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The association of serotonin reuptake inhibitors and benzodiazepines with ictal central apnea☆

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ABSTRACT

Objective: Ictal (ICA) and postconvulsive central apnea (PCCA) have been implicated in sudden unexpected death in epilepsy (SUDEP) pathomechanisms. Previous studies suggest that serotonin reuptake inhibitors (SRIs) and benzodiazepines (BZDs) may influence breathing. The aim of this study was to investigate if chronic use of these drugs alters central apnea occurrence in patients with epilepsy.
Methods: Patients with epilepsy admitted to epilepsy monitoring units (EMUs) in nine centers participating in a SUDEP study were consented. Polygraphic physiological parameters were analyzed, including video-electroencephalography (VEEG), thoracoabdominal excursions, and pulse oximetry. Outpatient medication details were collected. Patients and seizures were divided into SRI, BZD, and control (no SRI or BZD) groups. Ictal central apnea and PCCA, hypoxemia, and electroclinical features were assessed for each group.
Results: Four hundred and seventy-six seizures were analyzed (204 patients). The relative risk (RR) for ICA in the SRI group was half that of the control group ($p = 0.02$). In the BZD group, ICA duration was significantly shorter than in the control group ($p = 0.02$), as was postictal generalized EEG suppression (PGES) duration ($p = 0.021$). Both SRI and BZD groups were associated with smaller seizure-associated oxygen desaturation ($p = 0.009$; $p \ll 0.001$). Neither presence nor duration of PCCA was significantly associated with SRI or BZD ($p \gg 0.05$).
Conclusions: Seizures in patients taking SRIs have lower occurrence of ICA, and patients on chronic treatment with BZDs have shorter ICA and PGES durations. Preventing or shortening ICA duration by using SRIs and/or BZD in patients with epilepsy may play a possible role in SUDEP risk reduction.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is second only to stroke as a neurological cause of total years of potential life lost in the United States [1]. Video-electroencephalography (VEEG)-monitored SUDEP cases suggest that breathing dysfunction following generalized tonic–clonic seizures is involved in mechanisms of death, and terminal postconvulsive central apnea (PCCA) precedes asystole [2]. These observations, together with imaging [3] and neuropathological [4] evidence, suggest both functional and structural compromise of brainstem function. Some SUDEP and near SUDEP cases occur with focal seizures without secondary generalization [5]. Ictal central apnea (ICA) is frequently seen during focal seizures (37–44%) and can be prolonged (≫60 s) [6]. Prolonged ICA may predispose to fatal outcomes and has been proposed as a potential biomarker of SUDEP [7,8].

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Serotonin (5-HT, 5-hydroxytryptamine) is a neurotransmitter important to chemoreception (CO_2 and pH) [9] and arousal [10], both of which may be compromised in SUDEP [11,12]. Serotonergic dysfunction has been posited as central to both SUDEP and sudden infant death syndrome (SIDS) [13–15] mechanisms, and SUDEP animal models of serotonin deficiency lend support to this hypothesis [16]. Postictal apneic deaths in one such model (DBA/2 mice) can be prevented by pretreatment with serotonin reuptake inhibitors (SRIs), probably through promotion of respiratory rhythmogenesis, rather than increase in ventilatory drive [17,18]. Human evidence is scant; there is only one study that found that focal onset seizures in patients on SRIs have less frequent hypoxemia (peripheral capillary oxygen saturation (SpO_2) ≪ 85%), but whether SRIs do so through decrease in periictal apnea incidence or duration is unknown or unconfirmed [19].

Gamma-aminobutyric acid (GABA), the major inhibitory central nervous system neurotransmitter, critically regulates respiratory rhythmogenesis and is required for normal respiratory motor pattern generation [20]. Benzodiazepines (BZDs) are $GABA_A$ receptor positive allosteric modulators and efficacious antiepileptic drugs [21,22]. Therapeutic doses have minimal breathing suppression effects if any, but in excess or in conjunction with opiates, they may cause breathing dysfunction [23] and respiratory arrest [24]. Animal and human studies of chronic BZD use at therapeutic doses have demonstrated stimulant, probably tachypneic, breathing responses [25,26].

A recent study has shown that ICA duration is associated with the presence of PCCA [27]. We hypothesized that periictal central apnea can be prevented by chronic treatment with SRIs and/or BZDs. We investigated the presence and duration of ICA and PCCA, hypoxemia, and electroclinical features in seizures in patients being treated with and without SRIs, as well as with and without BZDs.

