Zonisamide reduces obstructive sleep apnoea: a randomised placebo-controlled study

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ABSTRACT Carbonic anhydrase inhibition reduces apnoeic events in sleep disordered breathing. Zonisamide inhibits carbonic anhydrase, and induces weight loss in obese patients. This study explored the relative influence of these two properties, which may both alleviate obstructive sleep apnoea (OSA). Continuous positive airway pressure (CPAP) was used as a standard care comparator.

47 patients with moderate-to-severe OSA and a body mass index of 27–35 $kg \cdot m^{-2}$ were randomised to receive either zonisamide, placebo or CPAP for 4 weeks. The open extension phase (20 weeks) compared CPAP and zonisamide. Polysomnography, biochemistry and symptoms were evaluated.

At 4 weeks, zonisamide reduced apnoea/hypopnoea index (AHI) by a mean$\pm$SD 33$\pm$39% and oxygen desaturation index by 28$\pm$31% ($p=0.02$ and 0.014, respectively; placebo adjusted). The mean compliance adjusted reduction of AHI after zonisamide and CPAP was 13 and 61%, respectively, ($p=0.001$) at 24 weeks. Body weight was marginally changed at 4 weeks, but reduced after zonisamide and increased after CPAP at 24 weeks (-2.7$\pm$3.0 kg *versus* 2.3$\pm$2.0 kg, $p<0.001$). Zonisamide decreased bicarbonate at 4 and 24 weeks. Side-effects were more common after zonisamide.

Zonisamide reduced OSA independent of body weight potentially by mechanisms related to carbonic anhydrase inhibition. The effect was less pronounced than that obtained by CPAP.

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Introduction

Obstructive sleep apnoea (OSA) is characterised by a partial or total collapse of the upper airway leading to intermittent hypoxia, hypercapnia and transient arousals. The main consequences of OSA include cardiovascular and metabolic morbidities, and increased daytime somnolence [1, 2]. Continuous positive airway pressure (CPAP) constitutes the mainstay of therapy in OSA although long term compliance with the device is incomplete and may be as low as 50% [3]. Therefore, alternative or complementary forms of therapy are actively sought [4, 5].

Zonisamide is a marketed drug used in the treatment of convulsive disorders [6]. Its weight reduction properties have been demonstrated in randomised controlled trials by a net body weight reduction of 3–5% in obese patients [7, 8]. Among multiple pharmacological properties zonisamide has an inhibitory effect on several of the abundant carbonic anhydrase isoenzymes [9]. Other compounds with carbonic anhydrase inhibitory properties (*e.g.* acetazolamide and topiramate) have been shown to reduce central apnoeic events in heart failure patients [10] and obstructive events in patients with OSA [11, 12]. The mechanism behind this effect is not fully understood but may relate to a shift of the acid–base balance towards a more acidic state, which results in respiratory stimulation [10, 11]. The potential dual effect of zonisamide in reducing body weight and modifying respiratory control in patients with OSA has never been studied. We hypothesised that the carbonic anhydrase inhibitory properties of zonisamide would lead to a reduction of apnoeic events in overweight/obese patients with OSA. The pharmacological mechanism incorporates both a direct carbonic anhydrase related effect on breathing and an indirect effect mediated by weight loss. Moreover, we compared the overall therapeutic effect of zonisamide with CPAP after taking aspects of compliance into account.

Methods

Subjects

Patients with an OSA diagnosis and scheduled for CPAP treatment were screened at the Dept of Sleep Medicine, Sahlgrenska University Hospital (Gothenburg, Sweden) (n=715). Inclusion criteria were an apnoea/hypopnoea index (AHI) of >15 events·h^{-1}, body mass index (BMI) between 27 and 35 kg·m^{-2} and an Epworth Sleepiness Scale (ESS) score of >6. Exclusion criteria included seizure disorders, unstable cardiovascular, pulmonary or gastrointestinal disease, depression, alcohol or drug abuse, and medication interfering with the study protocol. Patients with an occupational hazard resulting from sleepiness and those with severe nocturnal hypoxaemia (>10 episodes with an arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) <50% or poor resaturation capacity) were also excluded. A total of 50 (out of 70 eligible) patients aged 18–75 years consented to participate in the study. The protocol was approved by the Ethics Committee at the University of Gothenburg (697-09). Informed consent was obtained from all participants prior to study entry.

Study design and procedure

This was a randomised, double-blind, placebo-controlled, parallel study with an open extension phase (fig. 1). Patients were randomly allocated to receive zonisamide, placebo or CPAP for 4 weeks according to a randomisation list (block randomisation (n=6); drug A or B, C=CPAP) prepared by the independent Apoteket Produktion och Laboratorier (Stockholm, Sweden). Study procedures and protocol adherence were supervised by an independent monitor at the university hospital. In the open extension phase (20 weeks), all participants except those randomised to CPAP received zonisamide.

