A retrospective study on pregabalin toxic cases referred to poison control Center

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KEYWORDS
Pregabalin,
Neuropathic Pain,
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ABSTRACT

Pregabalin is a psycho-active medicinal drug that exhibits analgesic, anticonvulsant, anxiolytic, and antidepressant effects. In the United States, pregabalin is approved for the treatment of neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, epilepsy (partial-onset seizures), and fibromyalgia. The aim of the study them to study the relation between pregabalin toxicity and sociodemographic data (age - sex- occupation), outcome, risk factors of pregabalin toxicity, and the relation between pregabalin abuse and abuse of other drugs. Our retrospective descriptive study was conducted on 70 patients referred to the poison control center (PCC) in Ain-Shams University Hospital due to acute toxicity with pregabalin and admitted to the intermediate or intensive care unit (ICU). There was a very high statistically significant relationship between mode of intoxication regarding sex, occupation, and co-ingestion. There was no statistically significant relationship between the dose group regarding the duration of stay, coma degree, CNS manifestations, and arterial blood gases. There was a statistically significant relationship between co-ingestion and admission, duration of stay, coma grade, CNS manifestation, and ABG. All the 70 cases showed complete recovery, no complications, and no cases died. Pregabalin is nearly safe when used in therapeutic doses and its toxicity appears when it was taken with other drugs of abuse.

Introduction

Pregabalin is a psychoactive prescription medication that acts as an analgesic, anticonvulsant, anxiolytic, and antidepressant. It was introduced in 2004 in the European Union and the United States of America under the trade name Lyrica (Pfizer, NY, USA). Pregabalin is authorized in the European Union (-EU-) for the treatment of epilepsy, neuropathic pain, and generalized anxiety disorder. Pregabalin was the first medication authorized by the United States Food and Drug Administration (FDA) for the treatment of fibromyalgia (Boomershine, 2010). Pregabalin is authorized to treat neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, epilepsy (partial-onset seizures), and fibromyalgia in the United States (Chiappini and Schifano, 2016).

The typical therapeutic dose of pregabalin is 150–600 mg per day divided into 2–3 doses. Pregabalin has been identified within the 30 most prescribed medications in the USA in 2011 (Grosshans et al., 2013). Post-mortem blood concentrations of pregabalin in individuals prescribed the drug were reported to range from 0.4 to 17 mg/L (median 5.6 mg/L) in femoral blood and 1.5 to 11 mg/L (median 4.6 mg/L) in heart blood (Barallon, 2014).

However, the chemical is often used off-label for a variety of clinical diseases, including bipolar disorder; alcohol/narcotic withdrawal states; attention-deficit/

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hyperactivity disorder; restless legs syndrome; trigeminal neuralgia, and non-neuropathic pain syndromes (Kruszewski et al., 2009).

Pregabalin is increasingly being reported to have a high risk of abuse (Piskorska et al., 2013). Pregabalin prescribing has grown 350% in the United Kingdom during the last five years (Spence, 2013).

Persheim et al. (2013) examined developments in Norway's drug re-imbursement system from 2008 to 2011 in terms of expenditures on possibly addictive medicines in patients with severe/non-malignant chronic pain and discovered that about one-third of accepted applications were for pregabalin.

There is an anecdotal indication that the black market for gabapentinoids is increasing, with gabapentinoids purportedly available without a prescription through internet pharmacies (Schifano, 2014).

Pregabalin initially appeared in UK mortality records in 2006 and has been associated with an increasing number of deaths since then. Other nations, including the United States of America, France, and Finland, have found similar findings (Wills et al., 2014).

Pregabalin is classified as a Schedule V substance, suggesting that it possess abuse potential (albeit less potential than Schedule IV, III, and II drugs). In Egypt, the minister of health put pregabalin as schedule III. It was scheduled for at least two reasons. In clinical trials (N=5500 participants), the percentage of patients reporting euphoric effects was significantly greater in those receiving pregabalin vs placebo (4 percent versus 1%, respectively) (Zacny et al., 2012).

Pregabalin's package insert describes research in which the drug's manufacturers administered pregabalin (450 mg) and diazepam (30 mg) in separate sessions to 15 recreational users of sedative/hypnotic substances, including alcohol (it is possible that there was a placebo session but this is not stated). Both medicines raised subjective evaluations of "excellent drug effect," "high," and "liking" to the same extent. The patient information leaflet that comes with the prescription lists frequent adverse effects, one of which is "feeling high" (Zacny et al., 2012).

