Effects of diazepam and chlormethiazole on ventilatory control in normal subjects

J. J. GILMARTIN, P. A. CORRIS, T. N. STONE, D. VEALE & G. J. GIBSON

Department of Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne NE7 7DN

We have studied the effects of chlormethiazole and diazepam given orally on the ventilatory and mouth occlusion pressure ($P_{0.1}$) responses to CO_2 in a placebo controlled study in 10 healthy volunteers. Diazepam 10 mg produced a significant reduction in both the ventilatory and $P_{0.1}$ responses to CO_2 , and this was not associated with any effect on respiratory muscle power. Chlormethiazole 250 mg produced less drowsiness than diazepam 10 mg. Therefore in a subsequent study chlormethiazole 500 mg was compared with placebo. Chlormethiazole in either dose had no effect on CO_2 responses or on maximum static respiratory pressures. We conclude that diazepam has a direct depressant effect on chemoreceptors and its effects on indices of ventilatory control are not due to impaired muscle function; chlormethiazole in the doses used has no such effects despite producing drowsiness.

Keywords diazepam chlormethiazole ventilatory response $P_{0.1}$ response respiratory muscle strength

Introduction

Hypnotic drugs depress central nervous function and in sufficient dosage all suppress ventilation (Widdicombe, 1981); assessment of the effect of an hypnotic on ventilatory control is therefore of potential clinical importance. The methods available for assessing the effects of hypnotic and sedative drugs on ventilatory control have recently been reviewed (Cohn, 1983). The ventilatory response to rebreathing CO_2 (Read, 1967) is the traditional method for assessing chemosensitivity, but it is dependent on the mechanics of the respiratory system. More recently the response of the occlusion pressure measured 100 ms after the onset of inspiration ($P_{0.1}$) to increasing concentrations of CO_2 has been introduced. Because it may be less dependent on respiratory mechanics, it has been suggested as a more direct index of central neural output than the ventilatory response (Whitelaw *et al.*, 1975).

Chlormethiazole is an extensively used hypnotic in the elderly and in alcohol withdrawal. Calverley *et al.* (1984) have shown that chlor-

methiazole does not depress the response of normal young subjects to hypoxia but no information is available on its effect on responsiveness to CO_2 . Variable effects of diazepam on ventilatory control have been reported in normal subjects: Sadove *et al.* (1965) and Steen *et al.* (1966) found that parenteral diazepam had no effect on CO_2 response while Utting & Pleuvry (1975) found that 5 mg of oral diazepam reduced CO_2 responsiveness. Diazepam is also known to have a relaxant effect on skeletal muscle (Tseng & Wang, 1971) so we speculated that its effect on the ventilatory response might be due at least in part to an action on the respiratory muscles, rather than to an effect on central drive. Such an effect could reduce ventilatory responses as is seen in muscle weakness produced either by partial curarization (Holle *et al.*, 1984) or by muscle disease (Serisier *et al.*, 1982). No information is available on the effects of diazepam on the $P_{0.1}$ response or on respiratory muscle function.

For these reasons we have undertaken a

Correspondence: Dr J. J. Gilmartin, Royal Infirmary, Sunderland SR2 7JE

placebo-controlled study of the effects of diazepam and chlormethiazole on ventilatory control measured by both the ventilatory and $P_{0.1}$ responses to CO_2 . We have also assessed any possible contribution of respiratory muscle weakness by measurement of vital capacity and maximum respiratory pressures.

Methods

Ten healthy non-smoking male subjects aged 24–36 years with no history of respiratory or neurological disease were studied. The subjects refrained from coffee and tea for 3 h before each experiment. The subjects were familiarised with the apparatus and the measurements were made in a quiet room with the subjects relaxed.

