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Variations in Serum Hemoglobin, Albumin, and Electrolytes in Patients Receiving Intravenous Immunoglobulin Therapy

A Real Clinical Threat?

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Abstract

Background and objective: Intravenous immunoglobulin (IVIg) is a solution of globulins containing antibodies derived from pooled human plasma of donors and used in the treatment of a number of immune deficiencies and autoimmune diseases. However, several investigators have reported biochemical alterations with use of IVIg. The objective of this study was to evaluate the effects of IVIg therapy on selected biochemical and hematologic parameters in patients with autoimmune mucocutaneous blistering diseases (AMBDs).

Methods: In this preliminary clinical study, ten patients with AMBDs (seven with pemphigus vulgaris and three with mucous membrane pemphigoid) received 133 cycles of IVIg for a total of 399 infusions. We evaluated the effects of IVIg therapy on serum hemoglobin (Hb), albumin, and electrolyte levels, including sodium (Na^+), potassium (K^+), chloride (Cl^-) and calcium (Ca^{2+}). Values of these parameters were measured 24 hours before, during, and 24 hours and 4 weeks after the 3-day infusion period.

Results: The observed variations in serum electrolyte levels were physiologically and clinically negligible. Furthermore, 24 hours after the last infusion, mean electrolyte values had spontaneously returned to normal levels without the need for additional supplementation: Na^+ 137.59 ± 1.42 mmol/L ($p = 0.6091$ vs baseline); K^+ 3.97 ± 0.5 mmol/L ($p = 0.2689$); Cl^- 103.4 ± 2.69 mmol/L ($p = 0.0388$); and Ca^{2+} 9.07 ± 0.44 mg/dL ($p = 0.5332$). Conversely, significant variations in mean Hb and albumin levels were observed. When measured 24 hours after the last infusion, mild/moderate decreases in Hb (11.62 ± 2.12 g/dL; $p = 0.009$ vs baseline) and/or albumin (mean 3.14 ± 0.24 g/dL; $p = 0.0016$ vs baseline) were evident. Such changes may, albeit very rarely, be of sufficient clinical significance in individual patients as to necessitate additional treatment.

Conclusion: In patients receiving intravenous IVIg for AMBDs, electrolyte values should be monitored but do not represent a real clinical threat. Hemoglobin and albumin values may be altered sufficiently to require additional treatment but this is a very rare occurrence. These findings confirm and extend previous reports of the safety of IVIg therapy.

Intravenous immunoglobulin (IVIg) therapy is a safe and effective treatment for several autoimmune and inflammatory diseases, such as idiopathic thrombocytopenic purpura or Kawasaki syndrome.[1] Over the last decade, this therapy has even been used carefully in patients with autoimmune mucocutaneous blistering diseases (AMBDs)[2-6] such as pemphigus vulgaris,[7-9] pemphigus foliaceus,[10] mucous membrane pemphigoid,[11] bullous pemphigoid,[12] and epidermolysis bullosa acquisita.[13] All these disorders belong to a heterogeneous, rare, and systemic group of intraepithelial (pemphigus vulgaris, pemphigus foliaceus) or sub-epithelial (mucous membrane pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita) bullous inflammatory diseases

that affect skin and mucous membranes with stratified squamous epithelia and sometimes may lead to serious and potentially fatal consequences.[14,15] These disorders are triggered by an aberrant immune response that is based on a 2-fold effect: autoreactive B and T cells, and direct and indirect autoantibodies against specific proteins mediating cell-cell (cadherins, specifically desmoglein 1 and 3) and cell-matrix (basement membrane zone proteins) adhesion in the skin and mucosae, leading to an inflammatory cascade and then to blister formation.[16-18] Although conventional therapy in these cases has always included several different immunosuppressant agents, some patients do not respond to these drugs or experience serious adverse effects, which is why alternative treatments such as plasmapheresis, extracorporeal photopheresis, immunoabsorption techniques, and high-dose IVIgs have been recommended.[7,12,19]

IVIg represents one of the alternative therapies used in the management of patients affected by severe AMBDs who are refractory to conventional immunosuppressive therapy.[3,14] IVIg is made up of a highly purified IgG fraction that is extracted from pooled human plasma collected from thousands of healthy donors and consists mostly of intact IgG molecules, with traces of IgA and IgM, and some cytokines and other immunomodulators found in serum (soluble CD4, CD8, HLA molecules, and transforming growth factor-β).[20]