2. Methods

2.1. Patients and clinical settings

We prospectively studied 476 seizures in 204 patients. Of these, 312 seizures were part of a study of ICA incidence [6]; 148 generalized clonic seizures (GCS) were reported in another partially overlapping study that analyzed ICA and PCCA incidences [27,28]. All were consented participants in the National Institute of Neurological Disorders and Stroke (NINDS) Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multicenter project (U01-NS090407) and its precursor, the Prevention and Risk Identification of SUDEP Mortality (PRISM) Project (P20NS076965).

Patients aged ≥16 years with intractable epilepsy (failure of adequate trials of at least two antiepileptic medications) [29], who were undergoing VEEG evaluation in the epilepsy monitoring units (EMUs) of participating centers from September 2011 to April 2018, were studied. Inclusion criteria included patients with thoracoabdominal belts during recorded seizures in the EMU. Exclusion criteria were status epilepticus and unavailable plethysmography or video during recorded seizures.

Demographic and clinical data were collected, including epilepsy duration, epilepsy syndrome, and awake or sleep states at seizure onset. Seizures were divided into two groups: generalized convulsive (GCS) and nonconvulsive (NCS) seizures.

2.2. Serotonin reuptake inhibitors (SRIs) and benzodiazepines (BZDs)

Regular outpatient medication details were collected during EMU admissions in all patients. Information regarding treatment with SRIs and BZDs was collected. Serotonin reuptake inhibitors included selective SRIs (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). Only patients chronically treated with BZDs were included, including those whose home medications were discontinued during admission. Patients acutely administered BZDs or treated with opioids were excluded from analysis in order to prevent a confounding influence on breathing metrics [30,31]. Analysis of SRIs and BZDs was performed separately; patients were divided into the following: SRI, BZD, control group (no SRI or BZD), or both (SRI/BZD). Patients on both SRIs and BZDs were excluded from SRI and BZD groups to avoid confounding bias.

2.3. Cardiorespiratory monitoring and VEEG monitoring

All patients had prolonged surface VEEG monitoring using the 10–20 International Electrode System. Electroencephalography (EEG) and electrocardiogram (EKG) were acquired using Nihon Kohden (Tokyo, Japan), Micromed (Modigliani Veneto, Italy), and Xltek (Natus) acquisition platforms. Peripheral capillary oxygen saturation was monitored using pulse oximetry (Nellcor OxiMax N-600x [Convidien], Masimo Radical-7 [Irvine], and SenTec Digital Monitoring System [Therwil BL]) and plethysmography (Ambu [Ballerup, Denmark] Sleepmate and Perfect Fit 2 [Dymedix]). Chest wall and abdominal excursions were recorded using inductance plethysmography (Ambu, Ballerup, Denmark and Sleepmate or Perfect Fit 2, Dymedix, St Paul, MN, USA).

We defined central apnea as breathing cessation of ;≥5 s without alternative explanation (i.e., speech, movement, or intervention). This definition is based on minimum apnea period induced by cortical stimulation [32] and is different to that used in sleep studies. In sleep studies, a minimum apnea period of 10 s has been a constant definition. On the other hand, in epilepsy studies, ICA definition has varied between different studies from one or two missed breaths [28,33] to 10 or 15 s [6,7,34]. More recently, it has been found that using ;≥5 s may be a more accurate definition during seizures, and using the sleep definition of apnea may underestimate this phenomenon in epilepsy. This conclusion is based on stimulation studies aiming to identify the symptomatogenic zone of ICA [32]. They have demonstrated that stimulation of such areas typically induces a minimum apnea period of 5 s, even during short stimulation sessions of 2 s [32]. Ictal central apnea was assessed in NCS and in the preconvulsive phase in GCS, either in focal or generalized epilepsies, since in the generalized epilepsies, absence, myoclonic, or electrographic seizures can occur before the convulsive phase. Ictal central apnea was not evaluated during GCS, because of invariable artifact presence in breathing channels due to generalized tonic posturing or clonic movements. Postconvulsive central apnea referred to apnea that occurred after GCS. Breathing evaluation was made through careful composite analysis of inductance plethysmography, video recording, and SpO_2. Baseline hypoxemia was defined 2 min preictally as mean SpO_2 in a 15-second, artifact free epoch. For GCS and NCS, the overall desaturation nadir referred to the lowest SpO_2 value registered during and up to 3 min after the seizure. To evaluate respiration in the preconvulsive phase of GCS, an additional desaturation nadir was considered during this phase.