FEV_1 and VC were measured using a bellows spirometer. The subject was then asked to indicate his degree of drowsiness on a 100 mm visual analogue scale (VAS), marked 'normal' and 'drowsy' at either end. Maximum inspiratory and expiratory pressures were measured at the mouth using a Validyne pressure transducer, at functional residual capacity and total lung capacity respectively. The ventilatory and $P_{0.1}$ responses to CO_2 were measured simultaneously with the subject seated in a pressure compensated body plethysmograph (Stanescu *et al.*, 1972) to allow measurement of minute ventilation. The occlusion pressure device was placed on the inspiratory side of a rebreathing circuit which was completed by a 6 l bag containing 95% O_2 and 5% CO_2 . The occlusion was activated during expiration, approximately one breath in five without the knowledge of the subject; the pressure was recorded 100 ms after the onset of inspiration. End tidal P_{CO_2} was measured using an infrared analyser. The ventilatory and $P_{0.1}$ responses were recorded in triplicate and expressed as the slopes of ventilation

$$\frac{(\Delta \dot{V}E)}{\Delta PA_{CO_2}} \text{ and } P_{0.1} \frac{(\Delta P_{0.1})}{\Delta PA_{CO_2}}$$

plotted against PA_{CO_2} on a linear scale. Each subject was studied on three separate days and on each day he was given 15 ml of elixir containing placebo, chlormethiazole 250 mg or diazepam 10 mg double-blind and in random order. Spirometry, VAS, maximum respiratory pressures, ventilatory and $P_{0.1}$ responses were performed before and 1 h after administration of drug or placebo. All results were calculated by one of the authors who was unaware of the compound given.

Differences between data collected before and after placebo, diazepam and chlormethiazole

were sought by paired *t*-tests. Significance was assumed if the probability was less than 5% ($P < 0.05$). Reproducibility of the measurements was assessed by calculating the within subject coefficient of variation for each index using the three sets of data obtained before administration of drug or placebo. The smallest difference in each index detectable with 95% confidence was calculated from the pooled variances of the differences before and after administration.

Since chlormethiazole 250 mg produced less sedation than 10 mg diazepam we subsequently compared the effect of chlormethiazole 500 mg with an identical placebo in 10 subjects, six of whom were common to both studies.

Results

Study 1

Diazepam 10 mg and chlormethiazole 250 mg produced significant drowsiness compared with placebo but that produced by chlormethiazole was significantly less than that by diazepam. Chlormethiazole caused rhinorrhoea and smarting of the eyes in eight of the 10 subjects. Diazepam caused a significant reduction in the mean slope of both the ventilatory and $P_{0.1}$ responses ($P < 0.01$) but chlormethiazole produced no such effect (Table 1). Neither diazepam nor chlormethiazole caused any change in the measurements of respiratory muscle function (Table 1).

Study 2

Chlormethiazole 500 mg produced a degree of drowsiness similar to that produced by diazepam 10 mg in the first study. The effect on chemosensitivity varied between subjects, but the change for the group as a whole was not statistically significant (Table 2). Again no effect on respiratory muscle function was observed.

Discussion

We recognise that there may be two possible sources of type 2 error in this study. Firstly chlormethiazole has variable pharmacokinetics (Moore *et al.*, 1975) and, as we did not measure plasma levels of the drug, it is possible that our failure to observe an effect may reflect inadequate plasma concentrations in some subjects. This is very unlikely, however, since 500 mg of chlormethiazole produced a level of drowsiness similar to 10 mg of diazepam. Secondly, since the ventilatory and $P_{0.1}$ responses have large coefficients of variation, the least differences which could have

Table 1 Mean results before and after placebo, diazepam 10 mg and chlormethiazole 250 mg in 10 normal subjects.

		Placebo		Diazepam		Chlormethiazole		Mean CV%	Least detectable difference
		Pre	Post	Pre	Post	Pre	Post		
FEV ₁	(l)	Mean 4.75	4.75	4.80	4.80	4.7	4.75	2.6	0.11
		s.d. 0.58	0.57	0.55	0.53	0.50	0.50		
VC	(l)	Mean 5.70	5.70	5.7	5.65	5.65	5.60	2.0	0.14
		s.d. 0.93	0.87	0.9	0.81	0.72	0.86		
P ₁ max	(cm H ₂ O)	Mean 110	111	108	100	117	115	14.4	11.9
		s.d. 29.6	30.7	24.3	21.4	30.2	29.5		
P _E max	(cm H ₂ O)	Mean 124	127	134	128	134	131	10.3	10.6
		s.d. 39.1	43.3	45.4	37.9	38	29.2		
$\frac{\Delta \dot{V}_E}{\Delta P_{A\text{CO}_2}}$	(1 min ⁻¹ mm Hg ⁻¹)	Mean 3.30	3.06	3.30	1.99*	3.54	3.23	16.3	0.51
		s.d. 0.75	0.96	1.06	0.73	0.91	1.14		
$\frac{\Delta P_{0.1}}{\Delta P_{A\text{CO}_2}}$	(cm H ₂ O mm Hg ⁻¹)	Mean 0.54	0.56	0.62	0.24*	0.56	0.57	28.5	0.10
		s.d. 0.19	0.20	0.24	0.11	0.24	0.24		
ΔVAS	(mm)	4		56**		24**		-	16.2

