CASE REPORT

Pirfenidone-induced hyponatraemia: insight in mechanism, risk factor and management

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SUMMARY

Pirfenidone was approved in October 2014 in the USA for the treatment of idiopathic pulmonary fibrosis. Although not included in the adverse events published in the CAPACITY-1 and CAPACITY-2 or ASCEND trials, hyponatraemia was reported in supplementary data with rate of 3.4% in the active therapy arm versus 0.3% in the placebo arm. We performed a retrospective analysis of patients who were initiated on pirfenidone or nintedanib for the treatment of pulmonary fibrosis at our centre. Of the 52 patients who were started on pirfenidone, three (5.8%) developed severe hyponatraemia. Of the 29 patients who were started on nintedanib, none developed hyponatraemia. Laboratory data suggested syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by pirfenidone and the medication was discontinued. Hyponatraemia is a possible significant adverse effect of pirfenidone, able to induce SIADH in patients taking the medication.

BACKGROUND

Pirfenidone was approved in October 2014 in the USA for the treatment of idiopathic pulmonary fibrosis (IPF), a progressive lung disease usually resulting in death 3–5 years after time of diagnosis. It was shown to slow the rate of decline over 52 weeks in forced vital capacity by approximately 50%, and post hoc analysis of these trials have suggested a possible mortality benefit.^{1,2} Although not included in the adverse events published in the CAPACITY-1 and CAPACITY-2 or ASCEND trials, hyponatraemia was reported in supplementary data from CAPACITY-1 and CAPACITY-2 with a rate of 3.4% in the active therapy arm versus 0.3% in the placebo arm.³ Hyponatraemia was not reported in the open label extension studies (RECAP)⁴; however, monitoring of electrolytes and renal function was not routinely performed, so these data may not have been captured in these studies. The mechanism by which pirfenidone causes hyponatraemia is not known.

In this report, we present three cases of pirfenidone-induced hyponatraemia necessitating discontinuation of therapy. Further, we provide insight into the possible mechanism of hyponatraemia induced by pirfenidone and provide guidance regarding monitoring of this adverse effect.

CASE PRESENTATION

Patient 1 was a 72-year-old man who presented with progressive dyspnoea and cough over 18 months.

High-resolution CT (HRCT) scan of the chest demonstrated interstitial lung disease with probable usual interstitial pneumonia (UIP). Comorbidities included hypertension, type 2 diabetes mellitus, hyperlipidaemia, gastro-oesophageal reflux disease, coeliac disease, symptoms of which had resolved since adhering to a gluten-free diet, and a remote history of cigar smoking. His medications included aspirin, atorvastatin, fenofibrate, metformin, multivitamin, omeprazole and triamterene–hydrochlorothiazide, which he had been on for the previous 7 years without change in dose. He was initiated on pirfenidone, with baseline laboratory examination revealing a sodium level of 137 mEq/L. Pirfenidone was started with the recommended up-titration schedule to three pills three times per day. No other new medications were initiated. Repeat laboratory testing 4 weeks later showed a sodium level of 128 mEq/L. Repeat testing 2 days later was 124 mEq/L. He was not having diarrhoea or vomiting and complained of a mild headache. Thyroid function tests were normal. Given stability of dose and controlled hypertension, the triamterene–hydrochlorothiazide was continued. Further evaluation demonstrated serum osmolality of 270 mOsm and urine osmolality of 508 mOsm, suggesting syndrome of inappropriate antidiuretic hormone secretion (SIADH). Pirfenidone was discontinued. Two weeks later, sodium level was 137 mEq/L and 4 weeks later 136 mEq/L.

Patient 2 was an 80-year-old woman with an HRCT consistent with UIP pattern with hypoxia first noted at elevation. She had long-standing mild hyponatraemia and her pre-sodium level ranged from 132 mEq/L to 138 mEq/L over the 3 months before initiation of pirfenidone. Other medications included aspirin, atorvastatin, levothyroxine and valsartan, which she had been taking for 9 years. The thyroid stimulating hormone level was normal 2 months prior. Two weeks after initiation of pirfenidone, the sodium decreased to 127 mEq/L, significantly lower than her baseline (and the first time her sodium level was less than 130 mEq/L). She experienced typical side effects of pirfenidone with mild dyspepsia, anorexia and fatigue, but she denied symptoms of emesis or diarrhoea. Repeat sodium measured 3 days later was 126 mEq/L. Dose reduction was attempted but the hyponatraemia and side effects persisted. Pirfenidone was discontinued and 2 weeks later sodium increased to 132 mEq/L. Three months later the sodium was 134 mEq/L. She did not have laboratory data performed for SIADH.

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Her serum glucose was 90–134 mg/dL on corresponding blood testing.

Patient 3 was a 77-year-old man with rheumatoid arthritis. His CT scan had a pattern consistent with UIP and he had been prescribed pirfenidone prior to his presentation to our programme. Other medications included triamterene–hydrochlorothiazide, metformin, atorvastatin, fenofibrate and cetirizine, and there had been no recent changes. His sodium was noted to be 127 mEq/L. On review of medical records, his sodium level was 134 mEq/L prior to the initiation of pirfenidone. Triamterene–hydrochlorothiazide was discontinued for 1 week, then further evaluation showed serum osmolality was 276 mOsm/kg and urine osmolality was 586 mOsm/kg, with persistent hyponatraemia and sodium 127 mEq/L, suggesting a diagnosis of SIADH. Due to hyponatraemia and a non-IPF interstitial lung disease diagnosis, pirfenidone was discontinued. Two weeks later, the sodium level was 132 mEq/L and 4 weeks later 134 mEq/L.

