Acute effects of zolpidem, triazolam and flunitrazepam on arterial blood gases and control of breathing in severe COPD

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ABSTRACT: Patients with severe chronic obstructive pulmonary disease (COPD) commonly complain of insomnia, but hypnotic drugs are generally not recommended due to their depressant effect on the respiratory centres. The aim of this study was, therefore, to compare the effects of a single dose of the benzodiazepine hypnotics, triazolam 0.25 mg and flunitrazepam 1 mg, and a new imidazopyridine compound, zolpidem 10 mg, in hypercapnic COPD patients.

Twelve stable COPD patients (mean±SD arterial oxygen tension (Pa_{O_2}) 9.3±0.8 kPa and arterial carbon dioxide tension (Pa_{CO_2}) 5.9±1.9 kPa) were included in the study. The following measurements were performed before and 2 h after drug administration: Pa_{O_2} and Pa_{CO_2}, minute ventilation ($\dot{V}_E$), mouth occlusion pressure ($P_{0.1}$), rebreathing CO_2 tests with ventilatory response to carbon dioxide stimulation ($\Delta\dot{V}_E/\Delta Pa_{CO_2}$) and mouth occlusion pressure response to carbon dioxide stimulation ($\Delta P_{0.1}/\Delta Pa_{CO_2}$). The measurements were performed in a randomized, double-blind fashion, each patient receiving a single dose of each drug on three different days, separated by a one week interval.

No difference was noted between control measurements and those taken 2 h after administration of zolpidem in the following parameters: Pa_{O_2}, Pa_{CO_2}, $\dot{V}_E$, $P_{0.1}$, $\Delta\dot{V}_E/\Delta Pa_{CO_2}$ and $\Delta P_{0.1}/\Delta Pa_{CO_2}$. Two hours after administration of triazolam and flunitrazepam, a significant difference was noted in $\dot{V}_E$ for triazolam and for flunitrazepam. After flunitrazepam administration, a significant decrease in Pa_{CO_2} (6±1.8 at baseline *versus* 7±0.4 kPa), and $\Delta\dot{V}_E/\Delta Pa_{CO_2}$ (0.44±0.20 at baseline *versus* 0.31±0.21 $l\cdot min^{-1}\cdot kPa$) were observed. Pa_{O_2} also decreased after flunitrazepam from 7.8±1 to 7.4±0.9 kPa.

This study demonstrates that when given at a single equivalent dose, the hypnotic drug zolpidem has no significant effect on arterial blood gases and control of breathing in severe COPD patients, in contrast to triazolam and flunitrazepam.
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Patients with chronic obstructive pulmonary disease (COPD) commonly report insomnia [1]. This complaint is particularly frequent in severely affected patients, in whom the progressive retention of carbon dioxide and the associated hypoxaemia may lead to disturbed sleep patterns. Furthermore, excessive dosing with either β_2-sympathomimetic compounds or theophylline, commonly used as bronchodilators, may also lead to insomnia in some patients. This, in turn, can contribute to poor daytime concentration, diminished memory, personality changes and depression. Although hypnotic drugs represent the main treatment of insomnia, there has been some concern about administering such medication to COPD patients, due to the depressant effects on the respiratory centres [2, 3]. Additionally, the use of benzodiazepine-type hypnotics, which represents the most common

treatment of insomnia, has been shown to further impair sleep architecture in COPD patients [4].

Zolpidem, a hypnotic belonging to a new chemical group, the imidazopyridines, has recently been synthetized [5]. This compound, contrary to the benzodiazepines, does not affect the quality of sleep in normal subjects [6].

The aim of this study was to evaluate the effect of zolpidem on respiratory control in severe COPD patients, and to compare its action to those of two hypnotic benzodiazepines, triazolam and flunitrazepam.

Methods

Twelve patients with chronic obstructive pulmonary disease (mean±SD age 60±3 yrs) were studied, whilst in a

clinically stable condition. The mean values obtained at baseline for pulmonary function indices and blood gases are listed in table 1. All patients gave their informed consent and the study protocol had received Ethics Committee approval (Hôpital Beaujon, Clichy, France).

