Nephrotoxicity of intravenous immunoglobulin

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Summary

Individual case reports have documented nephrotoxicity of intravenous immunoglobulin (IVIG) preparations, but the true incidence of renal dysfunction is unknown and many data sheets do not include renal impairment as a side-effect of these preparations. We determined the incidence of renal impairment in an unselected cohort of patients receiving two different preparations of IVIG over 20 months, administering 287 courses of IVIG to 119 patients for a variety of indications, including thrombocytopenia, systemic lupus erythematosus, neuropathy, Guillain-Barre syndrome and infections. Two different preparations of IVIG were used, Vigam (BPL) and Sandoglobulin (Novartis), which differ in the concentration of sucrose added as a stabilizer. Eight patients showed deterioration in renal function (6.7%), and in two, no renal recovery occurred (1.7%). There were no significant differences in the patient characteristics or dose or preparation of IVIG administered to those patients with or without changes in serum creatinine. There was no association between the amount of sucrose in the IVIG and development of renal failure. IVIG (regardless of the sucrose content) is associated with renal impairment which may be irreversible, with a maximum incidence of 6.7%. All patients should have their renal function monitored during the use of IVIG.

Introduction

Intravenous immunoglobulin (IVIG) is prescribed for an increasing number of conditions. It is generally well tolerated. The commonest side-effects include fever, nausea, chills, hypotension, facial flushing and back pain. Occasionally patients develop aseptic meningitis, haemolysis, transient neutropenia and anaphylaxis (in patients with IgA deficiency). Most trials of IVIG treatment have reported renal failure only rarely as a complication of therapy. In one study from New York of the use of IVIG in neurological disorders, one of 88 patients developed acute renal failure.¹ This patient was diabetic with pre-existing renal impairment. A review of 83 patients receiving IVIG for immune thrombocytopenia documented 12 cases of transient renal impairment and one case of acute renal failure.² Most other reports have been of individual cases of renal failure associated with use of IVIG.³⁻⁷

Recently the FDA reported details of 88 patients with renal adverse effects of IVIG identified between 1985 and 1998; 61% of the adverse effects were classified as ‘acute renal failure’.⁸ Patients had a median age of 61 years, 56% had diabetes, and 26% had prior renal impairment. For those patients in whom details were available, renal failure always occurred < 7 days after IVIG administration, with a peak time of 5 days, and mean peak creatinine of 6.2 mg/dl. Some 40% required dialysis, 15% died despite treatment (all with severe underlying disorders), and mean time to recovery in the survivors was 10 days. Renal histology showed extensive vacuolation of proximal tubules consistent with osmotic injury in 7/15 patients.
Previous reports have suggested that the renal injury provoked by IVIG preparations is caused by osmotic stress to proximal tubules, and is very similar to that observed historically in patients receiving high doses of intravenous sucrose.\textsuperscript{5,9,10} Many preparations of IVIG contain sucrose, which is added as a stabilizer to prevent aggregation of IgG. Of the patients with renal failure reported to the FDA, 90% had received a sucrose-containing IVIG compound; however, sucrose-containing preparations are most widely prescribed worldwide, and have been in regular use for longer.\textsuperscript{8}

Renal dysfunction or renal failure are not recorded as potential adverse effects in the data sheets or drug compendia of all IVIG preparations. Although renal physicians are well aware of individual cases of renal failure associated with the use of the drug, the incidence of the complication has not been established, nor the true mechanism. We determined the incidence of renal dysfunction in non-selected hospitalized patients receiving IVIG for a variety of indications in a single centre, and compared two different IVIG preparations containing differing sucrose concentrations.

Methods

A retrospective analysis was done of all patients receiving IVIG over 20 months at a single tertiary referral centre. Patients receiving IVIG were identified from pharmacy records. All preparations of IVIG prescribed within the hospital, and all IVIG issued to wards, had been recorded centrally over this time period. The drug charts of all these patients were subsequently reviewed to ensure all patients had actually received IVIG, and to determine the dose prescribed and dates administered. Patient notes were reviewed to identify potential confounding factors causing renal impairment. Renal function was assessed from routine measurements of serum creatinine, before and after the administration of immunoglobulin. Patients receiving IVIG as prophylaxis for graft versus host disease after bone marrow transplantation were excluded, since these patients were part of a randomized blinded controlled trial. Data were analysed using Mann-Whitney, Wilcoxon and paired t tests as appropriate.

