Gabapentin and severe hypoglycaemia

Introduction

Gabapentin (Neurontin®) is indicated for the treatment of *partial epilepsy* and *peripheral neuropathic pain, such as diabetic neuropathy and post-herpetic neuralgia* and was granted marketing authorization in the Netherlands in 1999. Gabapentin is structurally related to gamma-amino-butyric acid (GABA) but exerts its effect to other receptor systems than $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate (NMDA). Its binding site has been defined as the $alpha_2$-delta subunit of voltage dependent calcium-channels in the neocortex and hippocampus regions of the brain [1].

Hypoglycaemia in diabetic patients is defined as abnormally low plasma glucose concentration that exposes the individual to potential harm. During hypoglycaemia, symptoms like palpitations, tremor, hunger, sweating and neuroglycopenic symptoms are accompanied by measured plasma glucose concentration below 3.9 mmol/l (70 mg/dl). In the case of severe hypoglycaemia, the event requires assistance of another person to administer carbohydrates, glucagon or resuscitative actions [2].

The SmPC of gabapentin mentions blood glucose fluctuations in diabetic patients as a potential adverse drug reaction with unknown frequency [1].
The current observation describes the association between gabapentin and severe hypoglycaemia in diabetic and non-diabetic patients.

Reports

On January 21, 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained six reports (with one duplicate report by the marketing authorization holder) of a decrease in blood glucose or of severe hypoglycaemia associated with the use of gabapentin.

Table 1. Reports of decreased blood glucose and hypoglycaemia associated with the use of gabapentin.

Patient, Sex, Age, Reporter	Drug(s) Indication for use	Concomitant medication#	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
A 47818* M, 51-60 Pharmacist	gabapentin 3 dd 300mg diabetic foot ulcer, human insulin insulin isofane	prednisolone 0,37% eye drops , omeprazole, gramicidin neomycin-sulphate polymyxin B-sulphate eye drops, alfuzosin	drug interaction, hypoglycaemia	6 weeks administration time change recovered
B 48765* M, 51-60 MAH	omeprazole 1 dd 20mg gabapentin 3 dd 300mg	non specified insulin, alfuzosin, gramicidin neomycin-sulphate polymyxin B-sulphate eye unguent	tremor, hypoglycaemia, unconsciousness, coma	1 day no change recovered

Patient, Sex, Age, Reporter	Drug(s) Indication for use	Concomitant medication[#]	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
C 110739 F, 31-40 CCMO	pyridostigmine 3 dd 60mg complex regional pain syndrome, gabapentin 3 dd 600mg neuropathic pain		hypoglycaemia	not reported discontinued recovered
D 136225 F, 51-60 Specialist doctor	gabapentin 300mg pain		hypoglycaemia	3 weeks discontinued recovered
E 36573 M, 61-70 Specialist doctor	gabapentin 1dd 300mg neuropathic pain	tramadol, glimepiride temazepam , paracetamol	hypoglycaemia	1 day discontinued recovered
F 141444 F, ≥71 Pharmacist	gabapentin 1-2 dd 400mg neuropathy		hypoglycaemic unconsciousness	2 day discontinued recovered
G 136643 M, 51-60 Pharmacist	gabapentin 3dd 300mg neuropathic pain	insulin aspart, insulin aspart protamine, metformin	blood glucose decreased	2 day no change unknown

* A 47818 and B 48765 are duplicate reports.

Some of the characteristics of the reports are described below:

In patient A/B, an insulin dependent diabetic, severe nocturnal hypoglycaemia's occurred after administration of gabapentin on 12h, 18h and 24h. Administration on 9h, 12h and 18h did not induce hypoglycaemia. Drug interaction with insulin was suspected. Since omeprazole was started on the same date, the marketing authorization holder (MAH) reporter mentioned omeprazole as suspect drug as well. Effects on blood glucose are not mentioned in the SmPC of omeprazole [3]. Systemic adverse events of ocular administered prednisolone are possible after intensified therapy, but the dosage in this patient is low. Hypoglycaemia is not mentioned in the SmPC of prednisolone containing eye drops [4].

Patient C was brought to the emergency department because of syncope; blood glucose was 1.6 mmol/l. Before fainting she saw 'black spots', which she had been seeing for a few months. Gabapentin has been used for approximately one month. It is not known if she was a diabetic patient. Pyridostigmin is not associated with hypoglycaemia [5].

Patient D is a confirmed non-diabetic patient. She presented with a hypoglycaemia with a blood glucose of 1.3 mmol/l lasting for two days, which was corrected with intravenous glucose.

