Diabetes vignette

A 65-year-old man had had type 1 diabetes for six years, with meticulous attention to self-care, frequent blood glucose testing, careful carbohydrate counting and a basal bolus regimen of degludec and Novorapid. (Figure 1.) He would generally have one mild hypo which he could self-manage per fortnight, but in clinic pointed out that he had had just five hypos in two days. He wondered about the tramadol as the cause: he had started on tramadol to treat neck pain two days before the hypos. We replaced the tramadol with oramorph, and the hypos resolved.

Discussion

A nested case-control analysis within the UK Clinical Practice Research Datalink created a cohort of all patients newly-treated with tramadol or codeine for non-cancer pain between 1998 and 2012, and observed them for admissions for hypoglycaemia.1 Among 334 034 subjects, 1105 were hospitalised for hypoglycaemia; compared with codeine, tramadol was associated with a 50% increased risk of hypoglycaemia, particularly during the first 30 days of use. The frequency of hypoglycaemia was 7 per 10,000 users, but these were hospitalisations for hypoglycaemia, and it is likely that less severe hypos are not being recognised.2 The data also showed, not surprisingly, that the subjects with admission for hypoglycaemia were on average elderly, with multiple comorbidities and increased concomitant drug use.

A French pharmacovigilance study3 compared reports of hypoglycaemia associated with tramadol, dextropropoxyphene and codeine; it was found that there were 90 reports of hypos with dextropropoxyphene, 53 with tramadol and two with codeine – although the population at risk is not stated, it confirms the finding that hypos are more common with tramadol than codeine; also, some subjects became hypoglycaemic without being on antidiabetic agents, and hypos generally occurred during the first few days of tramadol use.

It has been noted that tramadol directly reduces hepatic gluconeogenesis and enhances peripheral glucose utilisation in diabetic rats.2

Tramadol is a commonly used analgesic; it is both a mu-opioid receptor agonist and a re-uptake inhibitor of serotonin and norepinephrine. The opioid activity is due to both the parent compound and the active metabolite which is metabolised by CYP 2D6 and gives inter-individual differences in pharmacokinetics and clinical effects. Tramadol increases risk of convulsions, and should not be mixed with other opiates, psychiatric medication or drugs that raise serotonin levels.2,4

In the linked editorial,2 Nelson and Juurlink wrote: ‘The increased prescribing of tramadol most likely reflects aggressive marketing coupled with the perception that it is a safe analgesic not prone to abuse. Whereas the drug’s analgesic effects are at best moderate, its toxic effects are dangerous and merit respect, particularly when doses are escalated.’

A useful review of other drugs that are known to cause hypoglycaemia includes alcohol, and pentamidine with a high risk of hypoglycaemia which is possible in the absence of diabetic hypoglycaemia treatment, and other agents with a lesser risk of hypos such as chloroquine, ACE inhibitors, beta blockers, salicylates, and fluoroquinolones such as ciprofloxacin. Recently, warfarin has been shown to increase hypoglycaemia rates in people on sulphonylureas,5 and quinine is known to cause hypoglycaemia, particularly in the setting of renal impairment causing quinine accumulation.7 The hypoglycaemic effects of these drugs occur via various mechanisms, often in the same drug, e.g. salicylate-induced hypoglycaemia may be caused by increasing insulin secretion, increasing insulin sensitivity, displacing sulphonylureas from protein-binding sites, and inhibiting renal excretion.3 Another common drug-related hypoglycaemia scenario occurs when a patient’s diabetes has been stabilised on glucocorticosteroids which are then reduced or withdrawn.

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Declaration of interests

There are no conflicts of interest.

References

References are available online at www.practicaldiabetes.com.
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A pain in the neck and hypoglycaemia

References