Patients were investigated at baseline, 4 and 24 weeks with sleep assessments, blood pressure measurements, blood samples, questionnaires (ESS [13], Fatigue Impact Scale (FIS) [14], and Zung self-rating depression [15] and anxiety [16] scales) and anthropometrics including body fat distribution. Zonisamide (100 mg Zonegran; Eisai Limited, Hatfield, UK) or placebo tablets were administered according to a stepwise titration scheme with weekly 100-mg escalations from 100 to 300 mg daily. Dosing could be reduced (100-mg steps) at the discretion of the investigator in the case of side-effects. The recommended time for medication intake was between 20:00 h and 22:00 h. Compliance with the study drug and placebo was determined by tablet count. No specific weight counselling was provided in this study.

Sleep studies

Sleep was assessed by ambulatory polysomnography (PSG) at home according to a standard procedure [17]. Two consecutive, full-night ambulatory PSGs (Embla A10 system; Flaga, Reykjavik, Iceland) were performed at baseline. Data from the second PSG night (not from first habituation night) were used for analysis. Patients subsequently underwent two single night PSG recordings at 4 and 24 weeks. The PSG included electroencephalograms (C3-A2, C4-A1, Fz-A2 and Oz-A1), left/right electrooculograms, chin and bilateral tibialis electromyograms, ECG, nasal cannula and oronasal thermistor, thoracic/abdominal

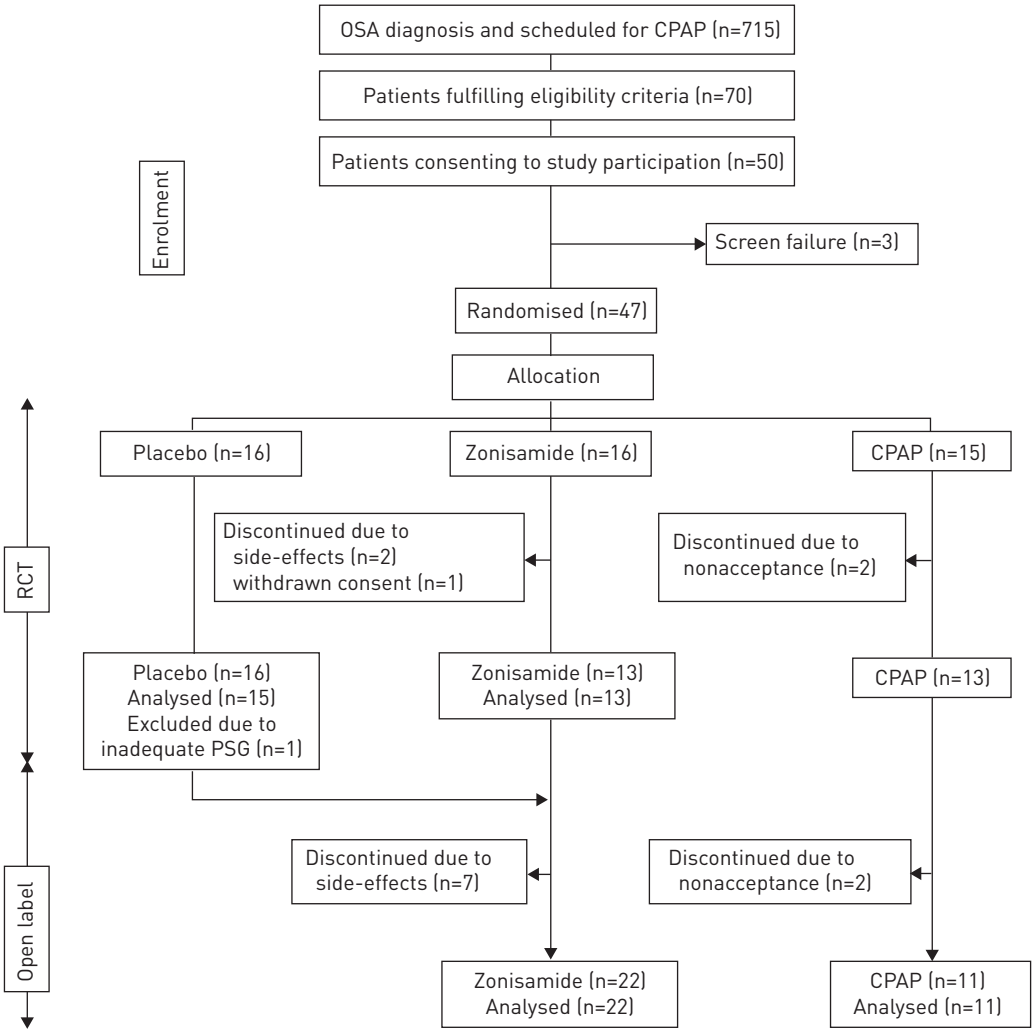

FIGURE 1 Study flow chart depicting the three study arms in the 4-week randomised controlled trial (RCT) and the open comparison between zonisamide and continuous positive airway pressure (CPAP) at 24 weeks. OSA: obstructive sleep apnoea; PSG: polysomnography.