Seizure duration was defined as the period from electrographic seizure onset to end. Duration of convulsive phase was defined as the period from onset of motor generalization to the end of the last clonic movement. The presence and duration of postictal generalized EEG suppression (PGES) [35] was analyzed by a validated automated EEG suppression detection tool [36].

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS, version 24; IBM Corp, Armonk, NY, USA). Summary statistics were reported as mean ± standard deviation (median, range). Relative risk (RR) for all the variables at a seizure level was assessed by generalized estimating equation (GEE) with the same subject exchangeable correlation to take into account the variable number of seizures per patient. Nominal patient characteristics were compared across medication groups with Pearson chi-square or Fisher exact tests. Continuous characteristics were compared by Mann–Whitney U tests or Spearman correlations. Binary logistic regression was used to

assess associations between dichotomous variables SRI (+/−) or BZD (+/−) with other variables. A p-value ≪0.05 was considered statistically significant.

3. Results

3.1. General description

A total of 476 seizures were analyzed (204 patients, 106 females [52%]). Mean age was 39.2 years ± 14.5 (36; 17–77). Mean epilepsy duration was 18.3 years ± 13 (18; 0–52). Epilepsy was classified as generalized in 28/204 (13.7%) patients (45 seizures) and focal in 173/204 (84.8%) patients (426 seizures). One patient (2 seizures) had both generalized and focal, and two (3 seizures) had indeterminate epilepsy. Seizures were classified as GCS (231/476 [48.5%] seizures in 126 patients) or NCS (245/476 [51.5%] seizures in 96 patients). Eighteen patients had both GCS and NCS. Two hundred and thirty-seven seizures (49,8%) occurred during wakefulness and 239 (50,2%) out of sleep. Postictal generalized EEG suppression was present after 164/238 (69%) GCS, with a mean duration of 39.3 s ± 22.1 (37; 1–169). No PGES was seen after NCS.

Thirty-four patients were on SRIs: 30 on SSRIs: escitalopram (9), citalopram (6), sertraline (5), vilazodone (2), fluoxetine (6), and paroxetine (2) and 6 patients on SNRIs: duloxetine (2), venlafaxine (1), and amitriptyline (3). Two patients were on both citalopram (SSRI) and duloxetine (SNRI). Twenty-six patients were on BZDs (clobazam [11], clonazepam [11], lorazepam [2], and alprazolam [2]). Six patients were concurrently treated with BZDs and SRIs and were excluded from the analysis of either drug.

3.2. Periictal central apnea

In 69/476 (14.5%) seizures, ICA could not be commented upon because of movement or acquisition artifact and/or obstructed video. In the remaining 407 seizures in 187 patients, ICA was present in 149/407 (36.6%) seizures in 77 patients (39.6%) and exclusively seen in focal epilepsy (p ≪ 0.0001). Mean ICA duration was 22.8 s ± 17.2 (17; 5–97). Of 231 GCS, seven seizures in seven patients were excluded from PCCA analysis because of postictal artifact. Postconvulsive central apnea was detected in 39/224 (17.4%) GCS in 28/119 patients (23.5%) with focal or generalized epilepsy. Mean PCCA duration was 11.7 s ± 12.9 (8; 5–85).

3.3. Serotonin reuptake inhibitors (SRIs) analysis SRIs and ictal central apnea (ICA)

The SRI was compared with the control group. Reliable inductance plethysmography and unobstructed video for ICA diagnosis was available in 315 seizures in 151 patients (Fig. 1). In the SRI group, ICA was seen in 15/78 (19.2%) seizures whereas in the control group, it occurred in 112/237 (47.2%), p ≪ 0.001 (Fig. 2 A). The RR for ICA was double in the control group compared with SRI (RR 2.013, confidence interval (CI) 95% 1.071–3.783, $p = 0.02$). Mean apnea duration did not differ between SRI (27.6 s ± 22.9) and control (23.8 s ± 17.6) groups ($p = 0.7$).

There were no significant differences between SRI and control in gender ($p = 0.7$), age ($p = 0.2$), epilepsy duration ($p = 0.6$), awake/sleep state ($p = 1$), type of epilepsy ($p = 0.7$), epileptogenic zone ($p = 0.3$), oxygen administration ($p = 0.8$), and airway suction ($p = 0.6$) after GCS.