Results

During the period of the study two preparations of IVIG were used in our centre: Sandoglobulin (Novartis) and Vigam (BPL). The choice of IVIG preparation in stock had been made centrally within the pharmacy. Sandoglobulin was available during the first half of the study period, and Vigam became the IVIG available during the second half of the study period. Individual physicians did not generally have a choice of IVIG preparation. Sandoglobulin contains 1.76 g sucrose/g immunoglobulin and Vigam contains 0.5 g sucrose/g immunoglobulin.

A total of 287 courses of IVIG was administered to 119 patients (median 3 courses per patient) over 20 months; 42 patients received 111 doses of Sandoglobulin and 77 patients received 176 doses of Vigam. IVIG was used for a large number of indications, including haematological (64% of patients), renal (14%), paediatric (8%) and neurological (7%). Underlying diagnoses included immune thrombocytopenia (ITP), viral infections in immunocompromised patients, SLE, immunoglobulin deficiency, dermatomyositis, polymyositis, Guillain-Barre syndrome, recurrent miscarriages and chronic inflammatory demyelinating polyneuropathy. There were no differences in the patient characteristics, baseline renal function or diagnoses of those receiving either Vigam or Sandoglobulin, nor in the number of doses of IVIG administered or the total dose each patient received. Patients receiving Sandoglobulin received a higher dose of sucrose than those receiving Vigam (mean 76 g sucrose per day vs. 20 g, p=0.34).

Thirteen patients (4.5% of administered courses) did not have any baseline measurement made of renal function, and 25 patients (9% of administered courses) did not have a serum creatinine checked in the month after receiving immunoglobulin. There was no change in serum creatinine in 97% of patients in whom data on renal function were available (comparison of pre-IVIG and post-IVIG creatinine). No patients receiving IVIG as regular replacement therapy for immunoglobulin deficiency developed renal impairment. However, eight patients showed deterioration in renal function (Table 1). In two of these cases (overall 1.7%), no renal recovery occurred. Peak creatinine occurred at a median of 5 days after initiation of therapy. There were no significant differences in the patient characteristics or dose of IVIG administered (mean 0.7 g/kg/day, range 0.2–2 g/kg/day) for those patients with or without changes in serum creatinine, or those receiving Vigam or Sandoglobulin (Table 2).

Patient 8 had underlying chronic renal impairment secondary to biopsy-proven AL amyloidosis (creatinine stable at 300 μmol/l) and received Vigam IVIG 0.4 g/kg/day for 5 days for chronic inflammatory demyelinating polyneuropathy. On day 5, his creatinine rose to 404 μmol/l, with no other causes for acute renal dysfunction. His renal
function continued to deteriorate, and he required dialysis 3 days later, and remains dialysis-dependent. The second patient with irreversible renal failure (patient 7) was a 23-year-old man with graft versus host disease and probable viral infection after an allogeneic bone-marrow transplant. He received 0.3 g/kg/day of Vigam over 3 days, during which time his creatinine rose from 73 to 298 μmol/l, having been stable prior to the use of immunoglobulin. He subsequently developed a sepsis syndrome and died with established renal failure 3 days later. The decline in renal function predated the sepsis, but severe infection may of course have contributed to his renal impairment, and in particular its further progression. A third patient who developed a substantial but reversible rise in serum creatinine (patient 5) had mildly impaired renal function (cause unknown) at the onset of treatment (creatinine 132 μmol/l). Six of the patients had normal renal function before treatment with IVIG.

