Br. J. clin. Pharmac. (1991), **31**, 193–196 ADONIS 0306525191000408

A dose-response study examining the effects of ritanserin on human slow wave sleep

C. IDZIKOWSKI, F. J. MILLS & R. J. JAMES
Clinical Pharmacology Unit, Janssen Research Foundation, Grove, Wantage, Oxon., OX12 0DQ

This study investigated the effects of placebo, 1 mg, 3 mg, 10 mg and 30 mg ritanserin and 10 mg diazepam on human sleep. Twelve normal volunteers participated in this randomized, double-blind, placebo-controlled cross-over sleep study. A clear dose-response relationship was found for ritanserin with higher doses evoking increased duration of slow wave sleep.

Keywords ritanserin sleep human dose-response

Introduction

Ritanserin, a potent 5-HT_2 receptor antagonist (Awouters *et al.*, 1988), increases the duration of human slow wave sleep (SWS) in fit young (Clarenbach *et al.*, 1986; Declerck *et al.*, 1987; Idzikowski *et al.*, 1986, 1987) and fit elderly subjects (Adam & Oswald, 1989), insomniac patients (Ruiz-Primo *et al.*, 1989) and patients suffering from dysthymia (depressive neurosis, DSM-III) (Paiva *et al.*, 1988). These laboratory observations have also been confirmed in the home (Solomon *et al.*, 1989). All these studies have used a single dose of either 5 or 10 mg ritanserin and no evidence of a dose-response relationship has been presented. Therefore this study was conducted to examine the dose-response relationship between ritanserin and SWS.

This study compared placebo, 1 mg, 3 mg, 10 mg and 30 mg ritanserin. Diazepam (10 mg) was used as a reference drug. Ritanserin's plasma half-life is approximately 40 h (Van Peer *et al.*, 1985).

This experiment has been presented at the 1987 American Professional Sleep Societies Conference held in Columbus, Ohio (Idzikowski *et al.*, 1987).

Methods

Twelve volunteers (10 females and two males) who gave written informed consent and were aged 18–51 years (mean 32.6 years) participated in this study. The study was approved by High Wycombe Ethics Committee. Volunteers were medically fit and had no known history of either sleep problems or alcohol or drug abuse. Subjects were not allowed to drive during treatment days and were transported to and from the laboratory. Subjects were required to refrain from alcohol and any medications.

Ten centimetre visual analogue scales measuring sleep quality (ranging from worst possible to best ever) and morning vigilance (ranging from marvellously alert and energetic to awfully sleepy and lack-lustre) were completed on awakening (Oswald *et al.*, 1978). Lights were turned off at 23.00 h and subjects arose out of bed at 07.00 h. Silver/silver chloride electrodes for measuring sleep were placed in a standard configuration (according to the 10–20 system EEG electrodes P4, O2, C4 and T4, EOG electrodes on the upper outer canthus of each eye and above each eye and EMG electrodes beneath the chin) and were connected to either a Nihon-Kohden 4221 or SLE TM 23 channel EEG machine. Sleep was scored blind using the criteria of Rechtschaffen & Kales (1965). Onset of stage 2 was used to determine sleep onset latency. Duration of SWS was calculated by adding the durations of Stage 3 and Stage 4. Sleep efficiency is the percentage of time spent asleep during the sleep episode. Wake in sleep time is the absolute duration of wakefulness during the sleep episode.

The study was double-blind, placebo-controlled, and of a latin-square cross-over design. There were six treatments: 1) placebo, 2) 1 mg ritanserin, 3) 3 mg ritanserin, 4) 10 mg ritanserin, 5) 30 mg ritanserin and 6) 10 mg diazepam. The treatments were separated by an interval of 2 weeks.

Subjects slept at the laboratory for 19 nights. The first night was used as a general adaptation night. Each condition consisted of: 1) an adaptation night, 2) a baseline night and 3) a drug night. Baseline–drug differences provided the raw data for analyses. Analysis of variance (ANOVA) was the main statistical instrument. If there was a significant drug effect *t*-values were calculated using the standard error of the difference of the mean.