In this study, we have decided to study pregabalin because recently in Egypt, pregabalin has become prevalent among drug abusers as an alternative to tramadol. Among cases of drug toxicity in the Poison Control Center in Ain-Shams University, many cases are due to pregabalin toxicity.

The study aimed to study the relation between pregabalin toxicity and sociodemographic data (age - sex-occupation), outcome, risk factors of pregabalin toxicity, and the relation between pregabalin abuse and abuse of other drugs.

Material and Methods:

Our retrospective descriptive study was conducted on 70 patients referred to Ain-Shams University Hospital due to acute toxicity with pregabalin and admitted to intermediate or ICU after approval of the Institutional Review Board and the director of Ain-Shams poison control center (PCC). The confidentiality of all recorded data was kept.

All patients referred to PPC in Ain-Shams University Hospital due to acute toxicity with pregabalin or co-ingestion, patients who were admitted to inpatient or ICU were enrolled into the study.

Exclusion criteria:

The patients, who receive treatment, were discharged and did not need to be admitted to the hospital (outcome).

All patients were subjected to the following: full history, clinical examinations, and laboratory investigations.

Treatment measures

Different treatment measures applied to each patient according to the case included: 1) Emergency treatment: endotracheal intubation, oxygen administration, and mechanical ventilation. 2) Supportive treatment: intravenous fluids, H2 blockers, antibiotics, antiemetics, steroids, dopamine, and other vasopressors therapy. 3) Decontamination measures: emesis, lavage, and activated charcoal.

Outcome: complete recovery, recovery with complication and mortality.

Statistical analysis

By the end of the study, the recorded clinical data of the patients were tabulated for statistical study. The collected data were coded and verified before computerized data entry. The collected data were statistically analyzed using Statistical Package for the Social Science (SPSS) version 16 program and expressed in tables and charts. Categorical variables were described as numbers (%) and were analyzed for significance using the Chi-square test while numerical variables were described as mean ± SD and were analyzed using a one-way ANOVA test. P-value is considered statistically insignificant if >0.05, significant if <0.05 and highly significant when p-value <0.001.

Results:

Age showed no statistically significant relationship with mode of intoxication. There was no statistically significant relationship between mode of intoxication regarding sex, occupation, and co-ingestion (Table 1)

Table (1): Comparison between age, sex, occupation, and co-ingestion in different mode of intoxication in studied patients in Ain Shams Hospitals during the study (no= 70).

		Mode of intoxication			Total	p value
		Accidental Addict	Suicide	Accidental non addict		
Age (years)	Mean	24.8	26.3	26.1	---	0.863
	± SD	11.6	9.4	12.3		
Sex	Male	23 (56.1%)	10 (24.4%)	8 (19.5%)	41 (100%)	0.000**
	Female	1 (3.4%)	25 (86.2%)	3 (10.3%)	29 (100%)	
Occupation	Worker	19 (70.4%)	8 (29.6%)	0 (0%)	27 (100%)	0.000**
	Student	3 (20%)	10 (66.7%)	2 (13.3%)	15 (100%)	
	Not work	2 (7.1%)	17 (60.7%)	9 (32.1%)	28 (100%)	
Co- ingestion	Co-ingestion	23 (92%)	2 (8%)	0 (0%)	25 (100%)	0.000**
	Non co-ingestion	1 (2.2%)	33 (73.3%)	11 (24.4%)	45 (100%)	

P-value is insignificant if >0.05, *statistically significant when P-value <0.05, **statistically highly significant when P-value <0.001. SD: standard deviation.

There was no statistically significant (p-value > 0.05) relationship between the dose group regarding the duration of stay, coma degree, CNS manifestations, and ABG (Table 2).

Table (2): Comparison between duration of stay, coma degree, CNS manifestations and ABG within different dose groups in the studied patients in Ain Shams Hospitals during the study (no= 70).