Table 1. – Mean lung function data and arterial blood gases before inclusion

	VC % pred	FEV_1 % pred	FRC % pred	TLC % pred	Pao_2 kPa	$Paco_2$ kPa
Mean	66	32.4	137	104	9.3	5.9
±SD	12.4	10	36.8	22	0.8	1.9

VC: vital capacity; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; TLC: total lung capacity; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; % pred: percentage of predicted values according to [7].

All measurements were taken with the patient in the sitting position. In each patient, absolute lung volume measurements were carried out with a constant pressure plethysmograph to determine functional residual capacity (FRC), and total lung capacity (TLC). Flow-volume curves were also obtained with a Hewlett-Packard spirometer, in order to determine the forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC). The patients breathed through a mouthpiece connected to a No. 3 Fleisch pneumotachograph. The inspiratory and expiratory lines were separated by a Hans-Rudolph one-way valve. The dead space of the circuit was 40 ml. The resistance of the inspiratory and expiratory lines was 1.4 and 1.8 $cmH_2O \cdot l^{-1} \cdot s$, respectively, at a flow of 1 $l \cdot s^{-1}$. Airway occlusions were performed by inflating a rubber balloon with a syringe on the inspiratory line during expiration, so that occlusion became effective from the onset of the next inspiration. Tidal volume was measured electronically using a pressure transducer (Northridge, CA, USA).

All signals were conditioned and displayed on a ALLCO EN 68 recorder, using a paper speed of 50 $mm \cdot s^{-1}$ during the periods analysed.

The respiratory response to CO_2 was measured using the method of READ [8]. Patients were connected to a closed circuit, where they breathed a mixture of 7% CO_2 in 55% oxygen from a 5–7 l rubber bag. This procedure lasted for 5 min, at the end of which time CO_2 was measured using a Perkin-Elmer mass spectrometer. End-tidal carbon dioxide tension ($PETCO_2$) was used as an equivalent to alveolar carbon dioxide tension ($PACO_2$) during these tests. The rate of increase in $PACO_2$ was in the order of 3–6 $mmHg \cdot min^{-1}$, according to Read's method. Arterial blood gases and pH were measured (ABL 3, Radiometer, Copenhagen) while the patients were breathing normal air.

Minute ventilation ($\dot{V}E$), tidal volume (VT), respiratory frequency (f) and mouth occlusion pressure at 100 ms ($P_{0.1}$) were calculated by standard techniques [9]. The ventilatory and mouth occlusion pressure response to CO_2 stimulation were expressed as the slope of the linear regression equation, method of least squares of ventilation and $PACO_2$ on the one hand, and mouth occlusion pressure and $\dot{P}ACO_2$ on the other.

Experimental procedure

The patients were studied in a randomized, double-blind, cross-over fashion, measurements being carried out on three different days separated by one week intervals. Measurements were taken prior to and 2 h after administration (coinciding with the peak plasma level of each drug) of a single equivalent dose of either zolpidem (10 mg), triazolam (0.25 mg), or flunitrazepam (1 mg). The patients did not change medication during the study period, or oxygen therapy (which was maintained at an identical flow rate and duration throughout the study) in those with hypoxaemia requiring oxygen.

Arterial blood gases were always measured during room air breathing.

The results are expressed as a mean±SD and the statistical analysis was performed using the Student's t-test for paired data, comparing values obtained 2 h after administration of either zolpidem, triazolam or flunitrazepam with the corresponding baseline measurements.

Results

Pulmonary function

No significant changes in vital capacity, forced expiratory volume in one second, functional residual capacity and total lung capacity were noted after drug administration of a single dose of zolpidem, triazolam and flunitrazepam.

Arterial blood gases

The effects of zolpidem, triazolam and flunitrazepam on arterial blood gas levels, are shown in table 2. The mean arterial carbon dioxide tension ($Paco_2$) increased from 6.0±1.8 to 7.0±0.4 kPa (p<0.05) and arterial oxygen tension (Pao_2) decreased from 7.8±1 to 7.4±0.9 kPa (p<0.05), 2 h after administration of a single dose of flunitrazepam. On the contrary, no significant change in arterial blood gases was noted after administration of zolpidem or triazolam.

Ventilatory function and mouth occlusion pressure

As shown in table 2, minute ventilation was not significantly affected by the administration of zolpidem, whereas the administration of triazolam and flunitrazepam resulted in a 1 l reduction (p<0.05). However, the pattern of breathing (tidal volume and respiratory frequency) was not significantly modified after administration of each drug. $P_{0.1}$ also remained unaffected after administration of each drug.