3.3.1. SRIs and postconvulsive central apnea (PCCA)

In the SRI group, 7/36 (19.4%) GCS had PCCA whereas in the control group, PCCA was seen in 27/162 (16.6%) GCS (Fig. 1). Neither presence ($p = 0.2$) nor duration ($p = 0.9$) of PCCA was significantly associated with SRI.

3.3.2. SRIs and hypoxemia

The SRI group had smaller seizure-related oxygen desaturations (Table 1; $p = 0.009$). To determine the phase of the seizure in which SRIs may have an effect, we looked at seizures that remained focal (NCS) and the focal phase of seizures that progressed to convulsions together, and found smaller oxygen decreases in this combined analysis ($p = 0.02$) [Fig. 2 B]. And then, we looked at the convulsive phase separately and confirmed that there were no significant differences

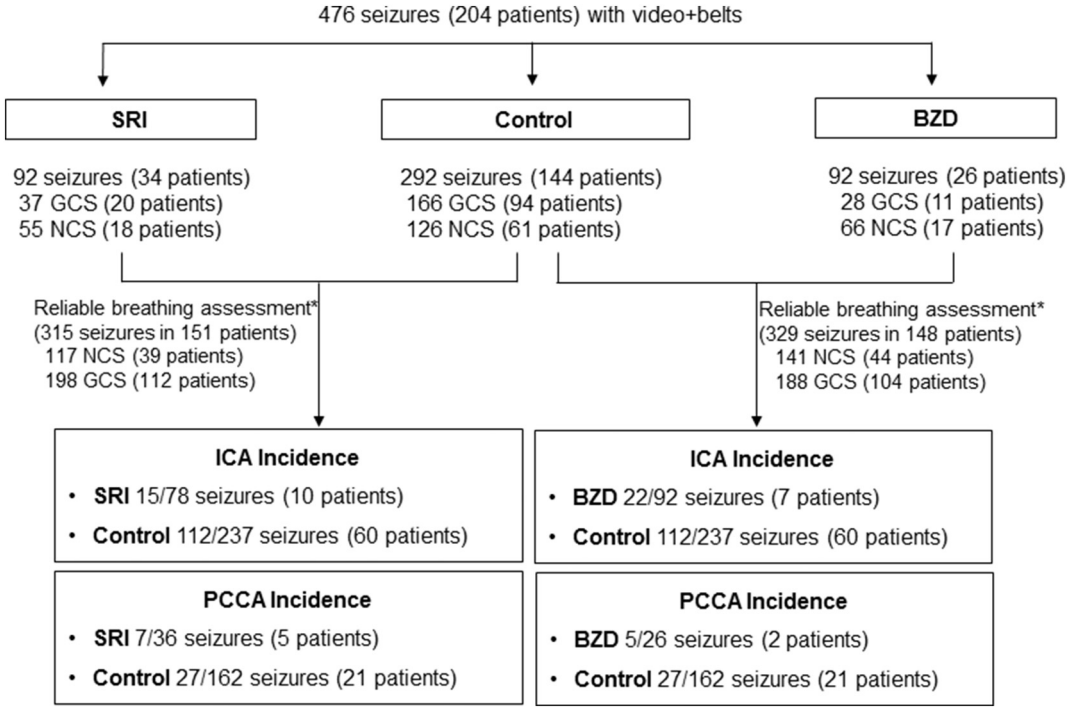

Fig. 1. Flowchart for study population. Legend: SRI: serotonin reuptake inhibitor, BZD: benzodiazepine, GCS: generalized convulsive seizures, NCS: nonconvulsive seizures, ICA: ictal central apnea, PCCA: postconvulsive central apnea. *Thoracoabdominal excursions signal not obscured by movement and/or acquisition artifact and unobstructed video.