Ritanserin was always administered in the morning after breakfast at 08.00 h. Diazepam was administered in the evening at 22.30 h.

Correspondence: Dr C. Idzikowski, Human Psychopharmacology Research Unit, Robens Institute of Health and Safety, University of Surrey, Guildford, Surrey GU2 5XH

Table 1 Mean difference from baseline and standard deviations of measures

		Ritanserin				Diazepam
	Placebo	*1 mg*	*3 mg*	*10 mg*	*30 mg*	*10 mg*
Sleep quality	4.8 ±4.9	−0.4 ±4.8	1.5 ±4.6	10.0 ±3.8	12.6 ±5.2	13.4 ±5.1
Morning vigilance	10.6 ±4.3	11.6 ±5.6	3.8 ±3.7	1.3 ±4.6	4.4 ±4.9	−8.3 ±5.0
Total sleep time	−3.6 ±55.5	19.5 ±56.2	−2.9 ±27.2	19.5 ±35.5	27.5 ±37.6	1.9 ±19.2
Sleep efficiency %	−0.6 ±11.7	4.1 ±11.7	−0.5 ±5.7	4.1 ±7.4	5.7 ±7.8	0.4 ±4.0
Log(e) sleep onset time	0.1 ±0.7	−0.5 ±1.0	−0.1 ±0.7	−0.4 ±0.8	−0.9 ±0.9	−0.3 ±0.7
REM latency time	−17.0 ±41.9	−4.9 ±29.5	−7.3 ±56.2	9.8 ±24.8	23.0 ±22.1	21.0 ±29.0
Stage 3 latency	−2.1 ±10.2	−3.9 ±9.0	−11.3 ±27.8	0.5 ±7.5	−1.0 ±6.0	−3.4 ±13.5
Number of REM periods	0.0 ±1.0	0.1 ±0.6	−0.2 ±1.2	−0.3 ±0.7	−0.7 ±0.7	−0.1 ±0.8
Wake in sleep time	2.8 ±16.2	2.5 ±7.1	1.4 ±8.9	3.4 ±8.7	5.8 ±10.0	2.6 ±11.9
Stage 1 time	−5.8 ±8.3	−5.5 ±7.8	−8.0 ±11.3	−0.7 ±6.4	−4.2 ±8.0	−9.8 ±2.4
Stage 2 time	−12.3 ±46.2	−32.7 ±46.0	−77.3 ±51.4	−53.5 ±51.4	−91.0 ±39.3	14.0 ±26.1
Slow wave sleep time	−1.7 ±33.6	51.5 ±40.2	80.4 ±37.6	99.5 ±54.7	134.8 ±36.5	−2.7 ±11.5
Stage REM time	12.5 ±30.6	7.5 ±24.6	7.5 ±22.8	−10.5 ±37.9	12.6 ±28.9	2.2 ±29.4
SWS %	0.3 ±5.8	10.3 ±7.7	18.5 ±8.3	20.5 ±11.2	27.7 ±7.1	−0.7 ±2.7
REM %	3.3 ±6.0	0.8 ±4.4	1.8 ±5.6	−3.4 ±7.2	−3.5 ±6.0	0.3 ±6.0

Analogue scales in mm, positive VAS values denote improvement, times in min.

Results

One subject left the study with an anomalous EEG after completing five out of the six conditions (1 mg ritanserin condition omitted). The change in EEG was not attributed to any of the drugs but to the reappearance of a pre-existing and hitherto undetected condition.

Table 1 shows the subjective rating results. There were no significant effects on sleep quality overall ($F = 1.25$, df = 5,55, $P > 0.05$) although there was a marginally significant linear trend ($F = 5.09$, df = 1,33, $P < 0.05$) indicating improvement of sleep quality with the ritanserin dose. Overall morning vigilance was unaffected by drug condition ($F = 0.55$, df = 5,55, $P > 0.05$) although diazepam affected vigilance adversely ($t = 2.62$, df = 55, $P < 0.01$).

