INFLUENCE OF BROtizOLAM ON THE VENTILATORY AND MOUTH-OCCLUSION PRESSURE RESPONSE TO HYPERCAPNIA IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

G.W. SYBRECHT

Medizinische Hochschule Hannover, Abteilung Pneumologie, Hannover, Federal Republic of Germany

- 1 Effect of 0.25 mg brotizolam on patients with chronic obstructive lung disease of moderate to severe degree was studied.
- 2 There was no difference between the slopes of ventilation vs alveolar CO₂ for brotizolam and placebo as compared with base line values. Mouth-occlusion pressures did not change under the influence of drug or placebo.
- 3 Brotizolam (0.25 mg) is without adverse side-effects on respiratory centre output or on mechanics of ventilation.

Keywords brotizolam hypercapnia chronic obstructive pulmonary disease

Introduction

Breathing abnormalities during sleep have been the subject of much interest in recent years (Remmers *et al.*, 1980). Our own interest in the control of ventilation and changes induced by drugs dates back to a study of patients suffering from hypnotic drug overdoses (Sybrecht *et al.*, 1979). In this study we were able to demonstrate that, under these circumstances, major changes in the mechanical properties of the respiratory system occur in addition to changes in respiratory centre output. From these data the conclusion could be drawn that studying the influence of hypnotic drugs on breathing always requires an evaluation of both the control system and the mechanics of the respiratory apparatus. In this paper, we report our data on the influence of brotizolam on the control and mechanics of ventilation in patients with moderate to severe chronic airways obstruction. The aim of this study was to evaluate potential adverse effects of brotizolam on breathing in these patients who, according to knowledge derived from recent studies (Douglas *et al.*, 1979; Coccagna & Lugares 1978; Tirlapur & Mir, 1982) suffer most from breathing abnormalities when asleep.

Before studying these patients, we documented the effect of 0.5 mg brotizolam on respiration in young healthy volunteers. In the latter subjects we could not detect any adverse effect on respiration and its regulation, i.e. in a double-blind study, neither the ventilatory nor the mouth-occlusion

pressure response to CO₂ rebreathing showed a significant change after double the dose of brotizolam used in the present study. Therefore, it seemed justified to test this short-acting sleep-inducing drug's action in a group of patients who could potentially suffer from the adverse effects of a hypnotic drug.

Methods

After they had given their informed consent, nine patients with proven chronic airways obstruction were studied in accordance with a double-blind cross-over design. Anthropometric data and the results of lung function studies are shown in Tables 1 and 2. All patients were normocapnic and complained of varying degrees of insomnia. Patients received their medication, either 0.25 mg brotizolam or placebo, after their evening meal. Prior to drug administration all measurements of respiratory control had been performed in duplicate, first, to familiarise the patients with the study procedure and, second, to provide baseline values for comparison.

Between 1-2 h after drug ingestion the study measurements were performed with the patients lying in their beds. Ventilatory and mouth-occlusion pressure responses, according to the methods of Read (1967) and Whitelaw *et al.* (1975),

Table 1 Anthropometric data of the patients

Patient	Age (years)	Height (cm)	Weight (kg)
1	63	162	60
2	71	174	87.2
3	32	183	106.7
4	53	174	46
5	54	172	79.5
6	52	171.5	85
7	52	180	72.3
8	71	165	79
9	60	172	68
Mean	56.44	172.61	75.97
s.e. Mean	±11.91	±6.51	±17.33

were measured under progressive hypercapnic and hyperoxic conditions using a rebreathing circuit which contained 6% CO₂ and 94% O₂. Within 4–6 min of being connected to the rebreathing circuit the patients reached alveolar CO₂ tensions of up to a maximum of 65 mm Hg. During the rebreathing exercise, flow at the mouth and volume, as determined by electronically integrating flow and mouth pressure 100 ms after random occlusion of a valve in the inspiratory line, were recorded continuously at a paper speed of 50 mm/s on a Hellige 330 P recorder. Up to 20 manual occlusions of the valve were carried out at irregular intervals and occlusion times of around 300 ms were recorded via the oscilloscope. The patients could neither see nor hear the valve being closed. Endtidal P_{CO₂} was measured continuously by an infrared analyser (Hartmann & Braun) and recorded on a Rikadenki recorder against time. All measurements were carried out in duplicate and for analysis both runs were used with regression lines calculated by the least square method.

During the measurement recording patients were awake and co-operative. All patients slept after

brotizolam administration and three out of the nine after placebo. All volumes were corrected to BTPS and for continuous non-invasive monitoring of ventilation the respiratory inductive plethysmograph (Respirtrace) as described by Sackner (1980) was used.

For purposes of calibration the signal of the sum of ribcage and abdomen was adjusted to the pneumotachographic signal after a calibration factor was calculated using two different body positions and a regression analysis. By means of the Respirtrace, ventilation could be monitored throughout the study and apnoea phases were documented during the study period which lasted for up to 2 h after drug ingestion.