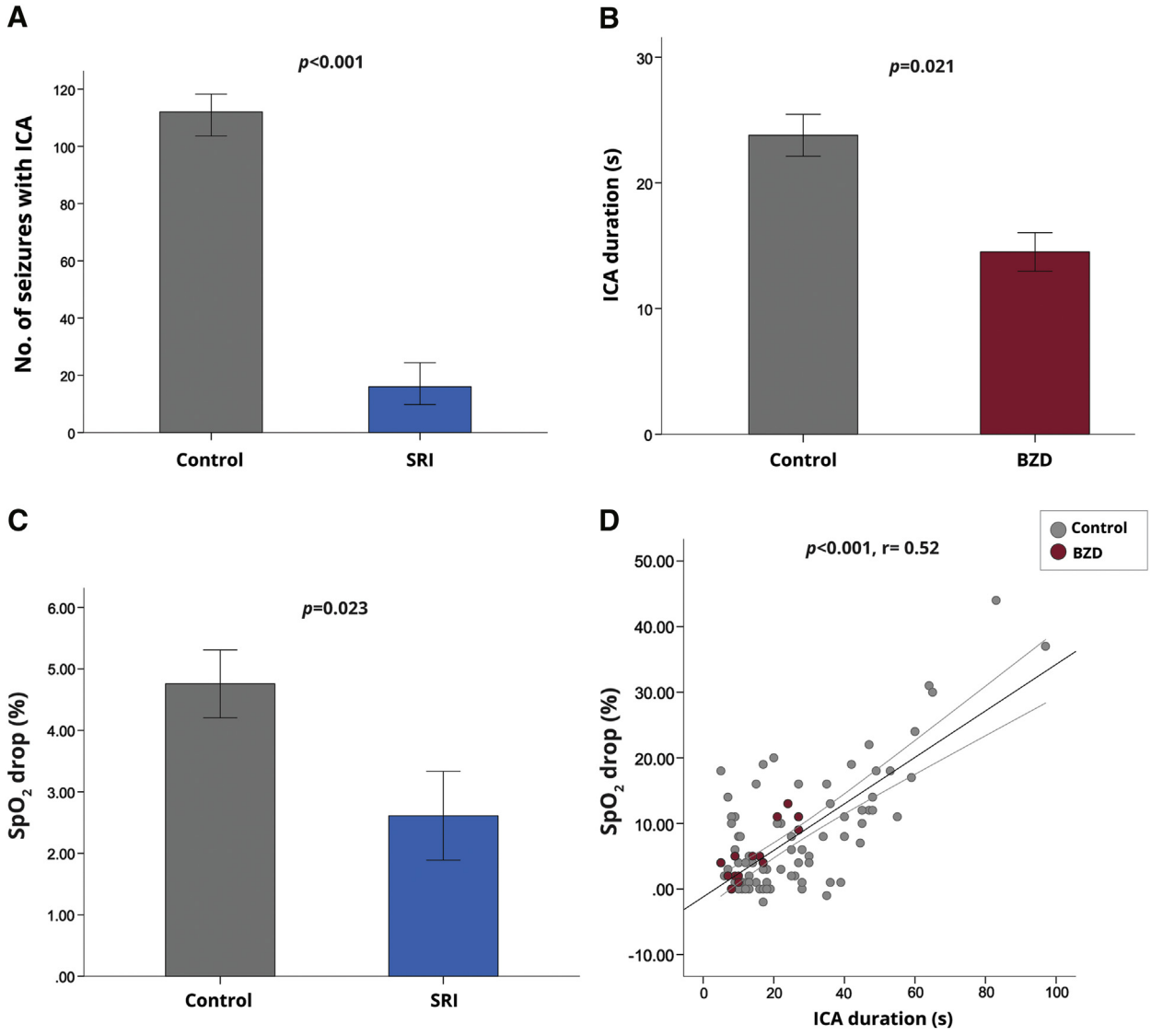

Fig. 2. SRI and BZD influences on periictal respiration. Legend: A and B) Bar plots for data from nonconvulsive seizures (NCS) grouped with the preconvulsive phase of generalized convulsive seizures (GCS), showing the association between A) SRI and ICA incidence and B) SRI and SpO_2 drop (percentage). In the BZD group, C) ICA duration was significantly shorter, and D) SpO_2 drops were smaller than in control. There was a positive correlation between ICA duration and SpO_2 drop as shown by a robust simple linear regression line and 95% confidence intervals. For parts A–C values are mean ± SEM. ICA: ictal central apnea, No: number, SpO_2: peripheral capillary oxygen saturation, SRI: serotonin reuptake inhibitor, BZD: benzodiazepine.

Table 1
Respiratory and electroclinical findings in SRI, BZD, and control groups.