Although its exact mechanism of action is still largely unknown, some investigations have shown that IVIg is able to perform several different immunomodulatory actions due to three different separate components of immunoglobulin. The first of these is the antigen-binding fragment $F(ab')_2$, which has antiproliferative effects, modulates apoptosis and cell cycles, has effects on cell adhesion, and modifies cytokine levels. The second component is the constant fragment Fc, which (i) inhibits phagocytosis and antibody-dependent cell-mediated cytotoxicity production and recycling through the FcRn receptor; and (ii) blocks access of immune complexes to FcRn IgG monomers, which are in turn involved in the pathogenesis and inflammatory effects of AMBDs. Thirdly, complement-Fc binding is involved in inhibition of deposition of activated complement.[21-23]

Specifically, in pemphigus vulgaris, IVIg is able to prevent blister formation by preventing IgG autoantibodies from binding to desmoglein 1 and 3,[24] thus reducing pemphigus vulgaris-related IgG-mediated acantholysis and cell death and upregulating endogenous caspase and calpain inhibitors.[25] Moreover, the effects of IVIg very much resemble those of plasmapheresis, which causes a selective and very rapid decline in circulating autoantibodies in the serum by accelerating the catabolism of all serum antibodies.[26] This results in a decrease in abnormal antibodies (IgG-pemphigus vulgaris) only, since normal antibodies are replaced by those present in the immunoglobulin preparation.[27]

Use of IVIg is associated with two major advantages: selective clearance of pathogenetic autoantibodies and the safety of the treatment procedures used.[2,28] However, it is also associated with a variety of mild, moderate, and severe adverse effects, with an incidence ranging from 1% to 42%.[29] Among these adverse effects, low-grade fever, headache, nausea, myalgia, and chills are particularly common, while arthralgias, flushing, abdominal cramps, and leukopenia have been less frequently described.[30,31] In addition, different investigators have also reported alterations in biochemical profiles, such as hypoalbuminemia,[29,32] an imbalance in serum sodium concentration leading to a true or pseudohyponatremia,[29,31,33-35] erythrocyte sequestration[36,37] and last, but no less importantly, an increased viscosity with consequent venous and arterial thromboembolic events in patients with high-risk factors, such as impaired circulation, underlying atherosclerotic diseases, bedridden status, advanced age, and obesity.[31,35,38,39]

To our knowledge, this preliminary clinical study is the first investigation aimed at evaluating the possible effects of IVIg therapy on serum sodium (Na^+), potassium (K^+), chloride (Cl^-), calcium (Ca^{2+}), hemoglobin (Hb), and albumin concentrations in patients with AMBDs. The study was conducted to provide all clinicians with further information on the management of patients who require IVIg treatment and to show that IVIg is a safe treatment, not only for 'on-label' diseases but also for 'off-label' diseases such as AMBDs.

Materials and Methods

Patients and Samples

The general model of our investigation was a preliminary clinical study. The sample of patients enrolled in this study, between November 2004 and October 2006, was obtained from the Division of Oral Medicine, Department of Odontostomatological and Maxillofacial Sciences, School of Medicine and Surgery, University of Naples 'Federico II', Naples, Italy. Conduct of the study was approved by the local ethics committee.

From 82 patients with AMBDs, we selected ten patients according to precise diagnostic, inclusion, and exclusion criteria. The criteria for diagnosis of AMBDs were (i) collection of a histopathologic specimen from the oral mucosa biopsy of the intact blister (presence of intra- or sub-epithelia bulla); (ii) direct immunofluorescence to detect the presence of IgG and complement C3 localized at the basement membrane zone or in the intercellular cement substance (fresh tissue was the preferred substrate for this study); and (iii) indirect immunofluorescence