Table 2. – Effects of administration of zolpidem, triazolam and ventilatory and mouth occlusion pressure response to carbon dioxide stimulation in 12 patients

	C1	Z	C2	T	C3	F
Pa_{O_2} kPa	7.8±0.9	7.8±1.0	8±0.5	7.0±1.0	7.8±1.0	7.4±0.9*
Pa_{CO_2} kPa	6.2±0.8	6.4±1.0	6.4±1.0	5.7±1.0	6.0±1.8	7.0±0.4*
$\dot{V}_E$ $l \cdot min^{-1}$	13.7±2.9	13.9±2.9	13.0±2.3	12.2±2.5**	13.5±3.0	12.5±2.6*
V_T l	0.74±0.17	0.76±0.15	0.74±0.13	0.70±0.10	0.68±0.10	0.69±0.13
f breaths·min⁻¹	19.2±3.9	18.6±3.4	18.0±3.2	17.6±3.0	20.0±4.4	18.4±3.0
$P_{0.1}$ cmH_2O	3.0±0.1	3.2±1.3	2.9±1.0	2.7±1.0	3.1±0.9	3.1±0.7
$\Delta\dot{V}_E/Pa_{CO_2}$ $l \cdot min^{-1} \cdot kPa$	0.54±0.25	0.43±0.27	0.48±0.23	0.49±0.32	0.44±0.20	0.31±0.21*
$P_{0.1}/Pa_{CO_2}$ $cmH_2O \cdot kPa^{-1}$	0.17±0.10	0.13±0.08	0.15±0.09	0.13±0.10	0.18±0.11	0.13±0.10

*: $p<0.05$; **: $p<0.01$, comparing values obtained 2 h after drug administration with the corresponding baseline measurements. Data are presented as mean±SD. $\dot{V}_E$: minute ventilation; V_T: tidal volume; f: respiratory frequency; $P_{0.1}$: mouth occlusion pressure; $\dot{V}_E/Pa_{CO_2}$: slope of ventilatory response to carbon dioxide stimulation; $P_{0.1}/Pa_{CO_2}$: slope of mouth occlusion pressure response to carbon dioxide stimulation; C1, C2 and C3: control periods; Z: zolpidem; T: triazolam; F: flunitrazepam. For further abbreviations see legend to table 1.

Ventilatory and mouth occlusion pressure response to carbon dioxide stimulation

The mean slopes (±SD) of the ventilatory and mouth occlusion pressure response to CO_2 for the 12 subjects, during control and after administration of each hypnotic drug are listed in table 2. The mean slope of the ventilatory response to CO_2 was reduced ($p<0.5$) 2 h after administration of a single dose of flunitrazepam, whereas the mean slope of mouth occlusion pressure response to CO_2 was unaffected. Zolpidem and triazolam had no significant effect on the ventilatory and mouth occlusion pressure response to CO_2.

Drug plasma levels

The individual plasma level of each drug are listed in table 3. Therapeutic plasma levels were reached in all patients.

Safety

No adverse events were recorded during this study.

Discussion

The present study shows that a single dose of the new imidazopyridine, zolpidem, had no significant effect on the respiratory centres of severe COPD patients. In contrast, flunitrazepam and triazolam (two other benzodiazepine compounds) had a significant depressant effect on the respiratory centres of these patients.

None of the drugs tested in this study had any effect on lung function. It is noteworthy, that 2 h after administration of each drug (corresponding to the peak plasma levels), no change in FVC, FEV₁ as well as FRC and TLC was noted. This lack of effect following the administration of the three hypnotic compounds, particularly on lung volume, contrasts with what has been reported

Table 3. – Plasma levels (ng·ml⁻¹) of zolpidem, flunitrazepam and triazolam

Patient no.	Sampling time p.m.	Zolpidem PL ng·ml⁻¹	Sampling time p.m.	Triazolam PL ng·ml⁻¹	Sampling time p.m.	Flunitrazepam PL ng·ml⁻¹
1	14.15	186.9	14.10	1.0	14.20	4.3
2	14.25	207.1	14.05	1.4	14.50	1.8
3	14.10	87.3	14.10	1.4	14.15	2.4
4	14.15	52.2	14.30	0.9	14.15	4.5
5	14.15	111.2	14.30	1.9	14.15	2.1
6	14.05	83.9	14.10	0.8	14.00	2.2
7	14.00	45.4	14.10	0.9	14.15	3.4
8	14.00	168.8	14.10	2.1	14.20	1.0
9	14.00	122.4	14.30	1.3	14.00	2.6
10	14.10	165.3	14.00	1.7	14.15	2.3
11	14.10	253.1	14.10	2.7	14.00	2.3
12	14.10	45.9	14.10	0.5	14.00	2.3