respiratory movement, body position, and oxygen saturation. The PSG recordings were manually scored according to the American Academy of Sleep Medicine criteria [18], by an experienced scorer blinded to the treatment allocation. Apnoea events were defined as a $\geqslant$90% drop of the airflow signal from baseline lasting $\geqslant$10 s. Hypopnoea was defined as an airflow signal drop of $\geqslant$50% from baseline with a duration $\geqslant$10 s accompanied by either a desaturation of $\geqslant$3% or an arousal. AHI was calculated as the number of apnoeas and hypopnoeas per hour of sleep. Oxygen desaturation index (ODI) was based on numbers of oxygen desaturations $\geqslant$4% per hour of sleep. The mean and minimum S_{pO_2}, and the time spent at $<$90% S_{pO_2} ($T_{<90\%sat}$) during the sleep recording were determined. One patient from the placebo group was excluded from data analysis due to inadequate PSG recording quality at 4 weeks.

Analysis

Sample size estimation

The sample size calculation was based on in-house data from previous treatment studies in OSA and assumed that a reduction of AHI exceeds that of placebo by a mean$\pm$SD of 7.5$\pm$6 events·h^{-1}. A parallel group design of 30 patients in each treatment arm would provide a power of 90% for detecting significant treatment group differences (two-tailed $p \leqslant 0.05$).

Efficacy variables

The primary end-point of the study was to explore the efficacy of pharmacological weight reduction in OSA by using the effective change in AHI as the primary variable. In addition, sleep apnoea alleviation (SAA) was

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analysed at 24 weeks. Secondary efficacy variables were the change of AHI and ODI at 4 weeks in the double-blind part of the protocol comparing zonisamide and placebo. Secondary efficacy variables also included: mean S_{pO_2}, minimum S_{pO_2} and time spent with $T_{<90\%sat}$; PSG-derived sleep variables including total sleep time and proportion of sleep stages; and anthropometric variables including body weight, BMI, body fat distribution, blood pressure and questionnaire scores at 4 and 24 weeks. The placebo-adjusted percentage change was calculated as the mean difference between the active and placebo treatment arms.

Sleep apnoea alleviation

SAA compares the therapeutic effect of CPAP and the drug, taking into consideration absolute use of CPAP (adjusted for habitual sleep time) during the 24-week treatment period [3]. The efficacy of CPAP treatment on AHI or ODI in relation to baseline was first calculated. CPAP compliance from the meter reading was adjusted for reported habitual sleep time. A composite measure of treatment efficacy (SAA) was then generated. Hence, a patient who experienced a reduction of AHI from 50 events·h^{-1} to 10 events·h^{-1} would have an 80% treatment efficacy. A CPAP meter showing a mean of 6 h usage per night and a habitual reported sleep time of 8 h per night would result in 75% treatment coverage (alleviation). SAA in this patient is 80% × 75%, which equals 60%. The rationale for using SAA was to provide a balanced comparison between the mechanical and pharmacological treatments in terms of absolute elimination of sleep apnoea. In the drug treatment arm, efficacy was calculated accordingly. Providing the patient was compliant with drug therapy the user time would equal habitual sleep time and the SAA would equal the measure of efficacy. Four patients refused to continue CPAP therapy (nonacceptors) during the course of the study and were excluded from the analysis.

Statistics

Randomised patients who completed the treatment period without protocol deviation were included in the data analysis. A per-protocol analysis was used to investigate the pharmacological effects of zonisamide undiluted by drop-out due to potential side-effects. An ANCOVA model was used to test the between group difference. Paired t-tests were performed on within group comparisons at 4 and 24 weeks. Spearman's correlation was used to assess the relationship between change of AHI and bicarbonate. Data are presented as mean±SD or mean change (95% CI). A p-value $\leqslant 0.05$ was considered statistically significant. Statistical analysis was conducted using SPSS 19 (SPSS Inc, Chicago, IL, USA).

Results

Study population

A total of 47 out of 50 screened subjects (42 males and five females; mean±SD age 52±12 years, BMI 31.3±2.2 kg·m^{-2}) were included (inclusion period Q2 2010 to Q3 2011). All except four patients (final dose 200 mg) reached peak dosing of 300 mg daily in the open-label phase generating a consumed daily dose of 286±44 mg zonisamide. The compliance of zonisamide and placebo at 4 weeks was 90.1±6.9% and 90.6±8.3%, respectively. Study drug compliance was 96.4±8.7% at 24 weeks. Averaged CPAP use over 24 weeks (n=11) was 5.2±1.4 h per night and administered pressure was 12.6±1.7 cmH_2O. Patients in the CPAP group reported a subjective sleep time of 7.7±0.9 h per night whereas the reported sleep time in the zonisamide group was 7.5±0.7 h per night (p=0.9).