* Significantly different from pre-drug value ($P < 0.01$)** Significantly different from placebo ($P < 0.02$)

CV = coefficient of variation

Table 2 Ventilatory control before and after placebo and chlormethiazole 500 mg in 10 subjects.

		Placebo		Chlormethiazole		Least detectable difference	
		Pre	Post	Pre	Post		
$\frac{\Delta \dot{V}_E}{\Delta P_{A\text{CO}_2}}$	(l min ⁻¹ mm Hg ⁻¹)	Mean	2.62	2.87	2.97	2.85	0.47
		s.d.	0.97	1.17	0.95	1.11	
$\frac{\Delta P_{0.1}}{\Delta P_{A\text{CO}_2}}$	(cm H ₂ O mm Hg ⁻¹)	Mean	0.43	0.42	0.45	0.39	0.09
		s.d.	0.21	0.23	0.22	0.17	
ΔVAS	(mm)		4		42*		13.8

* Significantly different from placebo ($P < 0.01$)

been detected by this study are also relatively large (Tables 1 and 2). It is therefore possible that a small effect of chlormethiazole on ventilatory control could have been missed by the techniques used. Although such an effect is unlikely to be of clinical significance in a normal individual, it might be important when ventilatory function or control were abnormal. A further problem was that because of nasal and eye irritation caused by chlormethiazole a double-blind comparison proved to be impossible.

Previous data on the effect of diazepam on ventilatory control have yielded varying results. A reduction in the ventilatory response to CO₂ has been found by several workers (Cegla, 1967; Dalen *et al.*, 1967; Herberg *et al.*, 1968; Catchlove & Kafer, 1971) but contrary results have been reported by others (Sadove *et al.*, 1965; Steen *et al.*, 1966). Most of these studies were performed following parenteral administration but Utting & Pleuvry (1975) found that 5 mg of oral diazepam reduced CO₂ responsiveness in eight normal subjects. None of these studies incorporated a placebo control. Another possible explanation for the discrepancies between these previous studies is the considerable variability in the ventilatory response both between and within individuals. Our results indicate a mean coefficient of variation of 16% within subjects for the ventilatory response. Although $P_{0.1}$ response may be a more direct index of central drive its reproducibility was less good (coefficient of variation 29%) and this may limit its value in studies such as these.

Our data show that diazepam in a dose of 10 mg produced a significant decrease in the ventilatory response to CO₂. This reduction was consistent in all 10 subjects. The mechanism of this effect appears to be a depressant action on

the chemoreceptors because a similar fall was seen in the $P_{0.1}$ response (Table 1) and there was no effect on respiratory muscle function. Bulow (1963) demonstrated a reduction in chemosensitivity during sleep and the decreased CO₂ responsiveness following diazepam administration has been considered by Rao *et al.* (1973) to be related to the drowsiness produced by the drug. We did not, however, find a correlation between the degree of drowsiness produced and the alteration in chemosensitivity.

Although chlormethiazole is used extensively very little is known about its effect on ventilatory control. We found no significant effect, compared with placebo, on CO₂ responsiveness of chlormethiazole 250 or 500 mg orally. Herberg *et al.* (1968) infused chlormethiazole until sleep was induced in five normal subjects and found that the ventilatory response to CO₂ was reduced in three of these. The variability of CO₂ responsiveness and the different study protocol make a comparison with our findings difficult. The clear contrast of the effect of chlormethiazole and diazepam suggests that chlormethiazole in the doses used does not reduce chemosensitivity. Although direct extrapolation of these results in normal subjects to patients with impaired CO₂ sensitivity may not be valid, the implication is that diazepam is more likely to precipitate ventilatory failure than is chlormethiazole.