PL: plasma level.

previously during anaesthesia in normal subjects [10]. Indeed, in the latter study, FRC rapidly decreased with anaesthesia. The difference between this study and those performed in anaesthetized subjects, in relation to the changes in lung volume, may be due to the agent administered, as well as to the dose of the compound given.

Although there was no change in lung function in the 12 patients studied, flunitrazepam administration resulted in a significant decrease in Pao_2 and increase in $Paco_2$. The latter could be secondary to an impairment in gas exchange, as previously shown with diazepam in normal subjects [3]. However, although a slight decrease in minute ventilation occurred with flunitrazepam, the pattern of breathing was not significantly altered. Thus, impairment in gas exchange appears to be unlikely in the genesis of the alteration in arterial blood gases observed after flunitrazepam administration.

The impairment of arterial blood gases after administration of flunitrazepam could also be secondary to a depression of the respiratory centres. Indeed, the mean slope of the ventilatory response to CO_2 was significantly reduced (table 2) 2 h after administration of flunitrazepam, suggesting that the drug had induced respiratory centres depression.

Benzodiazepine-type hypnotic drugs have previously been shown to decrease ventilation, a phenomenon which has been attributed to central respiratory depression [2, 3]. Ventilation, however, is a final product of respiratory centre output, its neuromuscular transmission to the inspiratory muscle and their subsequent contractions, which together result in a volume change according to the mechanical properties of the respiratory apparatus. Therefore, measurements of ventilation alone do not provide adequate information about the site of action of the drug, i.e. the respiratory centres, or the peripheral respiratory system (lung and chest wall).

Respiratory centre output has recently been evaluated in human subjects with the introduction of the mouth-occlusion pressure technique [11], and its application has been recommended for clinical use [12]. Mouth pressure generated 100 ms after the onset of an inspiratory effort against an occluded airway ($P_{0.1}$), is obtained under quasistatic conditions and is, therefore, independent of lung compliance and lung resistance [11, 13]. In the present study, although the ventilatory response to CO_2 was depressed after flunitrazepam administration, the $P_{0.1}$ response to CO_2 was unaffected. This discrepancy between the ventilatory and $P_{0.1}$ response to CO_2 stimulation after flunitrazepam administration, strongly suggests that this compound had induced some changes in the mechanical properties of the respiratory system. Indeed, flunitrazepam may have decreased the gamma-motoneuron activity of the intercostal muscles, which are rich in muscle spindles. This may have depressed intercostal muscle activity. Furthermore, the diaphragm, the function of which is compromised by the hyperinflation, may not be able to generate higher pressure during CO_2 stimulation. This phenomenon when it occurred would not, however, affect our data. Indeed, each patient was his/her own control and, therefore, had the same level of hyperinflation with each drug administration. Furthermore, loss of

recoil of the lung or chest wall, which may be responsible for the depressed ventilatory response to CO_2 and alteration in arterial blood gases, has previously been described during anaesthesia [14, 15], and in patients acutely intoxicated with hypnotics [10, 16].

By contrast, no change in arterial blood gases and ventilatory response to CO_2, as well as $P_{0.1}$ response, was observed with the two other drugs tested, zolpidem and triazolam. Therefore, these two compounds have either no effect or less effect, compared to flunitrazipam, on respiratory control, despite the fact that the patients studied were all severe COPD, hypoxic and hypercapnic in stable state.

The different effects on respiratory control, observed with the three drugs, are unlikely to be linked to their differing action on the specific gamma-aminobutyric acid (GABA) receptors [17], of which two subtypes have been described ($\omega 1$ and $\omega 2$). In fact, even if benzodiazepines such as flunitrazepam or triazolam are more selective for either subtype [18], and zolpidem as an imidazopyridine, is highly selective for the $\omega 1$ subtype [19], triazolam did not markedly affect the respiratory control. Furthermore, it should be pointed out that drug administration was carried out during the day. The effect of only one single oral dose of each compound was evaluated. When the drug is administered before retiring at night, in a repetitive fashion (i.e. every night), sleep disorders may occur.