	Control		SRI		*p*-Value	BZD		*p*-Value
ICA incidence (%)	112/237 (47.2%)		15/78 (19.2%)		**≪0.001***	22/92 (23.9%)		0.130
PCCA incidence (%)	27/162 (16.6%)		7/36 (19.4%)		0.470	5/26 (19.2%)		0.314
	Mean	SD	Mean	SD	*p*-value	Mean	SD	*p*-value
ICA duration (s)	23.8	17.6	27.6	22.9	0.770	14.4	7.2	**0.021***
PCCA duration (s)	12.8	15.2	9.6	4.9	0.906	8.40	2.7	0.642
SpO_2 drop (%):								
For all seizures	20.5	19.5	12.6	16.7	**0.009***	10.6	17.5	**≪0.001***
For NCS and preconvulsive phase of GCS	4.8	7.7	2.6	5.5	**0.023***	1.7	3.4	**0.004***
For convulsive/postconvulsive phase of GCS	31.6	16.9	32.8	13.2	0.756	31.1	13.7	0.916
Seizure duration (s):								
NCS	72.7	47.2	104.4	121.1	0.357	65.1	48.6	0.103
GCS	126.1	55.9	153.4	136.9	0.392	101.1	96.5	0.057
Convulsive phase	59.0	25.0	59.0	24.9	0.121	43.5	14.0	**0.016***
PGES duration (s)	40.2	22.0	39.5	22.0	0.735	28.8	18.3	**0.021***

Legend: SRI: serotonin reuptake inhibitor, BZD: benzodiazepine, ICA: ictal central apnea, PCCA: postconvulsive central apnea, GCS: generalized convulsive seizures, NCS: nonconvulsive seizures.

* Statistically significant difference (p value < 0.05).

between SRI and control regarding oxygen decrease in the convulsive postconvulsive phase compared with baseline ($p = 0.7$).

3.3.3. Electroclinical seizure features

Postictal generalized EEG suppression was observed in 28/37 (75.7%) SRI and in 115/166 (69.3%) control ($p = 0.5$) groups. No difference between groups was observed in PGES duration ($p = 0.1$), convulsive phase duration ($p = 0.1$), electrographic GCS duration ($p = 0.3$), or electrographic NCS duration ($p = 0.9$).

3.4. Benzodiazepines (BZDs) analysis

3.4.1. BZDs and ictal central apnea (ICA)

Reliable breathing assessment for ICA was available in 329 seizures in 148 patients from the BZD and control groups (Fig. 1). In the BZD group, ICA was seen in 22/92 (23.9%) seizures whereas in the control group, it occurred in 112/237 (47.2%). There were no differences regarding the RR for ICA occurrence when comparing BZD vs control ($p = 0.39$), after taking into account the variable number of seizures per patient.

Ictal central apnea longer duration was inversely associated with BZD ($p = 0.02$) [Fig. 2 C]. There were no significant differences between BZD and control groups in gender ($p = 0.6$), age ($p = 0.6$), epilepsy duration ($p = 0.2$), awake/sleep state ($p = 0.9$), type of epilepsy ($p = 0.4$), epileptogenic zone ($p = 0.4$), oxygen administration ($p = 1.0$), or airway suction ($p = 0.8$) after GCS.

3.4.2. BZDs and postconvulsive central apnea (PCCA)

Postconvulsive central apnea was found in 5/26 (19.2%) BDZ and in 27/162 (16.6%) control group (Fig. 1). Neither presence ($p = 0.3$) nor duration ($p = 0.6$) of PCCA was significantly associated with BZD.

3.4.3. BZDs and hypoxemia

The BZD group had smaller seizure-associated oxygen desaturation ($p \ll 0.001$) [Table 1&Fig. 2D]. To determine the phase of the seizure in which SRIs may have an effect, we looked at both seizures that remained focal (NCS) and the focal (NCS) phase of seizures that progressed to convulsions, and found smaller oxygen decreases in this combined analysis ($p = 0.004$). And then, we looked at the convulsive phase separately and confirmed that there were no significant differences between BZD and control group regarding oxygen decrease in the convulsive/postconvulsive phase ($p = 0.9$).

When absolute SpO_2 nadirs were analyzed, there was a significant difference between BZD and control groups in the preconvulsive ($p = 0.005$) but not in the convulsive/postconvulsive phase ($p = 0.9$).