		Dose group/day					Total	p-value
		1-5 tab	6-10 tab	11-15 tab	16- 20 tab	>20 tab		
Duration of stay	**1 day**	12 (27.9%)	28 (56.1%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	43 (100%)	0.461
	2 days	6 (24%)	12 (48%)	2 (8%)	1 (1%)	4 (16%)	25 (100%)	
	3 days	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	
Coma degree	**Coma I**	11 (33.3%)	18 (54.5%)	2 (6.1%)	0 (0%)	2 (6.1%)	33 (100%)	0.741
	Coma II	6 (18.2%)	21 (63.6%)	1 (3%)	2 (6.1%)	3 (9.1%)	33 (100%)	
	Coma III	1 (25%)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)	
CNS Manifestations	**Normal**	14 (31.8%)	24 (54.5%)	1 (2.3%)	2 (4.5%)	3 (6.8%)	44 (100%)	0.181
	Agitation	3 (23.1%)	8 (61.5%)	2 (15.4%)	0 (0%)	0 (0%)	13 (100%)	
	Convulsions	0 (0%)	10 (83.3%)	0 (0%)	0 (0%)	2 (16.7%)	12 (100%)	
	Extra pyramidal	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
ABG	**Normal**	14 (30.4%)	26 (56.5%)	1 (2.2%)	1 (2.2%)	4 (8.7%)	46 (100%)	0.461
	Metabolic Acidosis	3 (15%)	13 (65%)	2 (10%)	1 (5%)	1 (5%)	20 (100%)	
	Respiratory Acidosis	1 (25%)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)	

CNS: central nervous system, ABG: arterial blood gases**,** p-value is insignificant if >0.05, *statistically significant when p-value <0.05, **statistically highly significant when p-value <0.001. CNS: central nervous system,

There was a statistically significant (p-value <0.05) relation between co-ingestion and non-co-ingestion regarding admission, duration of stay, coma grade, CNS manifestation, and ABG (Table 3).

Table (3): Comparison between admission to inpatient or ICU, duration of stay, coma grade, CNS manifestations and ABG in patients co-ingestion with other drugs in Ain Shams Hospitals during the study (no= 70).

		Co- ingestion		Total	p value
		Co -ingestion	None		
Admission	In patient	4 (13.8%)	25 (86.2%)	29 (100%)	0.001*
	ICU	21 (51.2%)	20 (48.8%)	41 (100%)	
Duration of stay	1day	10 (23.3%)	33 (76.6%)	43 (100%)	0.009*
	2days	13 (52%)	12 (48%)	25 (100%)	
	3days	2 (100%)	0 (0%)	2 (100%)	
coma grade	Coma I	7 (21.2%)	26 (78.8%)	33 (100%)	0.004*
	Coma II	14 (42.4%)	19 (57.6%)	33 (100%)	
	Coma III	4 (100%)	0 (0%)	4 (100%)	
CNS Manifestations	Normal	10 (22.7%)	34 (77.3%)	44 (100%)	0.006*
	Agitation	6 (48.2%)	7 (53.8%)	13 (100%)	
	Convulsions	9 (75%)	3 (25%)	12 (100%)	
	Extra pyramidal	0 (0%)	1 (100%)	1 (100%)	
ABG	Normal	10 (21.7%)	36 (78.3%)	46 (100%)	0.001*
	Metabolic acidosis	11 (55%)	9 (45%)	20 (100%)	
	Respiratory acidosis	4 (100%)	0 (0%)	4 (100%)	

ICU: Intensive care unit, CNS: central nervous system, ABG: arterial blood gases, p-value is insignificant if >0.05, *statistically significant when p-value <0.05, **statistically highly significant when p-value <0.001.

The study showed that (65.70%) of cases of acute pregabalin intoxication in Ain Shams Hospitals have normal ABG, (28.60%) of cases have metabolic acidosis and (5.70%) of cases have respiratory acidosis (Figure 1).