Further studies will, therefore, be of interest in order to determine the effect of zolpidem in the long-term treatment of insomnia in severe COPD patients.

In summary, this study indicates that in severe COPD patients, zolpidem, in contrast to triazolam and flunitrazepam, given in a single dose, has no measurable effect on respiratory control.

References

1. Klink M, Quan SF. – Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. *Chest* 1987; 91: 540–546.
2. Lambertsen CJ. – Effects of drugs and hormones on the respiratory response to carbon dioxide. *In:* Fenn WO, Rahn H eds. Handbook of Physiology. Sec. 3. Respiration. Vol. 1. Washington DC, Am. Physiol. Soc., 1964; p. 545.
3. Catchlobe RHF, Kafer ER. – The effects of diazepam on the ventilatory response to carbon dioxide and on the steady-state gas exchange. *Anesthesiology* 1971; 34: 9–18.
4. Block JA, Dolly FR, Shayton PC. – Does flurazepam ingestion affect breathing and oxygenation during sleep in patients with chronic obstructive lung disease. *Am Rev Respir Dis* 1984; 129: 230–233.
5. George P, Rossey G, Depoortere H, *et al.* – *In:* Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in Sleep Disorders, New York, Raven Press, 1988; pp. 11–23.
6. Hermann WN, Kubicki ST, Waber W. – Zolpidem: a four week pilot polysomnographic study in patients with chronic sleep disturbances. *In:* Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in Sleep Disorders, New York, Raven Press, 1988; pp. 261–276.
7. Quanjer PhH. – Standardized lung function testing. Report of a working party "Standardization of lung function tests". *Bull Eur Physiopathol Respir* 1983; 19 (Suppl): 1–95.

8. Read DJC. – A clinical method for assessing the ventilatory response to carbon dioxide. *Aust Ann Med* 1967; 16: 20–32.

9. Aubier M, Murciano D, Fournier M, *et al.* – Central respiratory drive in acute respiratory failure of patients with chronic obstructive lung disease. *Am Rev Respir Dis* 1980; 122: 191–199.

10. Sybrecht GW, Taubner EM, Böhm MM, Fabel H. – Mechanical properties of the respiratory system and mouth occlusion pressure in patients acutely intoxicated with hypnotics. *Lung* 1979; 156: 49–61.

11. Whitelaw WA, Derenne JPh, Milic-Emili J. – Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol* 1975; 23: 181–198.

12. Milic-Emili J, Whitelaw WA, Derenne JPh. – Occlusion pressure, a simple measure of the respiratory center's output. *N Engl J Med* 1975; 293: 1029–1030.

13. Cherniack NS, Lederer DH, Altose MD, Kelsen SA. – Occlusion pressure as a technique in evaluating respiratory control. *Chest* 1976; 70: 137–141.

14. Rehder K, Sessler AD, Marsh HM. – General anesthesia and the lung. *Am Rev Respir Dis* 1975; 112: 541–563.

15. Derenne JPh, Couture J, Iscoe S, Whitelaw WA, Milic-Emili J. – Occlusion pressure in men rebreathing CO_2 under methoxyfluorane anesthesia. *J Appl Physiol* 1976; 40: 805–814.

16. Launois S, Fleury B, Similowski T, *et al.* – The respiratory response to CO_2 and O_2 in patients with coma due to voluntary intoxication with barbiturates and carbamates. *Eur Respir J* 1990; 3: 566–572.

17. Guidotti A, Toffano G, Costa E. – An endogenous protein modulates the affinity of GABA and benzodiazepine receptors in rat brain. *Nature* 1978; 275: 555.

18. Hunkeler W, Moehler H, Pieri L, *et al.* – Selective antagonists of benzodiazepines. *Nature* 1981; 290; 514–516.

19. Arbilla S, Langer SZ, Zivkovic B, Scatton B. – Un domaine spécifique (site ω1) du récepteur GABA A pourrait être impliqué dans les effets hypnotiques du Zolpidem. *Encéphale* 1990; XVI: 13–22.