3.4.4. Electroclinical seizure features

Postictal generalized EEG suppression was present in 18/28 (64.3%) BZD group and 115/166 (69.3%) control GCS ($p = 0.6$). There were no statistical differences regarding the RR of PGES when comparing BZD vs control ($p = 0.6$). However, BZD group was significantly associated with shorter PGES duration ($p = 0.02$), shorter convulsive phase duration ($p = 0.016$), and a trend toward shorter seizure duration ($p = 0.05$). On the contrary, in NCS, no difference was found in seizure duration ($p = 0.1$).

Based on these findings, we compared the group on both SRIs and BZDs (SRI/BZD) with SRI and BZD groups, to assess a possible additive effect upon the ICA. In the SRI/BZD group, ICA was seen in 4/10 (40%) seizures. There were no significant differences between SRI/BZD and SRI ($p = 0.226$) or BZD groups ($p = 0.463$) in ICA incidence. Similarly, mean apnea duration did not differ between SRI/BZD (21.5 s ± 1.3) and SRI (27.6 s ± 22.9) [$p = 0.705$] or BZD (14.5 s ± 7.2) [$p = 0.059$] groups.

4. Discussion

Our findings suggest that SRIs and BZDs may influence ICA and electroclinical seizure characteristics. Seizures in the SRI group were associated with lower ICA incidence and smaller oxygen desaturations, but they were not related to ICA duration, seizure duration, PGES, or PCCA. On the other hand, BZDs were associated with shorter ICA duration and smaller oxygen desaturations, but not with ICA incidence. In addition, in the BDZ group, GCS had shorter duration, as well as shorter PGES durations. In effect, both classes of drugs seem to influence ICA, and further, BZDs were also associated with reduced seizure severity, in terms of shorter GCS and PGES.

Ictal central apnea may be benign in the majority of cases, but may pose danger when prolonged [6–8], and has been linked to SUDEP and near-SUDEP cases [7,8]. Stimulation studies have shown that seizure spread to the limbic/paralimbic mesial temporal lobe structures is the most likely mechanism for inhibition or disruption of brainstem respiratory neuronal function in the medulla [37–39]. Postconvulsive central apnea appears to be a more deleterious phenomenon and has been linked to SUDEP and near-SUDEP cases [2,28]. Such breathing dysfunction propensity may result from longstanding injury to critical brainstem respiratory control structures, shown in imaging [3,40] and pathological studies [4] to be significantly damaged in patients with intractable epilepsy who succumb to SUDEP. Gray matter volume decline in periaqueductal gray, mesencephalic reticular formation, and raphe nuclei in SUDEP and high SUDEP risk patients suggests damage to structures that can influence breathing [41,42]. Neuropathological examination of SUDEP brainstems [4] shows structural injury in neuropeptidergic and monoaminergic systems, specifically somatostatin neurons and neurokinin 1 receptors, and serotonin transporter activity, in the medullary raphe and rostral ventrolateral medulla, in the region where the pre-Botzinger complex nucleus is located. Specifically, these findings indicate dysfunction of serotonergic and other inputs into respiratory nuclei and provide crucial anatomical and functional substrates that likely mediate respiratory dysfunction seen in near-SUDEP/SUDEP patients.

Serotonergic raphe neurons in the brainstem, which play a major role in chemoreception [9] and arousal [10], have long been suspected to play a role in SUDEP and SIDS [13,14]. The DBA1 & DBA2 mouse models of seizures and SUDEP have serotonergic abnormalities and exhibit fatal apnea in the postictal state if not resuscitated [16,43]. Respiratory arrest and death are preventable with SRI pretreatment [17,18] most likely due to promotion of respiratory rhythmogenesis and/or arousal rather than increased ventilation [17]. In human seizures, SRIs were found to correlate with reduced severity of hypoxemia [19], a finding confirmed in our study. These SRI effects were previously unexplained, since no reduction in seizure severity was noted [19]. Our findings suggest that ICA is a likely explanation for ictal hypoxemia, and mitigation of hypoxemia is primarily mediated by SRI prevention of ICA occurrence. However, SRIs did not shorten ICA duration, suggesting that this is driven by factors other than serotonergic tone. Bateman et al. [19] did not study ICA incidence but made a similar observation on the absence of SRIs' impact on ICA duration and hypoxemia duration. In our study, SRIs did not influence electroclinical seizure characteristics, including PGES, which is unsurprising since therapeutic SRI doses have little anticonvulsant effect [19,44]. Serotonin reuptake inhibitors can display proconvulsant properties only at toxic doses [45]. In one study, SRI use in patients with epilepsy neither protected nor elevated seizure-related mortality [46]. However, seizure-related deaths were a broad category, not limited to SUDEP. Further, mood and anxiety disorders (usually treated with SRIs) are associated with worse seizure control and thus, possibly increased mortality risk [47].