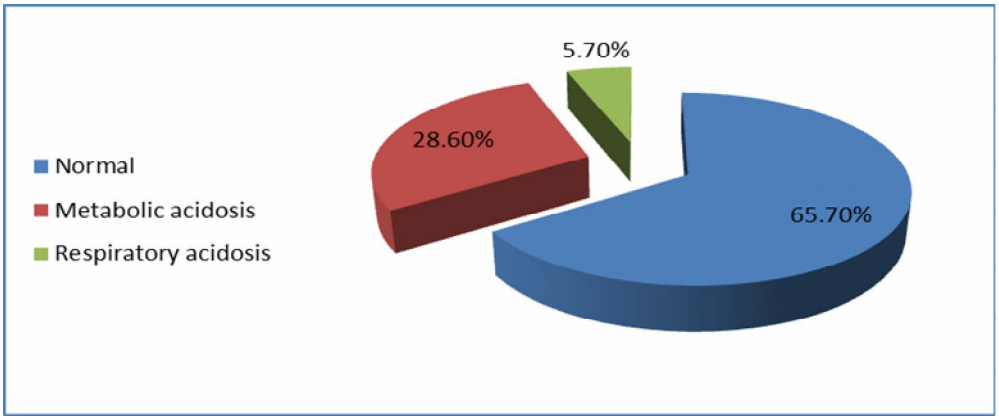

Fig. (1): Pie chart of arterial blood gases of cases of acute pregabalin intoxication in Ain Shams Hospitals during the study.

The study showed that (72.80%) of cases of acute pregabalin intoxication in Ain Shams Hospitals were treated by activated charcoal, (18.6%) of cases treated by gastric lavage, and (8.6%) treated by emesis and antidotes were not received in many cases (Table 4)

Table (4): Number of acute pregabalin toxicity cases who received treatment.

Procedure		Number
Decontamination	Induction of emesis	6
	Gastric lavage	13
	Activated charcoal	51
Enhancement of Elimination	No	70
	Multiple doses activated charcoal	0
	Dialysis	0
	Diuresis	0
Antidote	Yes	0
	No	70
Total		100

The study showed that (53%) of cases of acute pregabalin intoxication in Ain Shams Hospitals received IV fluids as a treatment, (27%) of cases were mechanically ventilated and (20%) of cases were on nasal oxygen (Figure 2).

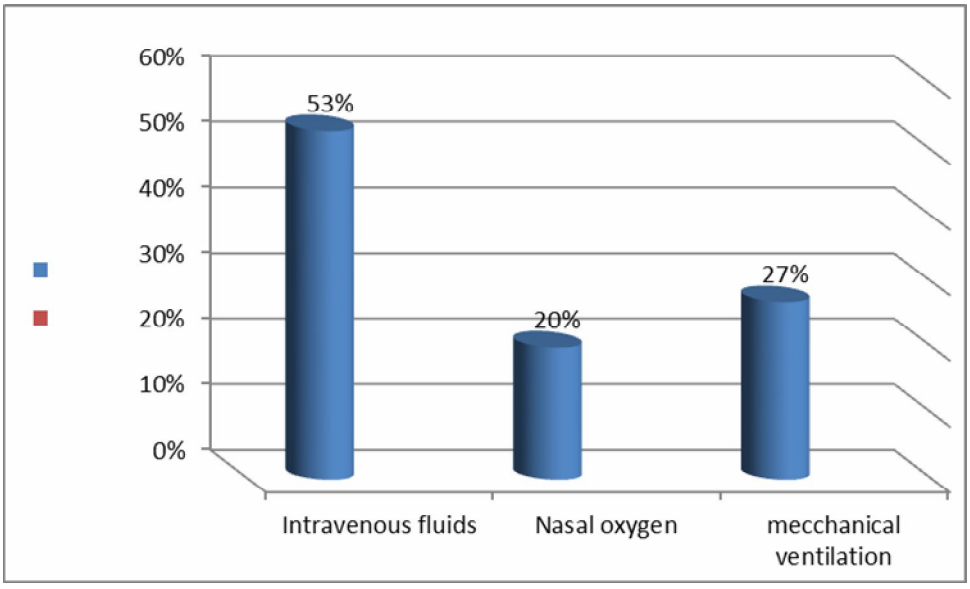

Fig. (2): Bar chart of distribution of supportive treatment of acute pregabalin intoxication in Ain Shams Hospitals during the study.

Discussion

Pregabalin is increasingly being reported as possessing a potential for misuse (Piskorska et al., 2013). In the UK, for example, pregabalin prescribing has increased by 350 in just 5 years (Spence, 2013).

The present study showed that the median age for studied patients was 25 years and the mean age was ± 24.2 years. It was found that 60% of patients fall in the age group 16-30 years. This agreed with Gahr et al. (2013) who found that the majority of patients were on average middle-aged (mean age 36 years), with Kriikku et al. (2014) who found that 79.6% of cases under the study were under the age of 40 years and also with Dworkin and Kirkpatrick (2005) in the USA who found that the majority of patients that abuse pregabalin is among young adults (18-29 years old) (53%).