The zonisamide (n=13) and placebo (n=15) groups were similar at baseline, except that waist/hip ratio was marginally higher in zonisamide patients (p=0.02, table 1). Patients randomised to CPAP were younger than the zonisamide group (44±10 *versus* 55±10 years, p=0.01). CPAP patients had a lower heart rate compared with zonisamide and placebo (66±7 *versus* 59±7 (p=0.02) and 59±10 beats·min^{-1} (p=0.04), respectively).

Effects of zonisamide and placebo at 4 weeks

Zonisamide was superior to placebo in the reduction of AHI (mean change (95% CI) -8.7 (-16.5–-0.9) events·h^{-1} *versus* 4.0 (-5.6–13.7) events·h^{-1}, p=0.039) and ODI (-8.8 (-15.6–-2.0) events·h^{-1} *versus* -0.5 (-4.7–5.6) events·h^{-1}, p=0.025) (table 2, fig. 2a–b). The placebo-adjusted zonisamide change in AHI and ODI at 4 weeks was -33±39% (p=0.02) and -28±31% (p=0.014), respectively. The significance remained after including baseline BMI as a covariate in the ANCOVA model (data not shown). The reduction of AHI appeared to be mainly due to a diminution of hypopnoea events. Zonisamide did not have an effect on supine AHI when compared to placebo (-7.9 (-21.6–5.9) events·h^{-1} *versus* 2.3 (-9.8–14.3) events·h^{-1}, p=0.24). The arousal index and mean S_{pO_2}, but not minimum S_{pO_2}, $T_{<90\%sat}$ and other sleep variables were improved after zonisamide (table 2 and fig. 2c). Body weight decreased marginally after zonisamide compared with placebo (-0.6 (-1.2–0.0) kg *versus* 0.7 (-0.1–1.4) kg, p=0.008) (table 3). ESS and FIS scores were not affected.

TABLE 1 Baseline characteristics

	Placebo	Zonisamide	CPAP
Subjects	15	13	13
Males/females	13/2	13/0	12/1
Age years	53±14	55±10	44±10[#]
Treated hypertension %	50	46	15
BMI kg·m^{-2}	31±2	31±3	31±2
Waist/hip ratio	0.99±0.06	1.03±0.10*	1.01±0.07
Neck circumference cm	43±2	44±2	44±3
Systolic BP mmHg	137±19	141±16	132±20
Diastolic BP mmHg	84±8	84±10	83±7
Heart rate beats·min^{-1}	59±10	59±7	66±6[#,¶]
AHI events·h^{-1}	50±23	42±24	48±26
ODI events·h^{-1}	43±21	35±21	44±25
ESS score	12±4	13±6	14±4

Data are presented as n or mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; BMI: body mass index; BP: blood pressure; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; ESS: Epworth Sleepiness Scale. *: p<0.05 for zonisamide *versus* placebo; [#]: p<0.05 for CPAP *versus* zonisamide; [¶]: p<0.05 for CPAP *versus* placebo.

The effects of zonisamide on blood pressure were further evaluated in an *ad hoc* analysis that suggested that the reduction of systolic blood pressure may be stronger in patients with comorbid hypertension. Among the 13 patients randomised to zonisamide, six (all on antihypertensive medication) had established hypertension. In this group, systolic blood pressure dropped from 152±15 mmHg to 142±9 mmHg (p=0.018).

Effects of zonisamide and CPAP at 24 weeks

CPAP (n=11) treatment was superior to zonisamide (n=22) in terms of reducing OSA (table 4). The difference in AHI and ODI reduction was still significant after adjustment for CPAP compliance (fig. 3a–b). The SAA after CPAP and zonisamide treatment (primary study end-point) was 61 (51–71)% and 13 (-4–30)%, respectively (p=0.001). Compared to zonisamide, CPAP increased rapid eye movement sleep and more effectively reduced the ESS and FIS scores. Compared with baseline zonisamide was associated with a reduction of AHI, ODI and $T_{<90\%sat}$ while mean S_{pO_2} and minimum S_{pO_2} were increased. Zonisamide was associated with increased apnoea duration and reduced rapid eye movement sleep.

TABLE 2 Effects of placebo and zonisamide on sleep apnoea and sleep-related variables at 4 weeks

