod and loaded grid tests are shown in Fig. 3. Both drugs produced dose-related motor deficits in all three tests. Statistical analysis showed significant drug effects on locomotion (zolpidem: $F(6,89) = 24.2$, $P < 0.001$; zaleplon: $F(5,98) = 18.9$, $P < 0.001$), rotarod (zolpidem: $F(3,44) = 22.9$, $P < 0.01$; zaleplon: $F(4,59) = 28.3$, $P < 0.001$) and loaded grid performance (zolpidem: $F(3,28) = 52.3$, $P < 0.001$; zaleplon: $F(5,90) = 118.1$, $P < 0.001$). For locomotor activity, there was considerable overlap between the two dose-response curves, so that the ED_{50} dose for zaleplon was only slightly lower than that for zolpidem. In contrast, zaleplon showed a 4–5 times greater potency than zolpidem to cause rotarod and loaded-grid deficits (Table 1).

3.3. Motor performance in rats

Zaleplon and zolpidem produced dose-related decreases in locomotion and rotarod performance deficits in rats (Fig. 4). Locomotion was more sensitive than rotarod performance with both drugs, and zaleplon was slightly more potent than zolpidem (Table 1). Statistical analysis showed that all effects were statistically significant. Locomotion: zolpidem: $F(3,28) = 12.3$, $P < 0.001$; zaleplon: $F(4,35) = 13.7$, $P < 0.001$. Rotarod: zolpidem: $F(4,69) = 19.0$, $P < 0.001$; zaleplon: $F(4,60) = 56.3$, $P < 0.001$.

3.4. Chlordiazepoxide discrimination

The effects of zaleplon and zolpidem in rats trained to discriminate a dose of 5 mg/kg of chlordiazepoxide from saline are shown in Fig. 5. The data shown for zaleplon and chlordiazepoxide are from the same group of animals whereas the zolpidem results were obtained previously in identically treated rats. The results are shown as the percentage of rats responding on the chlordiazepoxide-associated lever (upper panel) and the rates of lever pressing as a percentage of the rates obtained on saline days.

Zaleplon, like zolpidem, produced incomplete substitution for chlordiazepoxide. It was not possible to test higher doses of either drug because, as shown in the lower panel of Fig. 5, both drugs greatly reduced response rates. Chlordiazepoxide increased the response rates at the training dose and decreased the rates at the dose of 30 mg/kg.

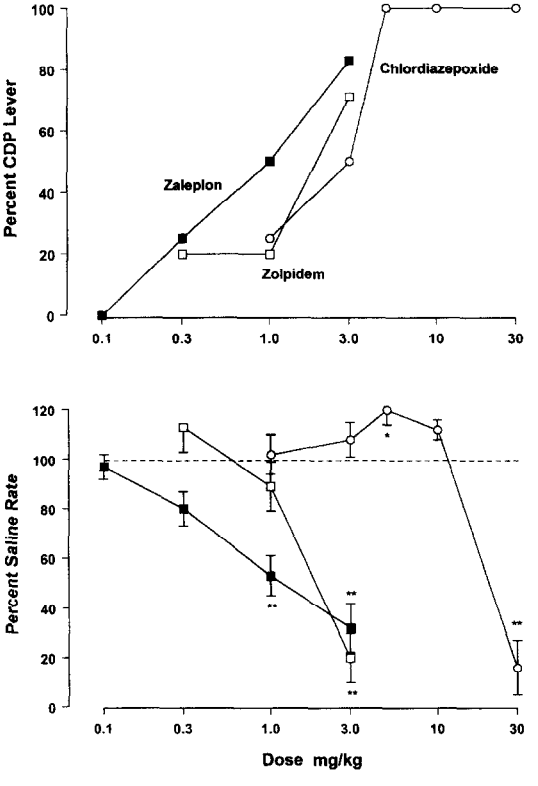

Fig. 5. Effects of chlordiazepoxide, zaleplon and zolpidem in rats trained to discriminate a dose of 5 mg/kg chlordiazepoxide from saline. The upper panel shows the percentage of animals tested at each dose which chose the chlordiazepoxide (CDP)-associated lever. The lower panel shows rates of lever pressing during the 15-min sessions as a percentage of rates after saline. The results shown for zaleplon and chlordiazepoxide were obtained in the same group of rats ($n = 12$). The zolpidem results were obtained earlier from a separate group of animals trained and tested using an identical procedure (Sanger and Zivkovic, 1987). * $P < 0.05$, * * $P < 0.01$ difference from saline rates.

4. Discussion

The purpose of the present study was to compare in detail the effects of the novel drug, zaleplon, which is currently in clinical development as a potential hypnotic, and those of the clinically used hypnotic, zolpidem. A range of behavioural tests with rodents showed that the two drugs had similar, but not identical, pharmacological profiles, producing anticonvulsant effects, decreases in locomotor activity, motor deficits and discriminative stimulus actions.