In this study, the majority of patients were males (60%). This agreed with Gahr et al. (2013), Kriikku et al.)2014), and Dworkin and Kirkpatrick (2005) who found that pregabalin abuse was more common in males.

In the study, most of the addict patients showed a low socio-economic state (79%), because pregabalin is cheap, available, and easy to obtain. This agrees with Dworkin and Kirkpatrick (2005) who found that patients with a low economic state (60%), abuse pregabalin more than patients with a high economic state (40%).

In the present study, (35%) of cases were addicts, and only (15.7%) were accidental non-addicts. This agreed with Häkkinen et al. (2014) who found that drug abuse was associated with 48.1% of the pregabalin findings and pregabalin poisoning accounted for 10.1% of all pregabalin cases.

This study agreed with most of the studies done on pregabalin like Gahr et al. (2013), Yazdi et al. (2015), and Driot et al. (2016) who found that nearly all patients with an overdose of pregabalin or pregabalin toxicity had normal blood pressure, respiratory rate, and temperature.

Most of the patients under the present study with no co-ingestion had presented mainly in coma grade I (57.8%), while most of the studied patients with co-ingestion had presented mainly in coma grade II (56%). This agreed with Gahr et al. (2013) who found that the drug pregabalin caused mild effects on some components of driving performance but no serious CNS side effects were found.

Most of the cases presented by convulsions and agitation were co-ingesting other illicit drugs.

Only 21 cases have manifestations other than CNS manifestations. There were ten cases manifested by vomiting, nine cases with wheezes and crepitation, two cases manifested by palpitation, and only one case had urine retention. This may be explained by the fact that pregabalin may exercise its gamma-aminobutyric acid (GABA) actions via modulating GABA metabolism and reversing neuronal/glial amino acid transporters, resulting in the release of GABA for interaction with extra synaptic GABA receptors (Richerson and Wu, 2003).

Do et al. (2017) found that an 88-year-old patient with cervical spinal cord injury suffered from severe neuropathic pain which had been treated with 150-mg pregabalin per day. Dosage for the pregabalin increased from 150 mg/d to 225 mg/d because of the severity of his pain. That afternoon, he presented with drowsiness and confusion, ABG was performed and there was respiratory acidosis with CO2 retention. He required tracheal intubation and ventilation. After discontinuation of pregabalin, the patient became normal.

The present study agreed with Gahr et al. (2013) who found that around half of the patients had a history of misuse or dependency on psychiatric medications other than pregabalin (49.1 %).

It is similar to the results of Kriikku et al. (2014) discovered that in 43.2 percent of the cases studied, five or more other medications were present in addition to pregabalin. The maximum concentration of additional medicines found in the examined sample was nine. Pregabalin was most frequently associated with benzodiazepines (90.8%), cannabis (54.4 %), and amphetamines (44.2 %). This also agreed with Eastwood and Davison (2016) who found that pregabalin was found in co-ingestion with other drugs (50 cases) benzodiazepine, (20 cases) morphine, (19 cases) alcohol, (15 cases) cocaine, (13 cases) methadone and (10 cases) heroin. Elliott et al. (2017) found that antidepressants, opioids, benzodiazepines, opiates, alcohol, antipsychotics, cocaine, cardiac medications, amphetamines, cannabis, anticonvulsants, and antihistamines were the most frequently discovered drug categories.

In Germany Erdoğan et al. (2011) found a patient with no cardiac history treated with 300 mg/kg pregabalin due to neuropathic pain, developed heart failure. After stopping pregabalin, the situation regressed. There are also three cases showing chronic heart failure and low ejection fraction by using pregabalin at a dose of 600 mg/day. This is due to pregabalin's effect on calcium channels and its ability to decrease potassium-dependent calcium entry. Rapid and unexplained weight gain is considered to be a symptom of fluid retention, which can aggravate congestive heart failure.

This study agreed with Aksakal et al. (2012) who found that a 65-year-old lady was hospitalized with dizziness and syncope. For eight months, she had been taking pregabalin 300 mg daily. With a heart rate of 39 beats per minute, an electrocardiogram revealed a full atrioventricular (AV) block and right bundle-branch block. This is due to pregabalin's impact on cardiac L-type calcium ++ channels.

