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Letter to the Editors

Six cases of (severe) hypoglycaemia associated with gabapentin use in both diabetic and non-diabetic patients

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Case reports

Gabapentin, a gamma-aminobutyric acid (GABA) analogue, is a commonly used drug in the treatment of partial epilepsy and peripheral neuropathic pain. Although the exact mechanism of action has not been elucidated, the binding site has been identified as the alpha$_2$-delta subunit of the voltage-gated calcium channels in the neocortex and hippocampal regions of the brain [1]. Hypoglycaemia in diabetic patients is defined as abnormally low plasma glucose concentrations (<3.9 mmol l^{-1}) accompanied by symptoms like palpitations, hunger, tremor, sweating and neuroglycopenic symptoms [2]. Although blood glucose fluctuations are a possible adverse drug reaction (ADR) of gabapentin [1], hypoglycaemia in relation to this drug was found in just one publication [3].

We received six cases of (severe) hypoglycaemia in both diabetic and non-diabetic patients exposed to gabapentin, which occurred between July 2002 and July 2012. Two cases are described in more detail below.

Patient A, a 36-year-old female with a history of a complex regional pain syndrome, presented to the hospital after syncope. Recently she started treatment with gabapentin for neuropathic pain (1800 mg daily) and pyridostigmine for a complex regional pain syndrome (180 mg daily). The drugs were started 1 month (gabapentin) and 13 days (pyridostigmine) prior to admission. On the day of admission she was not feeling well and complained of light-headedness without nausea or emesis. Prior to the syncope she had spots in front of her eyes. These complaints had been present to a lesser extent in the previous months. Upon admission she was hypoglycaemic (blood glucose 1.6 mmol l^{-1}) and was treated with intravenous glucose administration. Pyridostigmine was withdrawn and the dose of gabapentin was reduced, leading to recovery. No antidiabetic concomitant drugs were mentioned.

Patient B was a 54-year-old non-diabetic female with a history of re-entry tachycardia for which she was treated with ablation. She was hospitalized for hypoglycaemia 3 weeks after starting gabapentin in a dose reducing schedule for pain after surgery for a cervical herniated nucleus pulposus. The duration of hypoglycaemia was 2 days with a minimum blood glucose value of 1.3 mmol l^{-1}. After withdrawal of gabapentin and treatment with intravenous glucose she recovered. No concomitant medication was reported.

Information regarding four additional cases, including a causality assessment based on the Naranjo criteria [4], is described in Table 1. Previously, one case report was published describing hypoglycaemia in relation to gabapentin use. This concerned a 58-year-old non-diabetic female with end stage renal disease who had been on peritoneal dialysis for 6 years [3]. She received 4200 mg of gabapentin weekly for neuropathic pain, where 900 mg weekly was recommended for patients undergoing haemodialysis. Nadir blood glucose was 1.9 mmol l^{-1} which was corrected with dextrose. The patient recovered 3 days after withdrawal of gabapentin. Although renal failure is associated with hypoglycaemia, other causes were ruled out by the authors.

Although a mechanism for gabapentin-induced hypoglycaemia has not been established, two possibilities could be considered. First, GABA is present in the cytoplasm, insulin granules and microvesicles of the β-cells of the pancreas and can bind to the $GABA_A$ and $GABA_B$ receptor. Activation of the $GABA_B$ receptor is thought to inhibit insulin secretion whereas activation of the $GABA_A$ receptor leads to membrane depolarization and subsequent calcium influx, allowing the release of insulin [5]. Hypothetically, gabapentin-induced $GABA_A$ receptor activation could stimulate insulin release resulting in hypoglycaemia. Alternatively, direct binding to the alpha$_2$-delta$_2$ receptor of the voltage-gated calcium channels could also provide a

Table 1
Detailed patient characteristics

Patient	Gender	Age (years)	Diabetes mellitus (Y/N)	Positive dechallenge (Y/N)	Nadir blood glucose (mmol l^{-1})	Causality§
A	Female	36	NR*	Y	1.6	Possible
B	Female	54	N	Y	1.3	Probable
C	Male	59	Y	N†	NR	Possible
D	Female	71	Y	Y	NR	Probable
E	Male	68	Y	Y	1.7	Possible
F	Male	60	Y	N‡	3.9	Possible

§Causality assessment was based on the Naranjo criteria [4]. *No concomitant antidiabetic drugs were reported. †No dechallenge performed. Patient recovered after adjusting the daily time of gabapentin administration. ‡No dechallenge performed. NR = not reported.

pharmacological explanation. There are different varieties of this type of calcium-channel, consisting of several combinations of α1, β, α2-δ and γ subunits. Gabapentin has been shown to bind directly to the α2-δ1 and α2-δ2 subunit of the voltage-gated calcium channels [6]. The former is probably responsible for the neuronal activity of gabapentin, whereas the latter is found in, among others, the pancreas [7]. As with $GABA_A$ receptor activation, binding to the α2-δ2 subunit could result in calcium influx and subsequent insulin release.

In conclusion, these cases suggest that hypoglycaemia can occur in both diabetic and non-diabetic patients using gabapentin, possibly through $GABA_A$ receptor activation or binding to the α2-δ2 subunit of pancreatic voltage-gated calcium channels. In our opinion, patients using gabapentin who experience symptoms indicative of hypoglycaemia should be examined accordingly.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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