Table I. Patient characteristics

Patient	Age (y)	Sex	Bullous disease	Underlying diseases	Hb values (g/dL) before IVIg	Weight (kg)	Total dosage (g/cycle)	No. of cycles	Corticosteroids (mg/wk)	Azathioprine (mg/wk)
1	37	M	PV	Lithiasis	12.35	67.5	135	22	45	100
2	29	F	PV	Anemia	10.1	60	120	21	50	None
3	77	F	PV	Heart failure, osteoporosis, diabetes mellitus	12.61	60	120	19	30	250
4	42	F	PV	Lithiasis, anemia	11	60	120	9	45	150
5	65	F	MMP	Hypertension, gallstones, duodenitis, nephritis, anemia, diabetes	11.71	82.5	165	15	12	250
6	57	M	PV	Hypertension, renal cyst	16.03	75	150	9	15	50
7	57	M	MMP	Lithiasis, hypertension, psychosis	12.2	75	150	10	50	250
8	66	F	PV	Gallstones, osteoporosis	13.2	60	120	9	60	150
9	23	F	PV	None	14.32	60	120	9	60	None
10	76	F	MMP	Hypertension, atrial fibrillation, osteoporosis, atherosclerosis	12.4	67.5	135	10	50	250

Hb = hemoglobin; **IVIg** = intravenous immunoglobulin; **MMP** = mucous membrane pemphigoid; **PV** = pemphigus vulgaris.

using the patient's serum to assess anti-basement membrane zone or anti-intercellular cement substance antibody serum titer (monkey esophagus was the preferred substrate for indirect immunofluorescence).

The inclusion criteria were (i) patients aged between 18 and 90 years (both sexes, all races) with a diagnosed AMBD; (ii) presence of active bullous and erosive lesions on the skin and/or mucosae; (iii) lack of any remarkable (≥75% of disease) remission with conventional immunosuppressive therapy consisting of high-dose corticosteroids (deflazacort 120 mg/day) and azathioprine (150 mg/day) [duration of therapy 4–72 months]; (iv) development of considerable (requiring medical treatment) adverse effects with previous conventional immunosuppressive therapy; and (v) eligibility for receiving an IVIg preparation at a total dosage of 2g/kg/cycle given over 3 consecutive days (table I).

The exclusion criteria were (i) absence of AMBD; (ii) concomitant severe systemic disease, such as solid and/or non-solid neoplasm; viral, bacterial or fungal infections; myopathies; gastrointestinal disorders; and coagulation disorders; patients with severe kidney, liver, or heart disease, severe anaemia, osteoporosis or diabetes mellitus were also excluded from the study in order to avoid variations in serum electrolytes, albumin and hemoglobin related to such pathologies and to determine whether IVIg alone was having an effect on these parameters. Severe disease was defined as a disease that, despite medical treatment, was not kept under control; (iii) presence of other autoimmune pathologies, such as systemic lupus erythematosus, Sjögren syndrome, and systemic sclerosis with cutaneous and/or mucosal lesions and/or systemic manifestations, such as lichenoid lesions, granulomatous lesions, glomerulonephritis, endocarditis, pleuritis, myalgia, abdominal pain, diarrhea, and constipation; (iv) transplant recipients who had been treated with radio- or chemotherapy; (v) patients already receiving potential inducers of bullous diseases, such as antibacterials, analgesics, sulfhydryl-containing drugs, ACE inhibitors, β-adrenoceptor antagonists, interferon-β, and interleukin-2; (vi) pregnant or breastfeeding women; and (vii) drug addiction or alcoholism. Patients who developed any of these conditions during treatment were automatically excluded from the study.

The ten patients classified as non-responders to conventional immunosuppressive therapy consisted of three men and seven women who ranged from 23 to 77 years of age (mean 52.9 years). Seven patients had pemphigus vulgaris and three patients had mucous membrane pemphigoid.

