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CASE REPORT

Sustained hypoglycemia with therapeutic use of repaglinide

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Repaglinide is a short-acting insulin secretagogue used for the reduction in postprandial glucose levels in diabetic patients. It has a favorable safety profile with a low risk of hypoglycemia. Prolonged hypoglycemia appears exceptional due to the short serum elimination half-life.

A 67-year-old African man was admitted in the emergency department (ED) with altered consciousness and profound hypoglycemia (48 mg/dl). He had a long-lasting medical history of type 2 diabetes mellitus with retinopathy, peripheral arteriopathy, ischemic cardiomyopathy, arterial hypertension, atrial fibrillation and post-hepatitis C cryoglobulinemia with membranous proliferative glomerulonephritis. He was currently treated with numerous medications (Table 1). The only recent change was the self-administration of a daily dose of 1 mg colchicine over the last month to treat a gout attack. Repaglinide (1 mg b.i.d) had been introduced several months ago, as it was the case for clopidogrel. There was no insulin at the patient's disposition. He did not experience serious hypoglycemia before this episode. On admission, the other relevant biological investigations were: CRP 318.1 mg/dl (NR: < 5.0), serum creatinine 1.27 mg/dl (NR: 0.6–1.30), creatinine clearance 68 ml/min, potassium 3.30 mmol/l (NR: 3.5–5.0), total proteins 71 g/dl (NR: 64–83), glycated hemoglobin (HbA1c) 44 mmol/mol or 6.2% (NR: 4.0–6.0). Liver function tests were normal. Repaglinide, metformin and clopidogrel were stopped from hospital admission. The patient received 25 g intravenous hypertonic dextrose in the ED. *Streptococcus pneumoniae* was isolated from the sputum, with a right lung infiltrate on chest X-ray. Accordingly, the patient was treated with penicillin G for one week. He was transferred to the intensive care unit (ICU) for the adaptation of intravenous hypertonic dextrose administration. Further biological evolution is illustrated in Fig. 1. Dextrose infusion rate was 20 g/h over the first 26 h and then 10 g/h for the next 10 h. Insulin and corresponding C-peptide blood levels are also shown in Fig. 1.

Serial determinations of serum repaglinide concentration were obtained, starting at 18 h post-hospital admission, together with the first determination of insulin and C-peptide. The initial serum repaglinide level was 43.6 mg/l, within the usual therapeutic range. The serum terminal half-life calculated on four data points was 3.88 h.

The patient left the ICU on day 4 and was discharged home on day 8, with metformin as single therapy for diabetes mellitus. Further investigations ruled out the possibility of an insulinoma.

Repaglinide appears safe in diabetic patients with severe renal impairment, and no drug accumulation is observed. Repaglinide has usually a short serum half-life of 30-60 min [1]. Repaglinide is extensively metabolized by cytochrome P450 isoforms CYP2C8 and CYP3A4 [2]. This implies that genetic polymorphisms of these enzymes could influence the pharmacokinetics of repaglinide, with mean half-life variations up to 45% [3]. It seems, however, that genetic polymorphism on CYP2C8 plays a very limited role in the pharmacokinetics and pharmacodynamics of repaglinide given in a therapeutic dose [4]. It means also that inhibitors or activators of CYP3A4 or CYP2C8 activities might also influence repaglinide metabolism. The pharmacokinetic profile of repaglinide was altered by the administration of an inhibitor (ketoconazole) or an inducer (rifampicin) of CYP3A4, but without significant pharmacodynamics changes, suggesting that other metabolic pathways (and particularly CYP2C8) could play a significant role. Gemfibrozil reduces the clearance of repaglinide through the inhibition of CYP2C8 and is contraindication for administration with repaglinide. A

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Table 1 Patient's medications at the time of hospital admission and influence of liver metabolism

Drug	Liver metabolism
Apixaban	Substrate 3A4
Clopidogrel	Substrate 2C19, inhibitor 2C8
Pantoprazole	Inhibitor 2C9, 2C19
Losartan	Substrate 2C9
Lercanidipine	Substrate 3A4
Eplerenone	Substrate 3A4
Moxonidine	Not fully determined
Simvastatin	Substrate 3A4
Repaglinide	Substrate 3A4, 2C8
Metformin	–
Allopurinol	Inhibitor 1A2
Colchicine	Substrate 3A4

recent nested case–control study suggests that concomitant use of repaglinide and clopidogrel was associated with an increased risk of hypoglycemia compared to repaglinide alone [5]. Retrospectively, it appeared that our patient was taking together several competitive substrates for CYP3A4, including repaglinide. We found a threefold increase in repaglinide serum terminal half-life. The influence of CYP2C8 genetic polymorphism appears unlikely. The role of the recent introduction of colchicine remained speculative, as colchicine does not significantly influence CYP2C8. Colchicine is also not known to directly modulate insulin secretion. Finally, the patient admitted also that he had significantly reduced the consumption of soft drinks over the 2 days preceding hospital admission. We cannot exclude that lung infection played an additional role in hypoglycemia.

In conclusion, a sustained episode of hypoglycemia with high insulin and C-peptide levels was observed in a patient under repaglinide–clopidogrel therapy. Hypoglycemia was prolonged above the estimated duration of the suspected drug–drug interaction.

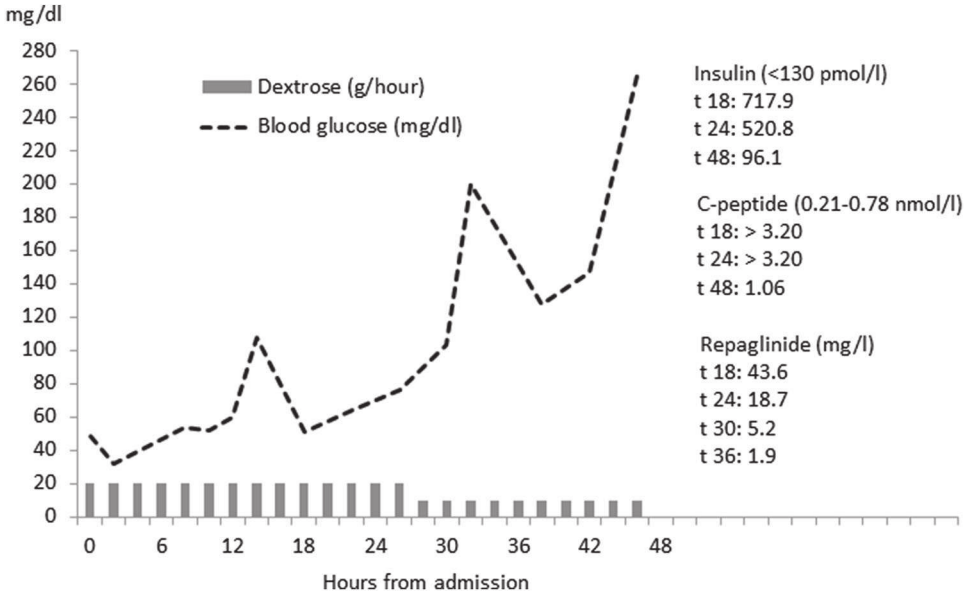

Fig. 1 Evolution of blood glucose level in relationship with dextrose infusion rate. Determination of serum insulin, C-peptide and repaglinide at different time (*t*) intervals (h)

Authors' contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Philippe Hantson, Pierre-François Laterre, Vincent Haufroid and Souleiman El Balkhi. The first draft of the manuscript was written by Philippe Hantson, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Human and animal rights disclosure All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A written informed consent was obtained from the patient.

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