Hyperglycaemia and ketosis induced by gamma hydroxybutyrate (GHB)

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To the Editor: Sodium oxybate (gamma hydroxybutyrate [GHB]), which is sold in the USA under the trade name Xyrem, is approved for and used in the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. However, approving GHB for these indications proved difficult, since GHB is used recreationally to enhance the ‘dancing experience in the club scene’, for date rape and for weight loss and body building [1]. Since GHB is a CNS depressant, its use with alcohol or other CNS depressant drugs is dangerous. As a result of these dangers and abuses, GHB was difficult to approve as an orphan drug and is therefore tightly regulated. In some countries GHB is banned, and in the USA can only be obtained from approved central pharmacies and prescribed by a limited number of approved neurologists [1].

While this little-used drug is mentioned in several ‘lists’ as a drug that can increase glucose levels, a specific study of the effects of GHB on glucose levels is not available [2]. The US manufacturers, Jazz Pharmaceuticals (Palo Alto, CA, USA), say that there were occasional and mild glucose elevations in their phase 3 studies, from which patients with diabetes were not excluded. It is, however, highly likely that there were very few diabetic patients in these studies and that most if not all of these had type 2 diabetes. Here, I document the first report of GHB causing hyperglycaemia and ketosis in a type 1 diabetic patient.

A 24-year-old white woman had developed type 1 diabetes at age 8 years and grand mal seizures at age

15 years. While her diabetes was reasonably controlled using insulin pump therapy, controlling her grand mal seizures had always been difficult. Eventually, with a combination of levetiracetam and lamotrigine she had been free of seizures activity for over 2 years. However, this therapy resulted in severe daytime fatigue and a diagnosis of narcolepsy, which was initially treated with modafinil. However, because of the lack of efficacy of this drug, and the intolerable side effects caused by it, modafinil was replaced with GHB.

GHB was initiated at a dose of 2.25 g twice daily, with doses being administered before and after bedtime. The first morning after starting GHB at this dose, the fasting glucose exceeded 28 mmol/l and the hyperglycaemia was accompanied by moderate levels of urinary ketones. After multiple doses of fast-acting insulin delivered hourly from an insulin pump, the serum glucose dropped below 11 mmol/l and the ketonuria resolved. Over the next few days supplemental insulin was required. However, the need for supplemental insulin gradually waned over the first 5 days. After increasing the dose to 3 g and later to 3.75 g twice nightly there were similar elevations of serum glucose, which necessitated the use of multiple doses of fast-acting insulin, with the need for supplemental insulin, again gradually resolving over the subsequent 5 days.

I have reported a case of acute hyperglycaemia and ketosis, which could have resulted in diabetic ketoacidosis, induced by GHB in a type 1 diabetic patient. Therefore, the initiation of GHB therapy in the type 1 diabetic patient can transiently worsen glycaemic control to the point where hyperglycaemia is accompanied by ketosis. Why does this occur? It has been well documented that GHB can stimulate growth hormone and ACTH and cortisol release, which will induce resistance to the action of insulin [3]. It has also been shown that recreational use

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of GHB, presumably in high doses, can result in pseudo-Cushing's syndrome [4]. It is therefore likely that increased GHB levels result in upregulation of GHB receptors in the anterior pituitary gland, which results in elevated levels of both ACTH and growth hormone. Later, owing to adaptation to the increased GHB levels, there is down-regulation of the anterior pituitary GHB receptors, and with each increase in the dose of GHB the receptors are again reactivated.

Endocrinologists, neurologists and other health professionals treating patients with type 1 diabetes should be aware that the initiation and advancement of GHB therapy is associated with worsening glycaemic control, and has the potential to induce ketosis or even ketoacidosis in the type 1 diabetic patient.

Duality of interest The author declares there is no duality of interest associated with this manuscript.

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