Gamma-aminobutyric acid, a major respiratory neurotransmitter along with glutamate and glycine, is responsible for tonic inspiratory and expiratory neuronal inhibition and contributes to respiratory rhythm generation [20,48] and vagal ventilatory reflexes [49].

Benzodiazepines are positive allosteric modulators of GABA receptors [21,22]. Therapeutic doses, in the absence of other respiratory suppressants, do not significantly reduce respiration but can do so in healthy subjects in high doses or with rapid intravenous administration [24]. On the contrary, therapeutic dose of BZDs may have stimulant respiratory effects, by enhancing phase switching and increasing respiratory rate; BZDs have been used effectively to prevent central sleep apneas [50]. Animal studies show augmentation in resting respiratory rate [25], due to shortened inspiratory and/or expiratory cycles; in a Rett syndrome mouse model, prone to severe apneic episodes, both BZD and a serotonin agonist showed significant apnea reduction [51].

We found BZDs to be associated with shorter ICA duration and with less profound decreases in SpO_2 and nadirs in the preconvulsive phase of GCS, without reducing seizure duration. In contrast to SRIs, BZDs significantly mitigated seizure severity through shortened convulsive phases of GCS. Benzodiazepines were associated with shorter PGES durations, which may be explained by their effects on shortening the generalized convulsive phase, and so patients on these drugs may recover faster from GCS; PGES is associated with greater postictal obtundation and slower recovery [52]. Similar to SRI use, one study showed increase incidence of all-cause mortality in patients with delayed development and nitrazepam usage, mostly due to aspiration pneumonia [53]. On the other hand, recent evidence suggests that SUDEP incidence may be higher in patients not on BZDs [54].

We did not find an additive effect upon ICA in the SRI/BZD group. This may be due to a small number of patients on both drugs, unbalanced groups, or the different effects of each drug on ICA, decreasing occurrence vs shortening ICA.

In our study, we found no effect of either class of drug on PCCA, suggesting that PCCA may have a higher threshold for prevention effects than ICA or else, the number of PCCA seizures was too small for an effect to be seen. A recent study with a larger number of seizures (558 in 218 patients) found that longer ICA duration was related to PCCA presence [27], and therefore, preventing ICA may have relevance in the prevention of PCCA.

Similarly, we did not find any effect of either class of drug on hypoxemia after GCS. Unfortunately, we did not have CO_2 measurements, which are a more reliable indicator of respiratory depression after a seizure than hypoxemia, because of the nonlinear relationship between partial pressure of oxygen (PaO_2) and SpO_2.

Several other limitations exist in our study. The cohort studied is heterogeneous in several respects. The SRI group contains individuals with depression who potentially have lowered endogenous serotonergic tone, although this is difficult to define and quantify. Our study was not sufficiently powered to examine different types of SRIs, BZDs, and their dosages, and there was no objective measure of the SRIs or BZDs use by the patients, for example, by measuring serum levels. Thus, a prospective controlled study examining types and dosage of SRIs and BZDs and blood levels will be necessary to confirm our findings. We also did not examine comparative effects of other seizure medications on breathing and electroclinical seizure characteristics, primarily because these do not have any known direct impact on respiration. However, they may influence other electroclinical seizure features and merit further study. Other confounding variables may have influenced our findings, although we found no differences between SRI, BZD, and control groups in gender, age, epilepsy duration, awake and sleep states, epilepsy type, or oxygen administration and postictal intervention. Larger studies with increased number of PCCA and ideally with CO_2 measurements would be crucial to confirm a possible protective effect of SRIs and/or BZDs on respiratory depression after GCS.

5. Conclusions

This study suggests that SRIs and BZDs may influence ICA and hypoxemia during seizures, both of which have been implicated in SUDEP pathomechanisms and are potential pharmacological SUDEP interventions. Benzodiazepines may have beneficial effects on electroclinical seizure features associated with reduced seizure severity. The importance of this study is that it may form the basis of a prospective randomized study of SRIs and BZDs in patients with epilepsy to determine their possible role in human SUDEP risk reduction.

Declaration of Competing Interest

Nuria Lacuey, Rita Martins, Johnson P. Hampson, Kingman Strohl and Catherine Scott report no disclosures.

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