	Placebo	Zonisamide	p-value
Subjects n	15	13	
AHI events·h^{-1}	4.0 (-5.6–13.7)	-8.7 (-16.5– -0.9)	0.04
ODI events·h^{-1}	-0.5 (-4.7–5.6)	-8.8 (-15.6– -2.0)	0.03
CAI events·h^{-1}	0.2 (-1.7–2.0)	0.1 (0.0–0.2)	NS
Apnoea index events·h^{-1}	0.1 (-5.8–6.0)	-1.9 (-10.2–6.3)	NS
Hypopnoea index events·h^{-1}	6.3 (0.9–11.6)	-5.2 (-10.8– -0.4)	<0.01
Apnoea duration s	0.1 (-2.9–3.1)	0.0 (-3.6–3.7)	NS
Arousal index events·h^{-1}	4.1 (-1.7–9.9)	-6.8 (-14.1–0.4)	0.02
Mean S_{pO_2} %	0.01 (-0.75–0.77)	1.27 (0.23–2.30)	0.04
Minimum S_{pO_2} %	0.7 (-2.1–3.6)	1.3 (-1.9–4.5)	NS
$T_{<90\%sat}$ %	-1.6 (-7.1–4.0)	-7.8 (-15.6– -0.1)	NS
TST h	-0.3 (-1.0–0.5)	0.0 (-0.7–0.6)	NS
Sleep efficiency %	-5.5 (-10.9– -0.2)	-0.2 (-4.2–3.7)	NS
Stage R % of TST	-2.1 (-4.9–0.8)	-1.1 (-6.2–4.1)	NS
Stage N3 % of TST	-1.3 (-4.6–2.1)	0.7 (-3.1–4.5)	NS

Data are presented as mean change (95% CI), unless otherwise stated. AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; CAI: central apnoea index; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; $T_{<90\%sat}$: time spent with S_{pO_2} <90%; TST: total sleep time; NS: nonsignificant (p>0.1).

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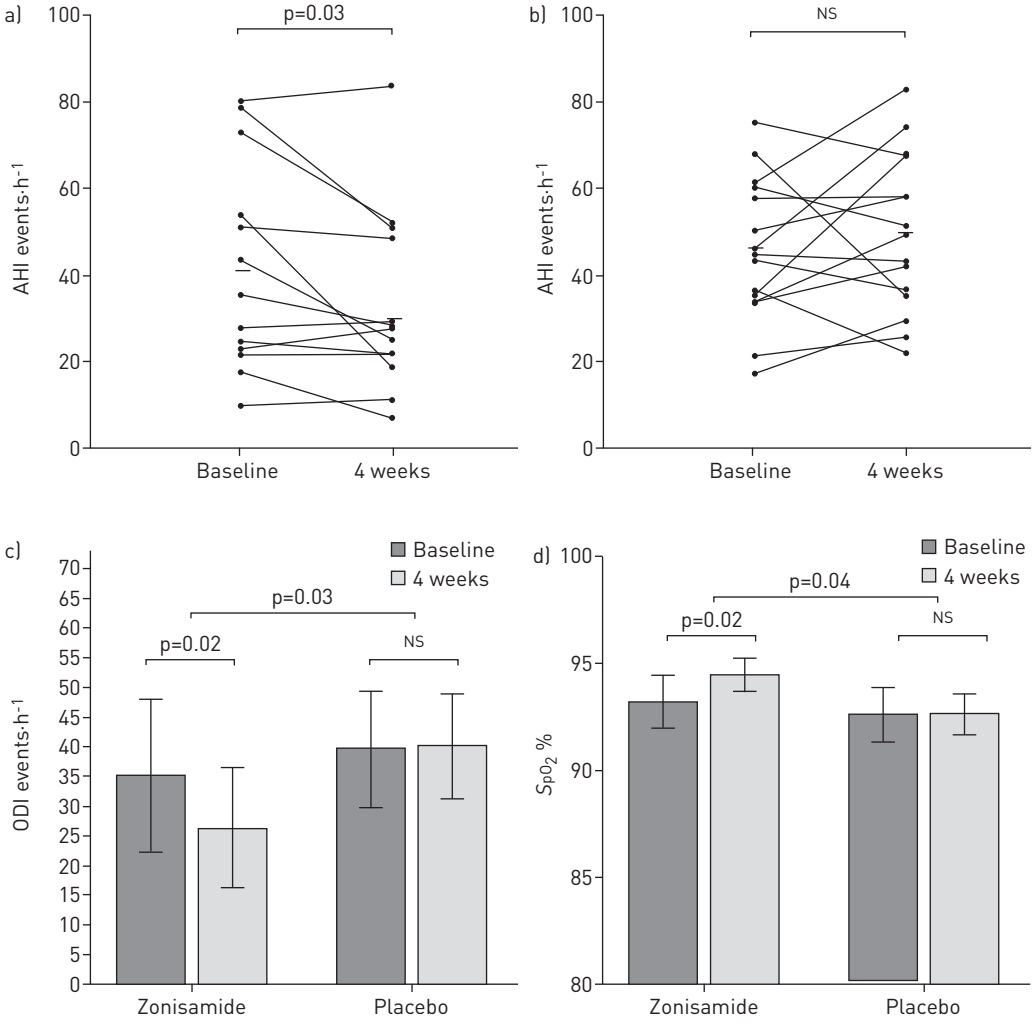

FIGURE 2 Individual data of apnoea/hypopnoea index (AHI) at baseline and 4 weeks in a) the zonisamide (n=13) and b) the placebo group (n=15). Mean AHI values at baseline and 4 weeks is indicated by the solid black lines. Mean c) oxygen desaturation index (ODI) and d) overnight arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) in the zonisamide and placebo groups at baseline and after 4 weeks of treatment. Error bars represent 95% confidence intervals.