Patient E, a non-insulin dependent diabetic patient, presented with hypoglycaemia with decreasing blood glucose measurements despite intravenous glucose infusion. Blood glucose measurement in the evening was 1.7 mmol/l. Blood glucose normalised one day after gabapentin was stopped. The patient had used glimepiride for one month. It is known that long-acting sulfonylurea's can cause hypoglycaemia. Although the SmPC of tramadol does not mention hypoglycaemia, it has been reported in literature [6,7].

Patient F, a non- insulin dependent diabetic presented with severe hypoglycaemia with loss of consciousness. She recovered after treatment with glucose and glucagon and withdrawal of gabapentin. Concomitant medication was not reported.

Patient G, an insulin-dependent diabetic, had decreased pre-prandial blood glucose measurements from 6.9 mmol/l to 3.9 -4.7 mmol/l after start of gabapentin.

In summary, four out of six reports (A/B, C, D, F) were reported 'serious' according to the CIOMS criteria, such as hospitalization or life threatening. In cases C, D, E and F hypoglycaemia subsided after stop of gabapentin, thus a positive de-challenge was found in these cases.
Despite a probable time relationship and positive dechallenges, a few confounding factors should be taken into account. In case A/B hypoglycaemia depended on time of administration, in case C some prodromal symptoms were already present before gabapentin was started, in case E glimepiride could have caused hypoglycaemia and in case F concomitant diabetes medication was not reported.

Other sources of information

SmPC

In the Dutch SmPC of gabapentin hypoglycaemia is not mentioned, it is mentioned as an infrequent adverse drug reaction in the FDA labelling text [8].

Literature

There is one published case-report describing gabapentin induced hypoglycaemia in a long term peritoneal dialysis, but non-diabetic, patient. Although renal failure is associated with a variety of abnormalities resulting in impaired glucose homeostasis, the authors ruled out that their patient was at risk for hypoglycaemia. The hypoglycaemia in their patient coincided with an increased dose of gabapentin, which was higher than was recommended for renal failure, and improved after withdrawal. Lowest blood glucose measurement was 1.9 mmol/l and was corrected with dextrose. Insulin and C-peptide concentrations were elevated during the hypoglycaemic event and suggest that the hypoglycaemia resulted from increased endogenous insulin secretion induced by gabapentin [9].

Databases

On January 21, 2013 the database of the Netherlands Pharmacovigilance Centre contained six cases of hypoglycaemia and related MedDRA Preferred Terms (PT) in association with gabapentin. The reporting odds ratio (ROR) was disproportional for hypoglycaemia, as well as for the combined ROR for all related preferred terms. See table 2.

Table 2. Reports of hypoglycaemia and related terms associated with gabapentin in the Lareb database.

Drug	Preferred terms	Number of reports	ROR (95% CI)
Gabapentin	Hypoglycaemia	4	4.7 (1.7-12.6)
	Hypoglycaemic unconsciousness	1	
	Blood glucose decreased	1	
Total		6	6.1 (2.7- 13.8)

The WHO database of the Uppsala Monitoring Centre contained 150 reports of hypoglycaemia and related Preferred Terms in association to gabapentin. The reporting

odds ratio (ROR) was disproportional only for the association with the PT blood glucose decreased. The ROR for hypoglycaemia and the combined ROR for all related preferred terms was not significantly disproportional. See table 3.

Table 3. Reports of hypoglycaemia and related terms associated with gabapentin in the WHO database.

Drug	Preferred terms	Number of reports	ROR (95% CI)
Gabapentin	Hypoglycaemia	88	1.0 (0.8-1.2)
	Hypoglycaemic unconsciousness	2	
	Hypoglycaemic coma	2	
	Blood glucose decreased	58	1.3 (1.0-1.7)
Total		150	1.1 (0.9-1.2)

A positive de-challenge was reported in 14 cases from the WHO database and two re-challenges are described. The outcome of 19 reports associated with gabapentin induced hypoglycaemia was fatal, although causality to hypoglycaemia as cause of death cannot be established in all reports. The seriousness according to CIOMS criteria of the other reports from the WHO database cannot be established.

Table 4. Reports of hypoglycaemia and related terms associated with gabapentin in the WHO database. Numbers of reports without diabetes related concomitant medication.

Drug	Preferred terms	Number of reports with any reported concomitant medication	Number of reports without diabetes related medication
Gabapentin	Hypoglycaemia	75	44
	Hypoglycaemic unconsciousness	1	1
	Hypoglycaemic coma	1	1
	Blood glucose decreased	48	17
Total		125	63

In table 4, the reports from the WHO database with any reported concomitant medication are listed. From these reports, approximately 50% of the reports do not contain any diabetes related medication. It should be kept in mind that the reported concomitant medication is not necessarily completely mentioned by the individual reporters.