Operative Phase

All enrolled patients received IVIg therapy for a total number of 133 cycles (table I), with the optimal dose, frequency, and duration of IVIg therapy being based on the Consensus Statement on use of IVIg therapy for the treatment of AMBDs.[3] During the IVIg maintenance phase (see later in this paragraph), all patients also received, as adjuvant therapy, a low dose of corticosteroids (deflazacort 12–60mg per week) and most patients also received an immunosuppressive agent (azathioprine 50–250mg per week) [table I]. All patients also received adequate hydration and premedication with acetaminophen (paracetamol) 500mg, chlorpheniramine (chlorphenamine) 20mg, and methylprednisolone 40mg 30 minutes before each infusion. Human immunoglobulin 5% solution was infused intravenously via an electronic pumping device (Optima® [1] MS) at a total dosage of 2 g/kg/cycle given over 3 consecutive days (table I). The infusion was administered slowly at ≤50 mg/kg/hour. Vital signs were monitored during the infusion. The total number of cycles of IVIg given per patient ranged from 9 to 22 (mean 13.3). These infusions were administered initially at an interval of 3 or 4 weeks between each cycle until complete clinical remission had been obtained with absence of new lesions. Thereafter, the intervals between infusions were slowly increased to 6, 8, 10, 12, 14, and 16 weeks (defined as the 'maintenance therapy period'). The IVIg endpoint of therapy was defined as that time at which patients were disease free for a 16-week interval. During this period the number of recurrences ranged from one to three, while the number of relapses ranged from one to six. Currently, in Italy, only eight different pharmaceutical preparations are marketed and we were able to use only three of these (Flebogamma®, Ig Vena N IV®, Endobulin®) because they were the only preparations available in our institution. The decision to give a patient one particular IVIg preparation rather than another depended upon the availability of IVIg preparations at our centralized pharmacy at that time.

We carefully evaluated the coagulation profile of all patients and introduced preventive measures to reduce the risk of thromboembolic events. This included aspirin (acetylsalicylic acid) therapy (six patients), as suggested by Katz and Shoenfeld,[38] and subcutaneous calcium heparin (two patients receiving polytherapy for multiple co-morbidities).

We also monitored, through blood tests, all patients' serum Hb, albumin, Na^+, K^+, Cl^- and Ca^{2+} levels 24 hours before, 24 hours after, 4 weeks after, and during the 3 days of each treatment cycle.

Statistical Evaluation

The arithmetic mean of the age of patients and of all variable values were calculated using the Σ test by Microsoft® Excel. We also calculated the standard deviation of all variables and compared values during the 3 infusion days (first, second, and third day) and at 24 hours and 4 weeks after IVIg with pretreatment values (24 hours before IVIg) using the two-tailed paired t-test and NCSS, PASS and GESS 2006 statistical and data analysis software. A p-value of <0.01 after the Bonferroni adjustment was considered significant.

Results

Of the ten patients evaluated in the study, five had cardiovascular diseases (e.g. hypertension and/or atherosclerosis) before starting IVIg treatment, four had renal diseases (e.g. lithiasis, nephritis, or renal cyst), three had anemia, and three had osteoporosis (table I). Despite these concomitant disorders, all patients completed all cycles.

Mean serum Na^+ levels did not show any significant increase or decrease during the 3 days of therapy, 24 hours after infusion (137.59 ± 1.42 mmol/L; p = 0.6091 vs level 24 hours before infusion), or 4 weeks later (138.7 ± 1.93 mmol/L; p = 0.0679 vs level 24 hours before infusion) [table II]. Similarly, mean serum Cl^- levels were shown to be stable, with levels of 100.32 ± 1.51 mmol/L 24 hours before infusion and 102.47 ± 2.46 mmol/L 4 weeks after treatment (p = 0.061). However, measurement of mean serum K^+ levels revealed a small possibility of development of very mild hypokalemia, but only on the third day of therapy (3.95 ± 0.58 mmol/L; p = 0.1766 vs level 24 hours before infusion) and 24 hours after the end of therapy (3.97 ± 0.5 mmol/L; p = 0.2689 vs level 24 hours before infusion). Mean serum Ca^{2+} levels also suggested the possibility of a very mild hypocalcemia, with levels decreasing from 9.14 ± 0.25 mg/dL 24 hours before infusion to 9.07 ± 0.44 mg/dL 24 hours after the end of therapy (p = 0.5332). Four weeks after ending IVIg, mean K^+ and Ca^{2+} levels showed statistically significant but clinically insignificant variations (table II).