Group comparisons showed that zonisamide was superior to CPAP in reducing body weight, neck circumference and sagittal diameter (table 4). The weight change was -2.7 (-4.1–-1.4) kg for zonisamide and 2.3 (1.0–3.6) kg for CPAP ($p<0.001$). The zonisamide-induced changes in body composition were not associated with alterations in AHI and ODI. Both zonisamide and CPAP led to a reduction of diastolic blood pressure ($p=0.01$ and 0.048, respectively) (table 4) but there were no between-group differences in changes of systolic blood pressure, diastolic blood pressure or heart rate.

Bicarbonate and respiratory variables at 4 and 24 weeks

Zonisamide was associated with a marked reduction of serum bicarbonate concentration at 4 and 24 weeks ($p<0.001$) (tables 3 and 4). This reduction was essentially maintained from -2.7 (-3.5–-1.9) mmol·L^{-1} at week 4 to -2.3 (-3.0–-1.6) mmol·L^{-1} at week 24 and was seen in almost all patients treated with zonisamide (online supplementary fig. E1). There was no significant correlation between changes of AHI/ODI and bicarbonate in patients receiving zonisamide at 4 or 24 weeks.

Side-effects, biochemistry and safety data

The majority of adverse events (33 out of 38, 87%), most commonly dysphoria (n=7, 18%), were recorded in patients receiving zonisamide treatment (online supplementary table 1). The Zung depression scale score was slightly increased in the zonisamide group compared with placebo at 4 weeks (table 3). There were no indications of suicidality. Four adverse events occurred in the CPAP group, among them upper airway infections. Only minor changes were recorded in the biochemistry variables (online supplementary

TABLE 3 Effects of 4 weeks treatment on anthropometric variables

	Placebo	Zonisamide	p-value
Subjects n	15	13	
Weight kg	0.7 (-0.1–1.4)	-0.6 (-1.2–0.0)	<0.01
BMI kg·m^{-2}	0.2 (0.0–0.4)	-0.2 (-0.4–0.0)	<0.01
Waist/hip ratio	0.007 (-0.008–0.022)	-0.004 (-0.015–0.067)	NS
Neck circumference cm	-0.1 (-0.5–0.7)	-0.8 (-1.4– -0.1)	0.06
Sagittal diameter cm	-0.8 (-1.8–0.4)	-0.3 (-0.9–0.4)	NS
Systolic BP mmHg	-1.1 (-7.4–5.1)	-4.9 (-11.3–1.5)	NS
Diastolic BP mmHg	-2.8 (-5.6–0.0)	-0.5 (-5.0–4.0)	NS
Heart rate beats·min^{-1}	0.5 (-3.5–4.6)	0.5 (-4.3–3.2)	NS
ESS score	-0.3 (-2.3–1.6)	1.4 (-0.6–3.4)	NS
FIS score	-2.3 (-11.4–6.9)	-0.2 (-6.9–6.5)	NS
Zung depression score	-1.9 (-4.5–0.8)	2.6 (-0.6–5.7)	0.03
Zung anxiety score	-1.9 (-5.5–1.7)	2.0 (-2.0–6.0)	NS
Bicarbonate mmol·L^{-1}	0.3 (-0.2–0.8)	-2.7 (-3.5– -1.9)	<0.01
Creatinine μmol·L^{-1}	-6.3 (-13.5–0.9)	8.1 (5.0–11.3)	<0.01

Data are presented as mean change (95% CI), unless otherwise stated. BMI: body mass index; BP: blood pressure; ESS: Epworth Sleepiness Scale; FIS: Fatigue Impact Scale; NS: nonsignificant (p>0.1).

TABLE 4 Effects of continuous positive airway pressure (CPAP) and zonisamide at 24 weeks