Results and discussion

As would be expected with the presence of different degrees of airways obstruction, individual ventilatory CO₂ responses of the patients differed markedly from each other. Therefore, in order to facilitate a comparison of the true effects of brotizolam and placebo, we defined the pre-drug result as 100%.

Figure 1 shows the slope of the ventilatory CO₂ response in the nine patients studied. There was a statistically insignificant increase in ventilation with increase in alveolar CO₂ tension after both brotizolam and placebo but certainly no decreased response as one might have anticipated with a hypnotic drug.

The increase in CO₂ sensitivity, though not statistically significant, is a surprising finding. It might be attributed to the fact that the patients had to be woken up for the rebreathing measurements so that there might have been an added central stimulus acting as compared to the situation in the pre-drug wakeful state. Ventilation at high chemical drive is shown in Figure 2.

Table 2 Lung function data of the patients

Patient	TLC (ml)	TLC (% pred)	VC (ml)	VC (% pred)	RV (ml)	RV (% pred)	FEV ₁ (ml)	FEV ₁ (% pred)	Resistance (cm H ₂ O l ⁻¹ s ⁻¹)
1	4150	70	2000	50	2150	121	1000	33	5.9
2	8750	135	3850	88	4900	251	1300	39	4.2
3	—	—	5550	93	—	—	3650	81	—
4	5300	76	2800	60	2500	119	1150	33	3.0
5	—	—	3200	66	—	—	1850	51	—
6	7240	109	3030	64	4210	211	2130	60	5.4
7	7150	92	4350	78	2800	120	2650	63	1.8
8	6100	101	3300	82	2800	154	2200	73	2.7
9	—	—	4100	86	—	—	2550	72	—
Mean	6448	97.2	3576	74.1	3227	163	2053	56	3.8
s.e. mean	±1621	±23.7	±1028	±14.65	±1079	±56	±845	±18	±1.6

Figure 1 Slope of the ventilatory CO_2 response in nine patients with chronic obstructive pulmonary disease.

As ventilation is the end-product of the various processes involved in its regulation, an unchanged ventilatory response cannot be considered proof of an unchanged system. Mechanical abnormalities, for instance, might have occurred with a load compensating mechanism acting to counterbalance them, thereby leaving ventilation per unit of CO_2 tension unchanged. This possibility can be assessed by the results of the mouth-occlusion pressure response. Mouth-occlusion pressure is not in-

Figure 2 Ventilation at high chemical drive in nine patients with chronic obstructive pulmonary disease.

fluenced by lung mechanics as it is developed under isometric conditions and therefore reflects more closely the respiratory centre output.

Figure 3 shows that there was no significant change in the slope of mouth-occlusion pressure per unit of alveolar CO_2 tension, i.e. that an unchanged respiratory centre output was present, after brotizolam administration. After placebo administration the results indicated that output was increased though not to a statistically significant extent. This finding complies with the increased ventilatory response described above. We attribute this phenomenon to the influence of the arousal response in patients being woken for measurements to be carried out. The overall increase in slope is mainly due to an increase at low CO_2 tensions, whereas, at high chemical drive, occlusion pressures were less changed compared with control conditions. This is demonstrated in Figure 4.

These results imply that neither the mechanical properties of the patients' respiratory systems nor their respiratory centre output changed under the study conditions. This also implies that for a given central stimulus a consistent increase in inspiratory flow was achieved. Figure 5 shows that identical mean inspiratory flow rates were achieved for a given stimulus of 3 cm H_2O mouth-occlusion pressure for all study conditions.

Figure 3 Slope of the mouth occlusion pressure CO_2 response in nine patients with chronic obstructive pulmonary disease.

Figure 4 Mouth occlusion pressure at high chemical drive in nine patients with chronic obstructive pulmonary disease.

Figure 5 Mean expiratory flow at a given mouth occlusion in nine patients with chronic obstructive pulmonary disease.

Table 3 Sleep apnoea phases of the patients studied

Patient	Number		Duration (s)	
	Placebo	Brotizolam	Placebo	Brotizolam
1	3	47	12.7 ± 3.1	11.3 ± 3.5
2	26	23	19.4 ± 7.7	22.7 ± 9.2
3	0	0	0	0
4	0	0	0	0
5	0	17	0	7.4 ± 2.3
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
9	0	0	0	0

All measurements carried out required a wakeful patient able and cooperative enough to cope with using a mouth-piece. Therefore, no conclusions can be drawn from these data with respect to the sleeping condition, and, as no polysomnographic method was used, no conclusions can be drawn regarding REM and non-REM sleep state.

Throughout the study, however, we monitored respiration non-invasively by means of the Resptrace and as a result some additional information can be presented. First, we found that three out of nine patients had apnoea phases after both placebo and brotizolam administration. Table 3 shows that during a mean study period of 86 min a total of 116 apnoea phases was seen in the three patients. Two patients had such episodes during both placebo and brotizolam treatment. One patient, however, only suffered apnoea after brotizolam. No definite conclusions can be drawn from these data as the time of the study was too short and as EEGs for evaluating sleep state were not recorded. The presence of apnoea phases of up to 22.7 ± 9.2 s, however, indicates how marked desaturation during sleep may be in these patients and suggests that drugs compromising either respiratory centre output or the mechanics of the respiratory system are potentially very harmful to patients with chronic airways obstruction.