In our study, (65.70%) of cases had normal ABG, (28.60%) had metabolic acidosis, and (5.70%) had respiratory acidosis. Abnormal ABG was more in studied patients with co-ingestions.

Kyung (2017) found that an 88-year-old patient had been treated with 225-mg pregabalin per day.He presented with drowsiness and confusion. Arterial blood gases were performed and there was respiratory acidosis with CO2 retention. He required tracheal intubation and ventilation.

Intravenous fluids administration was included in the majority of the patients (53%), mechanical ventilation in 27%, and oxygen alone in 20% of patients.

This agreed with Eastwood (2010) who found that a 54-year-old male presented to the Emergency Department (ED) after self-reported ingestion of 8.4 g of pregabalin without ingestion of any other drugs. Approximately 3 h post-ingestion, he deteriorated, becoming unresponsive with coma III. Due to his reduced consciousness level, he was intubated for airway protection and mechanically ventilated. His GCS improved over the next 24 h, enabling extubation 26 h after admission to ICU and discharge from hospital after three days.

And this also agreed with Miljevic (2012), there was a 54-year-old male in Russia who has been treated with 450 mg of pregabalin daily for generalized anxiety disorder. On presentation, he was the conscious and alert, cardiovascular stable, and respiratory rate of 18/min. On presentation, he had neither an electrocardiogram (ECG) nor arterial blood gases or renal function

performed. The patient was admitted more than two hours after ingestion and as he was clinically stable he was not administered any drug and was observed for signs of clinical deterioration for one day.

The patient was managed with general supportive care only, anticipating a spontaneous recovery. All the 70 cases of the study recovered with no complications.

This study agreed with Eastwood and Davison (2016) who concluded that the deaths in their study were due to multiple drug toxicity not due to pregabalin alone.

Conclusions:

All the 70 cases showed complete recovery, no complications, and no cases died. Pregabalin is nearly safe when used in the therapeutic dose and its toxicity appears when it was taken with other drugs of abuse.

Recommendations:

- There should be a method to detect pregabalin in blood or urine especially in drug abusers.
- Pregabalin is safe in its therapeutic dose and so it can be used in the treatment of seizures and fibromyalgia.
- There should be more studies to know the effect of pregabalin on the cardiovascular system, renal, and liver when pregabalin is used for a long time.

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دراسة مرجعية على حالات التسمم بالبريجابالين المحولة لمركز علاج السموم

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بريجابالين هو عقار مضاد للاختلاج تمت إجازته في عام ٢٠٠٦ كعلاج لآلام الأعصاب المصاحبة للاعتلال العصبي السكرى والألم العصبي التالي للحلأ النطاقي والألم العضلي الليفي وعلاج اضطراب القلق العام. ويعتقد أن آلية السمية تكون نتيجة تثبيط الجهاز العصبي المركزي مع فشل في الجهاز التنفسي ومضاعفات القلب. تهدف هذه الدراسة إلى تحليل نتائج سمية البريجابالين وتحديد العلاقة بين سوء استخدام البريجابالين وإساءة استخدام المخدرات الأخرى. تعد هذه الدراسة دراسة مستعرضة بأثر رجعي. تم اجراء الدراسة في مركز علاج التسمم في مستشفيات جامعة عين شمس في الفترة من يناير ٢٠١٨ حتى ديسمبر ٢٠١٨، للعثور على العلاقات الإحصائية بين سمية البريجابالين والعوامل المختلفة. وقد تبين وجود علاقة ذات دلالة إحصائية بين حالات التسمم فيما يتعلق بالجنس والمهنة وتناول مواد أخرى بجانب البريجابالين. لم تكن هناك علاقة ذات دلالة إحصائية بين الجرعة المتعاطة فيما يتعلق بمدة الإقامة بالمستشفى ودرجة الغيبوبة والآثار الظاهرة على الجهاز العصبي المركزي وغازات الدم الشرياني. كانت هناك علاقة ذات دلالة إحصائية بين تناول مواد أخرى بجانب البريجابالين و دخول للمستشفى ومدة الإقامة ودرجة الغيبوبة والآثار الظاهرة على الجهاز العصبي المركزي وغازات الدم الشرياني. ومن هذه الدراسة نخلص إلى أن البريجابلين يكاد يكون آمنًا عند استخدامه في حدود الجرعة العلاجية وتظهر سميته عند تناوله مع عقاقير أخرى مسببة للإدمان.