	CPAP	Zonisamide	p-value
Subjects n	11	22	
Weight kg	2.3 (1.0–3.6)	-2.7 (-4.1– -1.4)	<0.01
BMI kg·m^{-2}	0.7 (0.3–1.2)	-0.8 (-1.2– -0.4)	<0.01
Waist/hip ratio	-0.007 (-0.021–0.008)	-0.003 (-0.015–0.010)	NS
Neck circumference cm	0.2 (-0.4–0.7)	-1.3 (-1.7– -0.9)	<0.01
Sagittal diameter cm	0.4 (-0.8–1.5)	-1.9 (-3.0– -0.8)	0.01
Systolic BP mmHg	1.1 (-10.5–12.8)$^{\#}$	-5.7 (-13.0–1.5)	NS
Diastolic BP mmHg	-7.2 (-14.4– -0.1)$^{\#}$	-4.0 (-6.9– -1.1)	NS
Heart rate beats·min^{-1}	0.7 (-3.6–5.0)$^{\#}$	-2.1 (-4.3–0.1)	NS
AHI events·h^{-1}	-42.5 (-57.7– -27.3)	-8.0 (-15.9– -0.2)	<0.01
ODI events·h^{-1}	-40.4 (-55.2– -25.5)	-8.1 (-15.1– -0.2)	<0.01
Apnoea duration s	-4.3 (-10.3–1.7)	5.9 (0.8–11.0)	0.02
Arousal index events·h^{-1}	-28.6 (-44.6– -12.7)	-5.1 (-13.3–3.2)	<0.01
Mean S_{pO_2} %	2.8 (0.9–4.7)	0.8 (0.2–1.4)	0.01
Minimum S_{pO_2} %	8.1 (5.1–11.2)	2.4 (0.2–4.7)	<0.01
$T_{<90\%sat}$ %	-16.3 (-37.3–4.8)	-8.2 (-14.4– -2.1)	NS
TST h	0.4 (-0.3–1.1)	-0.2 (-0.8–0.4)	NS
Sleep efficiency %	-2.6 (-8.8–3.6)	-3.9 (-8.1–0.3)	NS
Stage R % of TST	5.4 (2.1–8.7)	-2.7 (-5.4–0.0)	<0.01
Stage N3 % of TST	-1.4 (-5.0–2.3)	0.1 (-3.1–3.4)	NS
ESS score	-4.4 (-7.0– -1.7)	-0.4 (-2.4–1.5)	0.02
FIS score	-19.0 (-29.2–8.8)	-3.6 (-12.8–5.5)	0.04
Zung depression score	-4.4 (-8.0– -0.8)	2.8 (-1.0–6.6)	0.02
Zung anxiety score	-3.1 (-5.4– -0.8)	0.7 (-2.1–3.4)	0.07
Bicarbonate mmol·L^{-1}	0.7 (0.1–1.3)	-2.3 (-3.0– -1.6)	<0.01
Creatinine μmol·L^{-1}	-0.6 (-5.5–4.2)	7.1 (2.6–11.6)	0.03

Data are presented as mean change (95% CI), unless otherwise stated. CPAP values are not corrected for compliance. BMI: body mass index; BP: blood pressure; AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; $T_{<90\%sat}$: time spent with S_{pO_2} <90%; TST: total sleep time; ESS: Epworth Sleepiness Scale; FIS: Fatigue Impact Scale; NS: nonsignificant (p>0.1). $^{\#}$: n=9.

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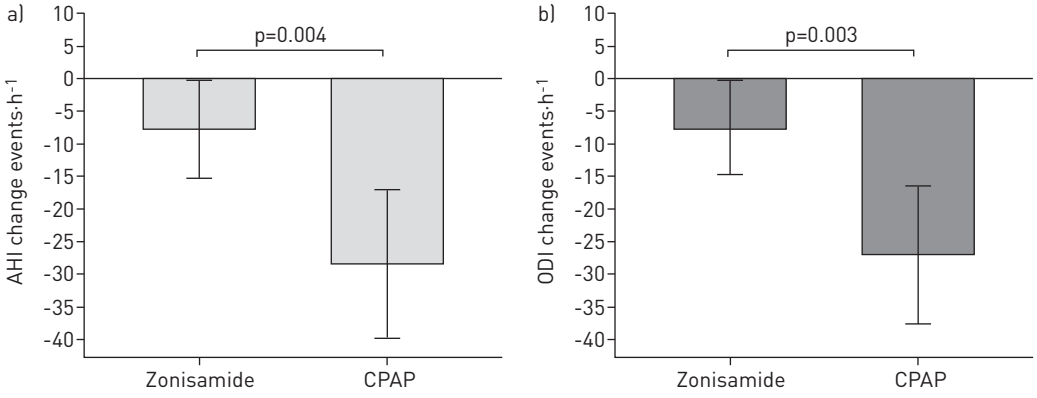

FIGURE 3 Mean a) change of apnoea/hypopnoea index (AHI) and b) oxygen desaturation index (ODI) in patients completing 24 weeks treatment with zonisamide or continuous positive airway pressure (CPAP). Zonisamide and CPAP effect are corrected for compliance. Error bars represent 95% confidence intervals.

material). As expected, zonisamide induced a significant increase in serum creatinine at 4 and 24 weeks (tables 3 and 4).

Discussion

This randomised controlled trial is the first to demonstrate that zonisamide improved breathing and oxygenation in overweight and obese patients with moderate-to-severe OSA. The effect was heterogeneous, independent of initial body weight and maintained over 6 months. Improved breathing during sleep was not accompanied by an evident reduction of daytime sleepiness. The overall effect of zonisamide was less pronounced than that obtained by CPAP even after adjustment for compliance.