**Discussion**

At least 20 case reports, including 58 patients, have described renal impairment probably attributable to IVIG, and the FDA reports at least 88 patients with renal adverse effects from IVIG over a 13-year period. But many physicians remain unaware of the risks associated with the use of IVIG. No mention of renal toxicity is found in the literature for Vigam IVIG, and only the most recent datasheets for Sandoglobulin IVIG include renal toxicity as a potential complication. In this retrospective study of a heterogeneous group of patients receiving IVIG, 2/119 patients (1.7%) suffered irreversible renal failure, and six others suffered a rise in serum creatinine contemporaneous with the use of IVIG (5%).
Furthermore, during 9% of administered courses of IVIG, no assessment of renal function was made after the use of the drug.

Renal impairment occurs about 5 days after initiation of treatment, and can occur in patients with normal baseline renal function. We have only been able to use serum creatinine to define renal function, and there is some evidence that IVIG can inhibit the tubular secretion of creatinine. Thus a rise in serum creatinine may not be indicative of reduced glomerular filtration rate per se, and this may account for the relatively modest rise in creatinine seen in five of the patients reported here. However two of the patients undoubtedly suffered acute renal failure, and one patient sustained a reversible increase in serum creatinine to over 300 μmol/l. There were no identifiable characteristics of the patients developing renal failure; however, two of those with the greatest rise in serum creatinine had pre-existing renal impairment. No patient receiving IVIG as replacement therapy for immunoglobulin deficiency developed renal impairment, and all of the patients reported here were receiving relatively high-dose IVIG therapy. In case reports, patients with nephrotoxicity attributed to IVIG have generally received high-dose therapy (0.8–5 g/kg), and frequently have had underlying renal dysfunction (at least 45% of cases). There is anecdotal evidence that the rate of infusion of IVIG may influence the development of renal problems, but we were unable to ascertain this information in our patients.

It has been suggested that the nephrotoxicity of IVIG preparations is due to an osmotic insult caused by the high sucrose content of most forms of IVIG. Sandoglobulin contains 1.76 g sucrose/g IVIG, and Vigam 0.5 g sucrose/g IVIG, and other preparations of IVIG associated with individual cases of renal failure have also contained sucrose. However, there are also case reports of renal failure in patients receiving IVIG without sucrose, but containing maltose, glycerine or glucose as inhibitors of IgG aggregation. In animal studies, intravenous sucrose can induce reversible acute renal dysfunction with proximal tubular pathology similar to that seen in the few patients who have had a renal biopsy after IVIG induced renal failure. A study in humans administered intravenous sucrose showed no effect on urea clearance of 200 ml 50% sucrose (100 g). However, six cases of renal failure have been associated with intravenous sucrose (used as an osmotic diuretic or to reduce intracranial pressure), in which patients received between 25 and 800 g sucrose. The aetiology of the proximal tubular damage is unclear, but may be caused by pinocytosis of sucrose into proximal tubular cells or to an osmotic effect.

The pathological changes seen on biopsy include extensive vacuolation and cellular swelling. A single patient has been reported in whom uneventful treatment with a maltose-containing IVIG preparation (Octagam, Octapharma) was followed by severe renal failure when the patient received the same dose of Sandoglobulin.

In our study, patients administered Sandoglobulin received an average of 76 g sucrose with each treatment, whilst those given Vigam received only 20 g sucrose per treatment (p = 0.34, non-significant). All three patients with the most severe renal impairment had received Vigam IVIG. The number of patients is too small to identify any relationship between degree of renal impairment and dose of sucrose received, although clearly IVIG preparations containing lower sucrose concentrations can still induce renal failure. Thus it is possible either that the small amount of sucrose present in Vigam IVIG is sufficient to induce renal impairment, or that sucrose is not the major nephrotoxin, and IVIG itself may be contributing to or causing renal damage.

Formal proof of a causative role for IVIG in renal impairment is lacking, and the exact role of sucrose remains unclear. Physicians using non-sucrose-containing IVIG preparations should report cases of renal impairment so the role of sucrose can be more clearly defined. However, our data suggest that all physicians using high-dose IVIG should be aware of the potential for these preparations to cause renal failure, albeit rarely, should avoid simultaneous use of other potential nephrotoxins, and should check renal function before and after administration of the drug, especially in patients with pre-existing renal disease. All patients should have serum creatinine measured 4–5 days after beginning high-dose therapy. It is likely that any preparation of IVIG can cause renal impairment.

References