Both zaleplon and zolpidem antagonised the tonic seizures produced in mice by pentylenetetrazole and electroshock and increased the latency to clonic seizures produced by isoniazid. Zaleplon differed from zolpidem as to the maximal increase in latency to the isoniazid-induced convulsions produced. The present findings with zolpidem are consistent with previous results showing that this drug produces a very large increase in this measure, greater than those seen with a variety of benzodiazepines (Zivkovic et al., 1988). Isoniazid blocks GABA synthesis by inhibiting the enzyme, glutamic acid decarboxylase, producing a decrease in GABA levels (Löscher and Frey, 1977). The maximal increase in latency to isoniazid-induced seizures produced by a test compound may therefore be taken as an index of enhanced GABAergic function. This test has been proposed as an in vivo measure of the intrinsic activity of BZ (ω) agonists at $GABA_A$ receptors (Mao et al., 1975; Perrault et al., 1990). The present results thus indicate that zolpidem may have greater intrinsic efficacy at $GABA_A$ receptors than zaleplon. This hypothesis would, of course, need to be investigated using appropriate in vitro electrophysiological methods. It is interesting to note, however, that zolpidem has been shown to produce a greater maximum potentiation of GABA-induced chloride currents than diazepam and flunitrazepam (Horne et al., 1992; Itier et al., 1996) which is consistent with the proposal that this imidazopyridine may show higher intrinsic activity in vivo than several benzodiazepines (Perrault et al., 1990; Zivkovic et al., 1988).

Isoniazid-induced convulsions in mice were also used to investigate the possible development of tolerance to the effects of zaleplon. Previous research has shown that tolerance can develop to the anticonvulsant effects of benzodiazepines (File, 1985; Garratt et al., 1988). However, zolpidem did not give rise to tolerance to its anticonvulsant effect against isoniazid-induced convulsions in mice under conditions where marked tolerance was observed with midazolam and diazepam (Perrault et al., 1992, 1993; see also Cox et al., 1988). It has also been found that little or no tolerance develops to the decrease in rates of operant responding produced in rats by zolpidem although clear tolerance was observed with chlordiazepoxide, midazolam and triazolam (Sanger and Zivkovic, 1987, 1992; Cohen and Sanger, 1994). In the present study, twice daily administration of oral doses fo 10 or 30 mg/kg of zaleplon produced little tolerance to the anticonvulsant effect of the drug against isoniazid-induced convulsions. Only at one dose (1.0 mg/kg), there was a statistically significant difference between mice treated chronically with drug or with vehicle. It is interesting to note that previous behavioural studies in rats have also found little tolerance to the effects of CL 218,872 or abecarnil (Ozawa et al., 1994; Löscher et al., 1991; Sanger and Zivkovic, 1992; McElroy et al., 1985) which, like zolpidem and zaleplon, have selectivity for BZ_1 (ω_1) receptors. The present results with zaleplon, therefore, are consistent with the hypothesis that receptor subtype-selective agents produce less tolerance than non-selective drugs (Perrault et al., 1992; Sanger et al., 1994).

After withdrawal of the repeated treatment with zaleplon there was no increase in the sensitivity of mice to isoniazid-induced convulsions. A number of previous studies have shown that chronic treatment with certain BZ (ω) receptor agonists can lead to decreased seizure thresholds on drug withdrawal, which may be taken as a measure of physiological dependence. However, zolpidem and alpidem did not produce such effects (Perrault et al., 1992, 1993; Von Voigtlander and Lewis, 1991) suggesting that BZ_1 (ω_1)-selective drugs produce less physiological dependence than do non-selective compounds. The present results with zaleplon are consistent with this view.

Zaleplon decreased locomotor activity and increased motor incoordination in both mice and rats, effects which are usually considered to reflect the sedative/hypnotic activity of BZ (ω) receptor agonists. It has previously been reported that, in contrast to benzodiazepines, zolpidem reduces locomotor activity at doses considerably smaller than those which produce muscle relaxation and motor incoordination (Perrault et al., 1990; Zivkovic et al., 1988). The present results with this drug confirm these previous findings although, for reasons which are still unknown, zolpidem had a lower potency to decrease locomotor activity in mice than had previously been reported (the ED_{50} of 9.1 mg/kg in the present study can be compared with a value of 1.2 mg/kg reported by Perrault et al. (1990)). Although there is no explanation for this difference, it can be pointed out that the activity cages used in the present study were different from those used to obtain the data described in the previous paper (Perrault et al., 1990). Zaleplon showed approximately similar potencies to decrease locomotor activity and to produce motor incoordination. Thus, in this respect, zaleplon had a profile intermediate between that of zolpidem and those of the benzodiazepines (Perrault et al., 1990; Zivkovic et al., 1988). It is possible that this is a result of differences in intrinsic activity between zolpidem and zaleplon as indicated by the isoniazid convulsions results.

Drug discrimination has been used extensively to investigate the effects of BZ (ω) receptor ligands. Only partial cross-substitution has been reported between benzodiazepines and zolpidem (Depoortere et al., 1986; Sanger

and Zivkovic, 1986) and evidence has been presented that the cue produced by chlordiazepoxide may be related to activity at the BZ_2 (ω_2) receptor subtype (Sanger and Benavides, 1993). Vanover and Barrett (1994) trained rats to discriminate a dose of zaleplon and found full or partial substitution by several BZ (ω) receptor ligands, including zolpidem. They concluded that zaleplon produced a distinct cue, possibly mediated by activity at BZ_1 (ω_1) sites. In the present experiment, zaleplon, like zolpidem, gave rise to partial substitution for chlordiazepoxide but only at doses which decreased response rates. This finding is also consistent with the reported BZ_1 (ω_1) selectivity of zaleplon.

The present results show that, in rodents, zaleplon has a pharmacological profile consisting of anticonvulsant effects, decreases in locomotor activity and motor deficits typical of effects produced by full agonists at BZ (ω) receptors. However, zaleplon showed a number of similarities to the BZ_1 (ω_1)-selective hypnotic, zolpidem, which differentiate both drugs from the benzodiazepines. It seems likely that this pharmacological profile is related to receptor subtype selectivity.

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