The major effect was to increase the duration of SWS with ritanserin ($F = 26.75$, df = 5,54, $P < 0.0001$). Curve fitting revealed a significant linear trend ($F = 29.5$, df = 1,32, $P < 0.0001$) with no curvilinear (quadratic) components (Figure 1). Every dose of ritanserin elevated the duration of SWS significantly including 1 mg ritanserin ($t = 3.5$, df = 54, $P < 0.0005$).

Sleep onset latency values were skewed so analyses were conducted using log(e) transformation. Significant effects on sleep onset latency were observed ($F = 2.6$, df = 5,54, $P < 0.05$). Three doses of ritanserin reduced sleep onset latency (1 mg: $t = 2.02$, df = 54, $P < 0.025$; 10 mg: $t = 2.01$, df = 54, $P < 0.025$; 30 mg: $t = 3.32$, df = 54, $P < 0.0025$). The 3 mg dose failed to reduce

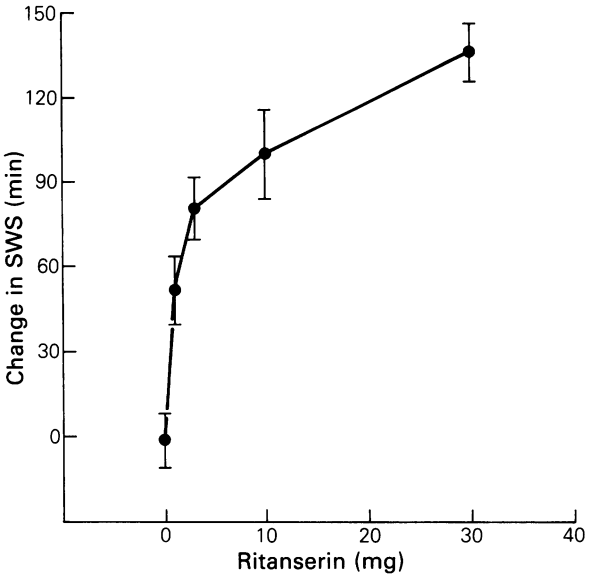

Figure 1 Relationship between the dose of ritanserin and the mean change in duration of slow wave sleep.

sleep onset latency ($t = 0.7$). There was no clear dose-response relationship.

REM latency was increased by higher doses of ritanserin (10 mg: $t = 1.82$, df = 54, $P < 0.05$; 30 mg: $t = 2.72$, df = 54, $P < 0.005$) and by diazepam ($t = 2.6$, df = 54, $P < 0.01$). REM expressed as a percentage of total sleep time was also reduced significantly ($F = 3.318$, df = 54, $P < 0.01$). The reduction occurred with the higher doses of ritanserin (REM % decreased: 10 mg: $t = 3.09$, df = 54, $P < 0.0025$; 30 mg: $t = 3.17$, df = 54, $P < 0.0025$).

Discussion

In normal volunteers, ritanserin had no effect on morning vigilance and only marginal effects on sleep quality. This result is similar to our previous work (Idzikowski *et al.*, 1986, 1987). Ritanserin's higher doses appear to have a mild hypnogenic action, a decrease in sleep onset latency and improvement in subjective sleep quality. The increase in SWS probably causes an increase in REM latency and certainly a decrease in the amount of stage 2.

Drugs with 5-HT_2-receptor antagonist properties, such as cyproheptadine, pizotifen, and trazodone (Montgomery *et al.*, 1983; Solomon *et al.*, 1989) may increase SWS whereas other 5-HT_2-receptor antagonists such as methysergide (Mendelson *et al.*, 1975) or metergoline (Solomon *et al.*, 1989) do not. Idzikowski *et al.* (1986) proposed that a functional antagonism between 5-HT_1 and 5-HT_2-receptors could account for the difference and this hypothesis is still being examined. The dose-response curve for ritanserin provides a tool for further quantitative investigation.