The principle of carbonic anhydrase inhibition for the treatment of sleep disordered breathing has been explored previously. Carbonic anhydrase is a highly abundant enzyme with a strong influence on carbon dioxide elimination in the human body [19]. Renal carbonic anhydrase inhibition generates a metabolic acidosis, which promotes ventilation *via* chemosensory mechanisms [20]. Carbonic anhydrase inhibitors have additional stimulatory effects on ventilation by partial inhibition of carbonic anhydrase enzymes in red blood cells and tissue [21]. Carbonic anhydrase inhibitors, in particular acetazolamide, have been used to eliminate high-altitude periodic breathing [21], central apnoea of Cheyne–Stokes type [10] and OSA [11, 22]. Zonisamide exerts carbonic anhydrase inhibitory properties in addition to effects on sodium channels and γ-aminobutyric acid function [23–25], and it is unclear whether these pharmacological effects may have influenced the treatment effects in the current study. A previous study on acetazolamide in OSA suggested a direct relationship between the change in bicarbonate concentration and reduction of apnoeic events [26]. However, although bicarbonate concentration was uniformly altered after zonisamide in the current study, there was no direct correlation between bicarbonate reduction and improvement of OSA. Mechanisms that might determine responsiveness remain unexplained but could include factors such as the degree of upper airway collapsibility, chemosensory function, arousal threshold or genetic differences [27, 28]. Recent work aiming to phenotype patients with sleep apnoea suggests that approximately one-third of patients may exhibit a modified respiratory control mechanism [27]. The carbonic anhydrase inhibitor acetazolamide selectively reduced loop gain in parallel to AHI in a small study of patients with moderate-to-severe OSA [29]. With a similar effect expected after zonisamide, we would have detected a reduction of AHI only in a subgroup of patients, which indeed was the case. Future studies using increased loop gain as a phenotypic trait for patient selection may be able to demonstrate a stronger treatment effect of zonisamide in OSA.

The association between OSA and obesity is well established and weight reduction points to an improvement of OSA. Zonisamide has been explored for its body weight reducing properties. In a 1-year randomised controlled trial, 400 mg zonisamide daily induced additional weight loss in obese patients when a lifestyle and diet programme was applied [8]. However, the influence of zonisamide on sleep disordered breathing was not addressed in that study. A recent trial investigating topiramate, a compound with similar carbonic anhydrase inhibitory properties, in combination with phentermine reported a substantial reduction of sleep apnoea which correlated directly with weight loss in obese OSA patients [12]. Our study (zonisamide 300 mg daily) included no weight counselling. The effect on OSA was most likely accounted for by a carbonic anhydrase inhibitory effect, which may be additional to the weight reduction properties provided by the drug. As shown in figure 2a there was a limited overall effect of zonisamide and only a subgroup of patients reached a clinically significant reduction of OSA. However, no specific predictor of

responsiveness could be identified in our small study sample. It is possible that the combination of weight counselling and zonisamide in OSA patients may further optimise the therapeutic effect.

The degree of apnoea alleviation was introduced as one of the outcomes in the current study. It was found that even after adjustment for compliance CPAP was superior to zonisamide in terms of OSA elimination. The improvement of subjective daytime sleepiness was only seen with CPAP. However, body composition measures favoured zonisamide and initiation of CPAP therapy was associated with a significant increase in body weight of 2.3 kg after 24 weeks. The exact influence of body weight gain in CPAP-treated OSA patients is still unclear. It has been suggested that the alteration may be related to changes in leptin level after CPAP [30] and associated with insulin resistance in obese OSA patients [31]. Side-effects were more common among zonisamide-treated patients but generally mild, as the proportion of patients prematurely terminating the study was similar in the zonisamide and CPAP groups. Although the comparison appears to favour CPAP, it should be noted that the zonisamide response was heterogeneous and individual patients responded well to pharmacological therapy.

This randomised, placebo-controlled study contained both an early evaluation of zonisamide effects on breathing during sleep and an extension phase. The design enabled analysis independent of major changes in body composition. It also permitted direct long-term comparison between the effects of zonisamide and compliance-adjusted CPAP on OSA. Study limitations include a failure to reach the preset number of patients prior to the study drug expiry date, due to recruitment difficulties. However, the study hypothesis was verified in spite of the lower number of study participants. Our study set out to prove the effects of zonisamide in unselected OSA patients and, therefore, no particular attempts were made to optimise weight reduction or to characterise specific phenotypic traits in the study population. Despite the randomisation procedure the patients in the CPAP group were younger than those in the zonisamide group at baseline. 20% of the zonisamide patients reported dysphoria as a side-effect at 24 weeks, although there was no difference at 4 weeks compared to placebo. Somnolence has been described as a common symptom of zonisamide treatment [32]. We did not find an increase of somnolence, as reflected by the ESS, in the zonisamide treatment group. Whether the reduction of OSA by zonisamide could have offset somnolence side-effects needs to be further investigated.

In conclusion, we demonstrated that the carbonic anhydrase inhibitor zonisamide reduced sleep disordered breathing in patients with OSA. The overall effect was less pronounced than that obtained by CPAP even after adjustment for compliance. The current study does not justify unselected use of zonisamide in patients with OSA. Our data suggest that carbonic anhydrase inhibition may be a useful target for further investigations into mechanisms related to the pathophysiology of OSA as well as its sequels, in particular hypertension.

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