INVESTIGATIONS

Two of the three patients had their serum and urine osmolality investigated. Both patients had a low serum osmolality and an elevated urine osmolality, while appearing euvoletic. Given these findings, SIADH was diagnosed and pirfenidone was discontinued. Follow-up electrolyte monitoring in all three patients revealed corrected sodium levels within 2 weeks of discontinuation of pirfenidone.

A total of 52 patients in our centre have been treated with pirfenidone at the time of analysis, of whom three (5.8%) developed hyponatraemia, similar to what was quoted in the CAPACITY trials. Twenty-nine patients were initiated on nintedanib, of whom none developed significant hyponatraemia.

DIFFERENTIAL DIAGNOSIS

SIADH was made based on laboratory data from both serum and urine, clinical history and physical exam. SIADH can be caused by other medications, malignancies and infections, though these were thoroughly investigated during each clinic visit.

TREATMENT

All three patients had their pirfenidone discontinued with resolution of sodium levels to normal within 2 weeks (figure 1). Two of the three patients transitioned to an alternative IPF medication, nintedanib, without any electrolyte issues.

Figure 1 Sodium levels for three patients before, during and after pirfenidone (Prf) treatment.

OUTCOME AND FOLLOW-UP

Two patients (patients 1 and 2, both with IPF) were transitioned to nintedanib; patient 1 tolerated nintedanib well and continues on the recommended dose of 150 mg twice a day. Patient 2 had gastrointestinal side effects and could only tolerate 100 mg daily, with a serum sodium of 131–134 mEq/L chronically. All three patients continued to have sodium levels greater than 130 mEq/L 4 weeks after discontinuation of pirfenidone.

DISCUSSION

Many drugs have been shown to induce SIADH. This can occur through increased hypothalamic production of antidiuretic hormone (ADH), such as with tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines and many others. It can also occur through potentiation of an ADH effect, such as with carbamazepine, chlorpropamide and others. Other drugs, such as amiodarone, can rarely cause hyponatraemia. Drug-induced SIADH usually resolves with discontinuation of the offending medication.⁵ Lancaster *et al* recently published the compiled data from three multinational phase 3 studies (CAPACITY (studies 004 and 006), ASCEND (study 016)) and two ongoing open-label studies (study 002 and study 012 (RECAP)) which included 1299 patients, median age 68 (range 42–88).⁶ The authors found gastrointestinal side effects (nausea (37.6%), diarrhoea (28.1%), dyspepsia (18.4%), vomiting (15.9%)) and rash (25.0%) to be common adverse events. In regard to laboratory data, the authors found a 3.1% incidence of elevated liver function tests; however, they did not report any incidence of hyponatraemia, although electrolytes and renal function were not collected in RECAP.⁶ Thirty-eight per cent (38.1%) discontinued treatment arm due to adverse event. The frequency of monitoring sodium levels is not detailed in the publication; however, routine clinical laboratory tests were performed at prespecified intervals in all five studies.⁶

There are several possibilities for the discrepancies between our incidence of hyponatraemia and that published in the literature. First, it is possible that the patients included here developed hyponatraemia due to other causes. However, after discontinuation of pirfenidone, the sodium levels normalised, suggesting pirfenidone was the offending agent. Second, the patients in this case report are typical of those cared for in our centre (and likely compatible with other clinical settings) versus patients enrolled in the aforementioned clinical trials. For instance, all three patients were significantly older than the median age in the trials and who may not have been eligible for enrolment in the clinical trials. Patient 1 had a diffusing capacity of the lungs for carbon monoxide (DLCO) of 27% predicted and therefore would have been excluded (DLCO inclusion criteria 30%–90% predicted). Patient 2 would have been included if enrolled prior to her 81st birthday, which she was near at the time of evaluation in our centre. Patient 3 would not have been included due to diagnosis of rheumatoid arthritis. Third, it remains unclear if pirfenidone alone resulted in SIADH or whether it was due to interactions with other medications, particularly the medications our patients were taking known to potentially cause SIADH. Finally, given the low incidence of hyponatraemia in the initial clinical trial CAPACITY, it is possible that instances of hyponatraemia were transient and therefore tolerated and resolved.

In conclusion, hyponatraemia is a possible adverse effect of pirfenidone; monitoring and caution should be taken after prescribing this medication. Older age may predispose to this complication. The mechanism of action appears potentially to be

due to induction of SIADH. The hyponatraemia resolved in the patients in our series with discontinuation of pirfenidone.

Learning points

- ▶ Hyponatraemia is a possible adverse effect of pirfenidone, with older age a potential risk factor.
- ▶ The mechanism of action of pirfenidone-induced hyponatraemia may be due to syndrome of inappropriate antidiuretic hormone secretion.
- ▶ Management of pirfenidone-induced hyponatraemia includes discontinuation of the medication with close monitoring of electrolytes for up to 4 weeks.

Contributors LS and SD cared for the three patients in this case report. PG assisted with follow-up care of the patients and review of the literature for this manuscript preparation. JC was the pharmacist involved in reviewing medication adverse events. All authors contributed to putting together the manuscript and care for the patients.

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