Case report
Ενδιαφέρουσα περίπτωση

A case of pregabalin intoxication

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Pregabalin, or S-(+)-3-isobutylgaba, is a lipophilic analogue of GABA. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. It is currently being licensed for epilepsy, neuropathic pain, and generalized anxiety disorder. There are few case reports that have demonstrated safety of pregabalin in case of intoxication. We report here a case of pregabalin toxicity with a moderate pregabalin concentration that was successfully managed with conservative treatment only. The case report describes a 54-year-old man who was treated with pregabalin for generalized anxiety disorder. After having experienced a significant stress on a job the patient ingested huge amount of pregabalin (4,2 r) together with bromazepam (21 mg) and chlorimipramine (125 mg). On presentation he was conscious and alert with a stable condition of cardiovascular and respiratory systems. The serum pregabalin concentration was 20.8 mg/L but the patient did not have any signs of toxicity. Thanks to his good and stable somatic condition the patient was managed with supportive treatment only. Although anecdotal, our case report points toward safety of pregabalin following deliberate self-poisoning. Our observation is in accordance with the recent international literature underlining that pregabalin was listed as the drug injested in only 1% of fatalities, usually in combination with other drugs.

Key words: Pregabalin, intoxication, psychopharmacology, anxiety.

Introduction

Pregabalin, or S-(+)-3-isobutylgaba, is a lipophilic analogue of GABA substituted at the 3-position to facilitate diffusion across the blood-brain barrier. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically.[1,2] Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. The alpha-2-delta site is an auxiliary protein associated with voltage-gated calcium channels. The binding of pregabalin and its structural analogues at the alpha-2-delta site has been shown

to reduce depolarization-induced calcium influx at nerve terminals, with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenalin, substance P, and calcitonin gene-related peptide (CGRP).[3–5] Pregabalin has no effects on GABA-ergic mechanisms. It is currently being licensed for epilepsy, neuropathic pain, and generalized anxiety disorder.[6,7]

We report here a case of isolated pregabalin toxicity with the highest recorded pregabalin concentrations to date that was successfully managed with conservative treatment only.

Case report

A 54-year-old male, with no relevant medical history, has been treated with 450 mg of pregabalin daily for generalized anxiety disorder. After having experienced a significant stress on a job the patient ingested 4.2 g of pregabalin together with 21 mg of bromazepam and 125 mg of chlorimipramine in order to relax. On presentation he was conscious and alert with a Glasgow Coma Score (GCS) of 30, cardiovascularly stable with a heart rate of 84 bpm and blood pressure of 110/70 mmHg, with a temperature of 36.8 °C and respiratory rate of 18/min. Pregabalin concentrations were measured in the plasma sample that had been obtained on admission using a previously described method.[2] Pregabalin concentration at the time of admission was 20.8 mg/L. A comprehensive toxicological screening of urine by gas chromatography mass-spectrometry detected only chlorimipramine and bromazepam which he had also ingested. As he was clinically stable on presentation, he had neither an electrocardiogram (ECG) nor arterial blood gases or renal function performed. The patient was admitted more then 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 clinical toxicology review was undertaken and it was decided that the patient should be managed with general supportive care only, anticipating spontaneous recovery. He remained cardiovascularly stable, with no signs of deterioration of his consciousness. As the patient had no ongoing features of pregabalin toxicity he was discharged after one day and his psychiatric treatment continued.

Discussion

We have described here a case of severe toxicity following self-poisoning, with pregabalin, bromazepam and chorimipramine. The serum pregabalin concentration in this patient of 20.8 mg/L is moderate compared to those previously reported, but we managed the patient with supportive treatment only.

Very little information is available regarding therapeutic serum/plasma concentrations of pregabalin. However, one report states that in samples collected at random times relative to dose from patients maintained on 600 mg/day, plasma pregabalin concentrations ranged from 0.9–14.2 mg/L.[8]

There are three previous reported cases of pregabalin toxicity following deliberate self-poisoning.[9–11] One patient presented with mild drowsiness following ingestion of an unknown amount of pregabalin and required supportive management only; that patient had pregabalin concentration of 29 mg/L 9 h post-ingestion.[10] The other case was a patient who ingested 11.5 g of pregabalin, together with 32 g of lamotrigine, who initially developed abnormal facial and generalised body movements and drowsiness.[9] The "initial" pregabalin plasma concentration was approximately 60 mg/L, but the sample also contained lamotrigine at a concentration of approximately 45 mg/L. Finally, the third patient had "initial" pregabalin plasma concentration of about 65 mg/L and had developed coma after 3 hours.[11]