Our study, on the other hand, shows that no such adverse effect could be seen after giving 0.25 mg brotizolam to patients with moderate to severe chronic airways obstruction.

Further studies using polysomnographic techniques are needed to evaluate whether the incidence and/or duration of apnoea phases are influenced by brotizolam and whether the absolute REM sleep periods are shortened leaving the patients at a lower risk of nocturnal hypoxaemia with its potential deleterious consequences.

References

- COCCAGNA, C. & LUGARESI, E. (1978). Arterial blood gases and pulmonary and systemic arterial pressure during sleep in chronic obstructive pulmonary disease. *Sleep*, **1**, 117–124.
- DOUGLAS, N.J., CALVERLEY, P.M.A., LEGETT, R.J.E., BRASH, H.M., FLENLEY, D.C. & BREZINOVA, V. (1979). Transient hypoxemia during sleep in chronic bronchitis and emphysema. *Lancet*, **i**, 1–4.
- READ, D.C.J. (1967). A clinical method for assessing the ventilatory response to CO₂. *Aust. Ann. Med.*, **16**, 20–31.
- REMMERS, J.E., ARCH, A.M. & DeGROOT, W.J. (1980). Respiratory disturbances during sleep. *Clinics in Chest Medicine*, **1**, 57.
- SACKNER, M.A. (1980). Monitoring ventilation without a physical connection to the airway. In *Diagnostic techniques in pulmonary disease, Part I.*, ed Sackner, M.A. pp 503–537. New York: Marcel Dekker, Inc.
- SYBRECHT, G.W., TAUBNER, E.M., BÖHM, M.M. & FABEL, H. (1979). Mechanical properties of the respiratory system and mouth-occlusion pressure in patients acutely intoxicated with hypnotics. *Lung*, **156**, 49–61.
- TIRLAPUR, B.G. & MIR, M.A. (1982). Nocturnal hypoxemia and associated electrocardiographic changes in patients with chronic obstructive airways disease. *New Engl. J. Med.*, **306**, 125–130.
- WHITELAW, W.A., DERENNE, J.P. & MILIC-EMILI, J. (1975). Occlusion pressure as a measure of respiratory centre output in conscious man. *Resp. Physiol.*, **23**, 181–198.

Der Einfluss von Brotizolam auf die ventilatorische und Mundokklusionsdruck Antwort auf Hyperkapnie bei Patienten mit chronisch obstruktiven Lungenerkrankungen

G.W. SYBRECHT

- 1 Die Wirkung von 0,25 mg Brotizolam wurde bei Patienten mit chronisch-obstruktiver Lungenerkrankung mittleren bis schweren Grades untersucht.
- 2 Es bestand kein Unterschied zwischen den CO₂-Antwortkurven für Brotizolam und Placebo im Vergleich zu den Ausgangswerten. Die Mundok-

klusionsdruck veränderte sich unter dem Einfluss der Substanz oder des Placebos nicht.

- 3 Brotizolam 0,25 mg zuzugabe keine Nebenwirkungen auf die Funktion des Atemzentrums oder die Atemmechanik.

Influence du brotizolam sur la ventilation pulmonaire et les pressions d'occlusion buccale en réponse à l'hypercapnie chez des patients atteints d'affection pulmonaire obstructive chronique.

G.W. SYBRECHT

- 1 Les effets de 0,25 mg de brotizolam chez des patients atteints d'affection pulmonaire obstructive chronique de degré modéré à grave ont été étudiés par l'auteur.
- 2 Il n'a pas été constaté de différence, pour le brotizolam et le placebo, entre les pentes de ventilation, comparées aux valeurs de base, par

rapport à la tension alvéolaire du CO₂. Les pressions d'occlusion buccale n'ont pas été modifiées par la préparation ou le placebo.

- 3 La dose de 0,25 mg de brotizolam n'a pas exercé d'effet négatif sur le débit du centre respiratoire ni sur la mécanique de ventilation.

Influencia de brotizolam sobre la ventilación pulmonar y la presión de oclusión bucal en respuesta a la hipercapnia en pacientes con enfermedad pulmonar obstructiva crónica

G.W. SYBRECHT

1 Se ha estudiado el efecto de 0,25 mg de brotizolam en pacientes con enfermedad pulmonar obstructiva crónica de grado moderado o grave.

2 No se produjo diferencia alguna entre las curvas de ventilación versus CO₂ alveolar para brotizolam o placebo en comparación con los valores basales.

Las presiones con oclusión bucal no se modificaron bajo la influencia del fármaco o del placebo.

3 La dosis de 0,25 mg de brotizolam carece de efectos secundarios desfavorables sobre la función del centro respiratorio o sobre la mecánica de la ventilación.