Conclusions

The main finding is that the increase of SWS is related to ritanserin dose and thus it is likely that drug receptor interactions can be explored quantitatively.

We would like to thank Liz Hardy, Vivien Muir and Tony Tarry without whose assistance this work would not have been possible.

References

Adam, K. & Oswald, I. (1989). Effects of repeated ritanserin on middle-aged poor sleepers. *Psychopharmacology*, **99**, 219–221.

Awouters, F., Niemegeers, C. J. E., Megens, A. A. H. P., Meert, T. F. & Janssen, P. A. J. (1988). The pharmacological profile of ritanserin, a very specific central serotonin-S_2 antagonist. *Drug Devel. Res.*, **15**, 61–73.

Clarenbach, P., Birmanns, B., Kratzschmar, S. & Jaursch-Hancke, C. (1986). Sleep pattern and nocturnal plasma profiles of HGH, prolactin and cortisol in man after the serotonin-antagonist ritanserin and the gaba-agonist gabapentin. *Sleep Res.*, **15**, 29.

Declerck, A. C., Wauquier, A., Van der Ham-Veltman, P. H. M., & Gelders, Y. (1987). Increase of slow wave sleep in human volunteers by the serotonin-S2 antagonist ritanserin. *Curr. Ther. Res.*, **41**, 427–432.

Idzikowski, C., Cowen, P. J., Nutt, D. & Mills, F. J. (1987). The effects of chronic ritanserin treatment on sleep and the neuroendocrine response to L-tryptophan. *Psychopharmacology*, **93**, 416–420.

Idzikowski, C., Mills, F. J. & Glennard, R. (1986). 5-Hydroxytryptamine-2 antagonist increases human slow wave sleep. *Brain Res.*, **378**, 164–168.

Idzikowski, C. & Mills, F. J. (1987). A dose-response study of the effects of ritanserin on slow wave sleep. *Sleep Res.*, **16**, 93.

Mendelson, W. B., Jacobs, L. S., Reichman, J. D., Othmer, E., Cryer, P. E., Triveldi, B. & Daughaday, W. H. (1975). Methysergide: suppression of sleep related prolactin excretion and enhancement of sleep related growth hormone secretion. *J. clin. Invest.*, **56**, 690–697.

Montgomery, I., Oswald, I., Morgan, K. & Adam, K. (1983). Trazodone enhances sleep in subjective quality but not in objective duration. *Br. J. clin. Pharmac.*, **16**, 139–144.

Oswald, I., Adam, K., Borrow, S. & Idzikowski, C. (1978). The effect of two hypnotics on sleep, subjective feelings and skilled performance. In *Pharmacology of the states of alertness*, eds Passouant, P. & Oswald, I., pp 583–586. Oxford: Pergamon Press.

Paiva, T., Arriaga, F., Wauquier, A., Lara, E., Largo, R. & Leitao, J. M. (1988). Effects of ritanserin on sleep disturbances of dysthymic patients. *Psychopharmacology*, **96**, 395–399.

Rechtschaffen, A. & Kales, A. (1965). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Bethesda: National Institute of Mental Health.

Ruiz-Primo, E., Haro, R. & Valencia, M. (1989). Polysomnographic effects of ritanserin in insomniacs in a crossed double-blind controlled study. *Sleep Res.*, **18**, 72.

Solomon, R. A., Sharpley, A. L. & Cowen, P. J. (1989). Increased slow wave sleep with 5-HT_2-receptor ant-

agonists: Detection by ambulatory EEG recording and automatic sleep stage analysis. *J. Psychopharmacology*, **3**, 125–129.

Van Peer, A., Gasparini, R., Woestenborghs, R., Heykants, J. & Gelders, Y. (1985). Intravenous pharmacokinetics and effect of food on the bioavailability of ritanserin in healthy volunteers. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **330** (Suppl), R15.

(Received 22 May 1990, accepted 3 September 1990)