The Eudravigilance database of the EMA contained 63 reports of hypoglycaemia and related Preferred Terms in association to gabapentin. The ROR for hypoglycaemia and the combined ROR for all related preferred terms was not significantly disproportional. See table 5.

Table 5. Reports of hypoglycaemia and related terms associated with gabapentin in the Eudravigilance database.

Drug	Preferred terms	Number of reports	ROR (95% CI)
Gabapentin	Hypoglycaemia	50	0.9 (0.8 – 1.3)
	Hypoglycaemic unconsciousness	1	
	Hypoglycaemic coma	0	
	Blood glucose decreased	12	1.0 (0.6 – 1.8)
Total		63	1.0 (0.8 – 1.2)

Prescription data

The number of patients using gabapentin in the Netherlands is shown in table 6.

Table 6. Number of patients using gabapentin in the Netherlands between 2007 and 2011 [10].

Drug	2007	2008	2009	2010	2011
Gabapentin (Neurontin ®)	32,554	31,264	30,599	30,437	30,622

Mechanism

In pancreatic beta-cells GABA is present in cytoplasm, insulin granules and micro vesicles. GABA is released from beta-cells by calcium dependent exocytosis upon and without glucose stimulation. Activation of $GABA_B$ receptors inhibits insulin secretion, where $GABA_B$ receptor blockade stimulates insulin release. In contrast, $GABA_A$ receptor activation leads to an increase of calcium influx and stimulates insulin release [12].
The autocrine signalling of insulin release thus involves GABA release, $GABA_A$ receptor activation followed by membrane depolarization leading to opening of voltage dependent calcium channels. The Ca^{2+} influx stimulates release of insulin.

Thus, a possible effect of gabapentin on pancreatic beta-cells involves either GABA receptors or voltage dependent Ca^{2+} channels.

All Ca^{2+} channels consist of $alpha_1$, beta, $alpha_2$delta and gamma subunits. There are several types of voltage dependent Ca^{2+} channels, depending on minor differences in $alpha_1$ subunits. L-type voltage dependent Ca^{2+} channels are involved in endocrine signalling, but are also found in the brain [13, 14]. The spinal N-type Ca^{2+} channel is very likely the analgesic action target of gabapentin [15]. There also are variants of the $apha_2$delta subunit, and gabapentin binds to $alpha_2$delta-1 and $alpha_2$delta-2 [16]. The first is thought to be target for neurological action of gabapentin. The latter is found in the pancreas amongst other organs [17].
Marais et al. found that binding of gabapentin to $alpha_2$delta-1 in other tissues than brain was much lower. They declared that a possible explanation was that binding of gabapentin on $alpha_2$delta is modulated by other subunits and the environment of the channel [13].
Thus, despite different types of voltage dependent Ca^{2+} channels and varieties in its subunits, there are possible binding sites for gabapentin in the pancreas. It is not clear why hypoglycaemia only occurs infrequently.

Discussion and conclusion

This quarterly report considers two aspects concerning hypoglycaemia and the use of gabapentin.
First, a number of cases of severe hypoglycaemia have been reported from multiple countries, as is shown in the Lareb and WHO databases. Since gabapentin is indicated for diabetic neuropathies, patients with diabetes should be aware of the risk of severe hypoglycaemia as a possible adverse drug reaction of gabapentin.
Second, nearly fifty percent of the reports in the WHO database, documented with concomitant medication, concern patients without prior use of blood glucose lowering medication. Although it is possible that not a complete list of concomitant medication has been reported, it is rather unlikely for reporters of hypoglycaemia related adverse drug reactions, to forget to report any diabetes related concomitant medication.
Since the patients with severe hypoglycaemia require help from others to recover, health care professionals and patients should be warned for this possible serious adverse drug reaction which can occur in non-diabetic patients.

In general, in some reports from Lareb and the WHO database a positive de-challenge was reported, which is supportive for this association.
A pharmacological mechanism shows that gabapentin has properties to increase insulin release by enhancing voltage dependent Ca^{2+} channels or as an agonist on the $GABA_A$ receptor. The case-report of Penumalee [9] supports the thought that insulin release increases after administration of gabapentin.

Severe hypoglycaemia as well as hypoglycaemia in diabetic and non-diabetic patients should be mentioned in the SmPC of gabapentin.

- Severe hypoglycaemia in diabetic as non-diabetic patients should be mentioned in the SmPC of gabapentin

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Nederlands Bijwerkingen Centrum Lareb
July 2013

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This signal has been raised on May 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

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