Metformin lactic acidosis, acute renal failure and rofecoxib

G. Price*

Department of Anaesthesia, Victoria Hospital, Kirkcaldy, Fife, Scotland, UK

*Present address: Department of Intensive Care The St George Hospital, Kogarah, Sydney, Australia. E-mail: grantprice@hotmail.com

A patient with acute renal failure associated with lactic acidosis as a result of concurrent treatment with metformin is described. Rofecoxib may have been a precipitating factor. The risk of renal failure with the use of traditional NSAIDs is well known. However, what is less well appreciated is the role that the COX 2 inhibitors may play in the development of renal failure which, when it occurs in a patient on metformin, can lead to a potentially disastrous outcome.

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Drug-related causes of morbidity and mortality are recognized increasingly. In recent years, a new class of non-steroidal anti-inflammatory drug (NSAIDs), the COX 2 inhibitors, have been developed. They reduce the incidence of gastrointestinal side effects compared with traditional NSAIDs. This benefit has made these drugs increasingly attractive, but it should be remembered that this benefit does not extend to the renal system.

The following describes a patient with acute renal failure and lactic acidosis as a result of concurrent treatment with metformin. Rofecoxib may have been a precipitating factor.

Case report

A 58-yr-old female presented with a 4-day history of increasing lethargy, anorexia, abdominal pain, and nausea. Her abdominal pain and nausea became worse on the fifth day and her family sought medical help when her conscious level began to become impaired. Her medical history included 10 years of type 2 diabetes mellitus treated with diet modification and metformin 500 mg bd, and mild osteoarthritis of the knees.

On arrival at the Accident and Emergency department she was severely agitated (GCS E3V3M4), ventilatory frequency 45, arterial pressure 130/70 mm Hg, heart rate 110 beats min⁻¹, peripheral oxygen saturation 95% on air and blood sugar 6.2 mmol litre⁻¹. Physical examination was unreliable because of patient agitation but abdominal palpation revealed a tender abdomen. Arterial blood gases were: pH 6.8, PaCO₂ 2.6 kPa, PO₂ 10.2 kPa, plasma bicarbonate 5 mmol litre⁻¹, base deficit 27.4 mmol litre⁻¹, and plasma lactate 19.8 mmol litre⁻¹. Her biochemical profile revealed a sodium of 140 mmol litre⁻¹, potassium 4.4 mmol litre⁻¹, urea 27.4 mmol litre⁻¹ and creatinine 796 mmol litre⁻¹. In view of her metabolic status and to allow further investigation and treatment she was intubated and ventilated. An abdominal CT scan was performed to rule out mesenteric ischaemia and to exclude obstructive causes of renal failure. A provisional diagnosis of type B lactic acidosis was made.

The cause of the renal failure was not apparent at this time. She was transferred to the Intensive Care Unit and underwent lactate-free continuous veno-venous haemofiltration (CVVH) and sodium bicarbonate therapy, but after 1 h of CVVH she required inotropic support with epinephrine and norepinephrine, which continued for 48 h. She was extubated after 2 days and required renal replacement therapy for 14 days in total.

A review of the patient’s notes confirmed the clinical history and her most recent pre-morbid biochemical profile from 2 months before admission revealed normal renal function. This patient was commenced on rofecoxib 1 month before hospital admission for painful arthritis. She made a full recovery and did not require further renal support.

Discussion

Metformin is a widely prescribed oral hypoglycaemic agent (OHA). It is used to lower blood glucose in patients with...
type 2 diabetes mellitus. It is widely prescribed because it has certain advantages over the other major group of OHAs (the sulphonylureas), namely it does not cause hypoglycaemia, weight gain, or hyperinsulinaemia. Metformin is the only biguanide OHA available in the UK. A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. This complication, although rare (0.03 cases/1000 patient yr), has a reported mortality of 50%.4,5

Metformin’s mechanism of action is thought to be by increasing glucose transport into glucose utilizing cells and by decreasing hepatic gluconeogenesis.3 Biguanide therapy decreases the activity of the enzyme pyruvate dehydrogenase and the transport of mitochondrial reducing agents, and thus enhances anaerobic metabolism.6 This shift to anaerobic metabolism is therefore not dependant on a lack of oxygen and, in the presence of reduced insulin, increases production of precursors for the tricarboxylic acid cycle.6

As inhibition of pyruvate dehydrogenase leads to a decreased ability to channel these precursors into aerobic metabolism this causes increased metabolism of pyruvate to lactate and an increase in lactic acid production. Any renal impairment will result in a reduced clearance of lactic acid and metformin.

Rofecoxib is a new COX 2 inhibitor. Various inflammatory mediators are derived from the phospholipid cell membrane via the cyclo-oxygenase and the lipoxygenase pathways to produce prostaglandins, thromboxanes, and leukotrienes. Prostaglandins are not only involved in inflammation but also in the maintenance of gastric mucosal integrity, and renal microvascular homeostasis.7 Prostaglandins are particularly important for maintaining glomerular filtration rate under conditions of suboptimal perfusion. Interference with this homeostatic mechanism can lead to nephrotoxicity; it is a well-described complication of NSAID therapy.8,9

There are two forms of the cyclo-oxygenase enzyme; COX 1 and COX 2.10,11 COX 1 is present in many tissues and is responsible for the maintenance of the physiologically protective functions such as renal blood flow and gastric mucosal protection. COX 2 is found in brain, kidney, and gravid uterus. However, it is usually undetectable in most tissues and expresses during inflammation.

COX 2 inhibitors have comparable analgesic efficacy when compared with traditional NSAIDS and are claimed to have additional benefits, especially a marked reduction in gastric toxicity. The large trials have focused mainly on the gastric safety profiles of these compounds rather than the renal safety.12 More recently, doubt has been cast on the findings of these trials,13–15 on the renal toxicity of these new agents suggesting a pattern of nephrotoxicity similar to the traditional non-selective NSAIDs. One study found a transient deterioration in renal function in patients treated with celecoxib and rofecoxib. Of importance was the age of these patients (63–73 yr old) and the fact that they had co-morbidity including cardiovascular disease, diabetes mellitus, and chronic renal failure.16

Many patients with type 2 diabetes mellitus are overweight and arthritic, as well as other musculoskeletal disorders, is common. The COX 2 inhibitors may have an improved side-effect profile with regard to gastric side effects, but their renal safety profile has not been established.

The risk of renal failure with the use of traditional NSAIDs is well known. What is less well appreciated is the role that the COX 2 inhibitors may play in the development of renal failure which, when it occurs in a patient on metformin, can lead to a potentially disastrous outcome.

References

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