Long-acting sulfonylureas — long-acting hypoglycaemia

Clinical records

Case 1: An 89-year-old woman was admitted to hospital from a nursing home with a 12-hour history of drowsiness, progressing to an unrousable state and inability to eat or drink. A low dose of long-acting morphine had been commenced 2 days earlier for painful arthritis. A capillary blood glucose (glucometer) reading taken in the nursing home on the morning of hospitalisation was 4.1 mmol/L.

Past history included well controlled type 2 diabetes mellitus associated with corticosteroid use, for which she had been prescribed glimepiride 0.5 mg daily 2 months previously. The last dose was given on the morning of hospital admission. She was taking multiple other medications for comorbid conditions.

The ambulance officers transporting her to hospital had recorded a "Lo" glucometer reading and administered 25 mL of 50% glucose. Within 5 minutes, a repeat glucometer reading was 14.7 mmol/L.

On arrival at hospital the woman was opening her eyes and responding appropriately to pain, but not verbalising. Her Glasgow Coma Score was 9/15. In emergency triage, a glucometer reading showed 4.8 mmol/L, but shortly afterwards her venous serum glucose concentration was 1.3 mmol/L and serum creatinine level was 0.19 mmol/L (normal range, 0.05–0.09 mmol/L). Results of a cerebral computed tomography scan were unremarkable. Over the next 15 hours, there were six more glucometer readings with levels < 3.5 mmol/L, including readings of 0.6 mmol/L and 1.8 mmol/L (18 and 27 hours after the last dose of glimepiride, respectively). Despite a total of 250 mL of 50% glucose in eight bolus doses and a 5% glucose infusion commenced at admission and continued throughout hospitalisation, her level of consciousness deteriorated. She died 18 hours after presentation.

Case 2: A 79-year-old woman living in a nursing home had been discharged from hospital several days earlier after internal fixation of a fracture of the femoral neck. She was readmitted after a sudden deterioration, characterised by drowsiness, decreased response to questions and dyspnoea.

Her past history included type 2 diabetes mellitus for 4 years, for which she was taking glibenclamide 2.5 mg twice daily, a dose which had not been changed for 3 years. Glucometer readings had ranged between 7 mmol/L and 9 mmol/L during her recent hospitalisation. Other major comorbidities included a dominant middle cerebral artery stroke resulting in persisting hemiplegia and dysphasia, atrial fibrillation, hypertension and congestive cardiac failure. Because of her multiple comorbidities she was taking numerous medications.

A glucometer reading was not performed before transfer to hospital. In the emergency department, the woman was initially treated for pulmonary oedema and pneumonia, which were evident clinically and radiologically. Her venous serum glucose concentration was 0.6 mmol/L and her serum creatinine level was 0.04 mmol/L (normal range, 0.05–0.09 mmol/L). Over the ensuing 27 hours, five more glucometer readings were < 3.5 mmol/L, including one of 0.7 mmol/L, and another of 2.3 mmol/L (24 and 36 hours after the last dose of glibenclamide, respectively). In total, she required 300 mL of 50% glucose in six bolus doses and a 5% glucose infusion for 48 hours.

Over the ensuing days, her condition improved and she was able to take a purée and thickened fluid diet. One week after presentation, she appeared to vomit and aspirate while eating, and suffered an asystolic cardiac arrest from which she could not be resuscitated.

SULFONYLUREAS ACT by stimulating insulin secretion from the pancreas and augmenting glucose-stimulated insulin secretion. Some, such as glibenclamide and glimepiride, are long acting and have metabolites that are excreted renally. Others, such as gliclazide and glipizide, are shorter acting and do not have active metabolites.[1]

Hypoglycaemia is the major risk associated with the use of sulfonylureas, particularly in elderly people. Serious hypoglycaemia is usually defined as that causing death, or requiring hospitalisation or emergency department admission. The rate is probably between 1% and 2% per year.[2] Previous reports suggest, and the cases described here demonstrate, that this may occur even with very low doses of a sulfonylurea. The resultant hypoglycaemia can be prolonged and recur for a period of more than 24 hours despite treatment. Case fatality rates of 4%–10% are reported and 5% of survivors may have permanent neurological impairment.[3]

In elderly people, the classical autonomic adrenergic symptoms and signs of hypoglycaemia may not be present (or evident), and neuroglycopenic features, such as drowsiness or confusion, may dominate the picture (as in the cases described), so the diagnosis can be easily missed.[4] Elderly patients with these symptoms who are taking medication for hypoglycaemia need immediate (and repeat) measurement of blood sugar level (BSL). If the BSL is low and the patient is alert and able to swallow, oral carbohydrate loading is the preferred management regimen — otherwise an ambulance should be called and the patient transported to hospital as a matter of urgency. While 10–25 g of carbohydrate delivered in 50% glucose is essential to restore the patient to euglycaemia in the short term, in the presence of sulfonylurea it stimulates more insulin secretion by the pancreas, and therefore can contribute to recurrent hypoglycaemia. The 50% glucose bolus should be followed immediately by an infusion of 5% or 10% glucose, usually at a rate of 100–200 g of carbohydrate daily, and BSL should be monitored for at least 24 hours. Subcutaneous synthetic somatostatin analogues may be used to reduce the likelihood of rebound hypoglycaemia and reduce glucose requirements, but there is no role for glucagon in the management of sulfonylurea-induced hypoglycaemia.[5]

Numerous studies show that longer-acting sulfonylureas are associated with a higher risk of hypoglycaemia, including serious hypoglycaemia. Gliclazide and glipizide have been shown to cause less hypoglycaemia than glibenclamide, and one study also suggested that glimepiride was safer than glibenclamide.[6-9] There are no published reports comparing glimepiride directly with gliclazide or glipizide for hypoglycaemia. Other risk factors for hypoglycaemia, evident in the cases described here, include advanced age, recent hospitalisation, multiple medications, and drug accumulation caused by renal or hepatic impairment (keeping in mind that renal function usually declines linearly with age).

Medication changes, including an increase in hypoglycaemics while a patient is unwell in hospital, may not be

Lessons from practice

- Long-acting sulfonylureas, such as glibenclamide (and perhaps glimepiride) should be used with extreme caution in frail elderly people.
- Recent hospitalisation is a major risk factor for sulfonylurea-induced hypoglycaemia and necessitates increased vigilance in monitoring the patient's condition and blood sugar levels.
- The classical adrenergic features of hypoglycaemia may be absent (or not evident) in frail elderly people.
- Drowsy or confused elderly patients taking sulfonylureas should have their blood sugar level measured urgently.
- Once sulfonylurea-induced hypoglycaemia is confirmed, oral carbohydrate loading is the preferred management regimen in alert patients, but those unable to take oral food or fluids should be transferred to hospital as a matter of urgency.
- Even with low-dose sulfonylurea therapy, hypoglycaemia can be severe, prolonged and recurrent over at least 24 hours.

adequately communicated to the patient's general practitioner, and recent hospitalisation is perhaps the major risk factor for sulfonylurea-induced hypoglycaemia. The presence of any of these risk factors should affect the choice and dose of medication and increase vigilance in monitoring BSL and renal function.

In conclusion, the above cases serve to remind us of the dangers of long-acting sulfonylureas, which should perhaps be avoided in elderly people. Shorter-acting sulfonylureas such as gliclazide and glipizide are safer options. Elderly patients with altered mentation taking sulfonylureas require an urgent BSL measurement and, if they are unable to take food or fluids orally, they should be referred to hospital promptly.

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