Apart from these case reports, there is limited information available about the frequency of pregabalin self-poisoning. For example, the American Association of Poison Control Centers annual reports do not include data on pregabalin, except when it was involved in a fatality.[12] In terms of pregabalin-associated fatalities in these annual reports, pregabalin was not mentioned in any fatalities prior to 2006. Between 2006 and 2008, pregabalin was listed as a drug used/ingested in approximately 1% of fatalities; none of these cases were isolated pregabalin cases.[12]

Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations within an hour of dosing and up to 90% oral bioavailability.[9] Pregabalin undergoes negligible metabolism in humans (<2% metabolism) and is excreted virtually unchanged by the kidneys. Pregabalin does not bind to plasma proteins.[13] It is also not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. Unwanted clinical effects, including dizziness, somnolence, weight gain, psychosis and myoclonus, have been reported during therapeutic use of pregabalin at doses of 50–600 mg/day.[14,15]

Pregabalin has a low volume of distribution (approximately 0.5 L/kg), low molecular weight (approximately 159 Da) and is not protein bound.[16] These pharmacokinetic features make it likely that elimination of pregabalin would be enhanced by the use of extra-corporeal methods such as haemodialysis and/or haemofiltration. Our case report describes a patient with a moderate serum pregabalin concentration who was managed with supportive treatment only and did not have any signs of toxicity. Although anecdotal, our case report points toward safety of pregabalin following deliberate self-poisoning.

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Περίπτωση τοξίκωσης από πρεγκαμπαλίνη

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Η πρεγκαμπαλίνη ή S(+)-ισοβουτυλο-γ-αμινοβουτυρικό οξύ είναι λιπόφιλο ανάλογο του GABA (γ-αμινοβουτυρικού οξέος). Αν και η πρεγκαμπαλίνη σχετίζεται δομικά με το GABA είναι ανενεργή στους υποδοχείς του GABA και δεν φαίνεται να μιμείται τη φυσιολογία του GABA. Η πρεγκαμπαλίνη δεσμεύεται ισχυρά στην άλφα-2-δέλτα (α2δ) υπομονάδα των τασεοεξαρτώμενων διαύλων ασβεστίου στο Κεντρικό Νευρικό Σύστημα. Έχει λάβει άδεια χρήσης στην επιληψία, στον νευροπαθητικό πόνο και στη διαταραχή γενικευμένου άγχους. Υπάρχουν ελάχιστες αναφορές περιπτώσεων που καταδεικνύουν την ασφάλεια της πρεγκαμπαλίνης σε περιπτώσεις υπερδοσολογίας. Παρουσιάζεται περίπτωση τοξικότητας πρεγκαμπαλίνης με μέτρια συγκέντρωση πρεγκαμπαλίνης στον ορό σε σύγκριση με τις προαναφερθείσες περιπτώσεις και που αντιμετωπίστηκε επιτυχώς μόνο με συντηρητική αγωγή. Η περίπτωση αφορά σε 54χρονο που ελάμβανε πρεγκαμπαλίνη για διαταραχή γενικευμένου άγχους. Μετά την εμφάνιση ιδιαίτερα έντονου στρες στην εργασία του, ο ασθενής έλαβε μεγάλη ποσότητα πρεγκαμπαλίνης (4,3 g) σε συνδυασμό με βρωμαζεπάμη (21 mL) και χλωριμιπραμίνη (125 mg). Η συγκέντρωση πρεγκαμπαλίνης στον ορό ήταν 20,8 mg/L αλλά ο ασθενής δεν είχε σημεία τοξικότητας. Χάρη στη σταθερά καλή σωματική του κατάσταση, ο ασθενής αντιμετωπίσθηκε με υποστηρικτική αγωγή μόνο. Η περίπτωση αυτή, αν και μεμονωμένη, παρέχει ενδείξεις υπέρ της ασφάλειας της πρεγκαμπαλίνης μετά από λήψη υπερβολικής δόσης. Η παρατήρησή μας έρχεται σε συμφωνία με την πρόσφατη διεθνή βιβλιογραφία όπου επισημαίνεται το γεγονός ότι η πρεγκαμπαλίνη έχει εκτιμηθεί ότι συμβάλλει μόνο κατά 1% στη θνησιμότητα από δηλητηριάσεις, συνήθως συγχορηγούμενη με άλλα φάρμακα.

Λέξεις ευρετηρίου: Πρεγκαμπαλίνη, τοξίκωση, ψυχοφαρμακολογία, άγχος.

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