In conclusion, our results indicate that diazepam reduced responsiveness to CO₂ and that this effect appears to be central and not mediated by an action on the respiratory muscles. Chlormethiazole in doses of 250 and 500 mg orally produced drowsiness but no significant effect on chemosensitivity or respiratory muscle function.

References

- Bulow, K. (1963). Respiration and wakefulness in man. *Acta physiol. Scand.*, **59**, (Suppl 209). 1–110.
- Calverley, P. M. A., Carmichael, G. L. M. & Scott, D. B. (1984). The effect of chlormethiazole on the hypoxic drive to breathing in normal man. *Br. J. clin. Pharmac.*, **18**, 163–167.
- Catchlove, R. F. H. & Kafer, E. R. (1971). The effects of diazepam on the ventilatory response to carbon dioxide and on steady-state gas exchange. *Anesthesiology*, **34**, 9–13.
- Cegla, U. H. (1973). The use of CO₂ response curves to determine the respiration-depressant action of drugs with diazepam as an example. *Pneumologie*, **149**, 219–228.
- Cohn, M. A. (1983). Hypnotics and the control of breathing: A review. *Br. J. clin. Pharmac.*, **16**, 245S–250S.
- Dalen, J. E., Evans, G. L., Banas, J. S., Brooks, H. L., Paraskos, J. A. & Dexter, L. (1969). The hemodynamic and respiratory effects of diazepam. *Anesthesiology*, **30**, 259–263.
- Herberg, D., Geisler, L., Bohr, W. & Urz, G. (1968). The use of CO₂ response curves to determine the effects of various drugs on the CO₂ sensitivity of respiratory centres in man. *Pharmac. Clin.*, **1**, 54–62.
- Holle, R. H. O., Schoene, R. B. & Pavlin, E. J. (1984). Effect of respiratory muscle weakness on P_{0.1} induced by partial curarization. *J. appl. Physiol.*, **57**, 1150–1157.
- Moore, R. G., Friggs, E. J., Shanks, C. A. & Thomas, J. (1975). Pharmacokinetics of chlormethiazole in humans. *Eur. J. clin. Pharmac.*, **8**, 353–357.
- Read, D. J. C. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann. Med.*, **16**, 20–32.
- Rao, S., Sherbaniuk, R. W., Prasad, K., Lee, S. J. K. & Spooler, B. J. (1973). Cardiopulmonary effects of diazepam. *Clin. Pharmac. Ther.*, **14**, 182–189.
- Sadove, M. S., Balagot, R. C. & McGrath, J. M. (1965). Effects of chlordiazeoxide and diazepam on the influence of meripidine on the respiratory response to carbon dioxide. *J. New Drugs*, **5**, 121–124.
- Serisier, D. E., Mastaglia, F. L. & Gibson, G. J. (1982). Respiratory muscle function and ventilatory control, (i) in patients with motor neurone disease, (ii) in patients with myotonic dystrophy. *Quart. J. Med.*, **51**, 205–226.
- Stanescu, D., Des Sutter, P. & Van de Woestijne, K. P. (1972). Pressure corrected flow body plethysmograph. *Am. Rev. resp. Dis.*, **105**, 30–35.
- Steen, S. N., Weitzner, S. W., Amaha, K. & Wartinez, L. R. (1966). The effect of diazepam on the respiratory response to carbon dioxide. *Can. Anaesth. Soc. J.*, **13**, 374–377.
- Tseng, T. C. & Wang, S. C. (1971). Locus of action of centrally acting muscle relaxants, diazepam and tybamate. *J. Pharmac. exp. Ther.*, **178**, 350–360.
- Utting, H. G. & Pleuvry, B. J. (1975). Benzocetamine – a study of the respiratory effects of oral doses in human volunteers and interactions with morphine in mice. *Br J. Anaesth.*, **47**, 987–992.
- Whitelaw, W. A., Derenne, J. P. & Milic-Emili, J. (1975). Occlusion pressure as a measure of respiratory center output in conscious man. *Resp. Physiol.*, **23**, 181–199.
- Widdicombe, J. (1981). The effects of psychotropic drugs on respiration. *Respiratory Pharmacology*, **104**, 129–163. Oxford: Pergamon Press.

(Received 21 October 1987,
accepted 27 January 1988)