Conversely, statistically and clinically significant changes were seen in mean Hb levels. Taking into account the standard deviation values, these decreased from 12.58 ± 1.76 g/dL 24 hours before infusion to 12.16 ± 2.02 g/dL during the first day of therapy (p = 0.115). On the second day of treatment, mean serum Hb decreased to 11.68 ± 1.96 g/dL (p = 0.007 vs level 24 hours before infusion), and decreased further to 11.62 ± 2.12 g/dL 24 hours after treatment (p = 0.009 vs level 24 hours before infusion). However, this

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Arithmetic means, standard deviations and probability levels (p-values) of variations in serum sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}) levels before, during, and after 133 cycles of intravenous immunoglobulin (IVIg) therapy in 10 patients with autoimmune mucocutaneous blistering diseases[a]

Phase of IVIg therapy	Na^+ (mmol/L)	p-Value[b]	95% CI	K^+ (mmol/L)	p-Value[b]	95% CI	Cl^- (mmol/L)	p-Value[b]	95% CI	Ca^{2+} (mg/dL)	p-Value[b]	95% CI
24h before	137.29 (± 2.01)		135.42, 139.15	3.77 (± 0.37)[c]		3.43, 4.11	100.32 (± 1.51)		98.92, 101.71	9.14 (± 0.25)[c]		8.9, 9.36
1st day	138.91 (± 1.82)	0.0019[d]	137.22, 140.6	3.96 (± 0.44)	0.1607	3.55, 4.37	103.75 (± 1.41)	0.0047[d]	102.44, 105.05	9.21 (± 0.5)[c]	0.5830	8.75, 9.67
2nd day	138.33 (± 2.69)	0.1896	135.84, 140.82	3.9 (± 0.31)	0.1452	3.61, 4.19	104.64 (± 2.11)	0.0049[d]	102.68, 106.6	9.2 (± 0.4)[c]	0.4417	8.84, 9.56
3rd day	137.88 (± 0.5)	0.4595	137.41, 138,34	3.95 (± 0.58)[c]	0.1766	3.41, 4.48	104.03 (± 1.91)	0.0054[d]	102.25, 105.8	9.0 (± 0.47)[c]	0.2179	8.53, 9.41
24h after	137.59 (± 1.42)	0.6091	136.26, 138.91	3.97 (± 0.5)[c]	0.2689	3.5, 4.44	103.4 (± 2.69)	0.0388	100.93, 105.92	9.07 (± 0.44)[c]	0.5332	8.65, 9.48
4wk after	138.7 (± 1.93)	0.0679	136.91, 140.49	4.03 (± 0.38)	0.0032[d]	3.67, 4.39	102.47 (± 2.46)	0.061	99.02, 105.92	9.47 (± 0.28)	<0.001[d]	9.08, 9.87

a Physiologic ranges: Na^+ 135–148 mmol/L; K^+ 3.5–5.3 mmol/L; Cl^- 97–112 mmol/L; Ca^{2+} 8.9–10.3 mg/dL.

b Compared with levels 24h before therapy.

c Indicates the value is below the physiologic range or could be below the range when the standard deviation is taken into account.

d Statistically significant (Bonferroni adjustment, $\alpha = 0.01$).

represented only a mild decrease from baseline values and the levels may still have been within the physiological range when the standard deviation values were taken into account.

Mean serum albumin concentrations were lower than the physiological range from the first day of therapy (3.32 ± 0.31 g/dL; $p < 0.001$ vs level 24 hours before infusion), reached their lowest value on the second day of therapy (3.09 ± 0.28 g/dL; $p < 0.001$ vs level 24 hours before infusion) and increased slightly 24 hours after treatment (3.14 ± 0.24 g/dL; $p = 0.0016$ vs level 24 hours before infusion). However, it is important to note that both Hb and albumin levels spontaneously returned to normal within 4 weeks of discontinuation of IVIg (table III).

No adverse effects occurred during IVIg therapy and no patient developed an electrolyte imbalance of sufficient severity as to require additional treatment. Blood transfusions and/or human albumin infusions were required on very few occasions (two blood transfusions in one patient and eight albumin infusions in four patients) and only within 24 hours after the last IVIg infusion. Three patients reached pathological Hb levels (<12 g/dL) after IVIg infusions: patient 2 (8.55 g/dL), patient 4 (10.97 g/dL), and patient 7 (10.37 g/dL). However, only one patient (patient 2: 21 cycles) occasionally reached a Hb concentration <8.0 g/dL. Four patients (patient 1: 22 cycles, patient 2: 21 cycles, patient 3: 19 cycles, patient 5: 15 cycles) reached an albumin concentration <1.8 g/dL.

No statistically or clinically significant differences in post-IVIg Hb and albumin levels were detected among patients receiving IVIg preparations manufactured by different companies or in patients with previous anemia (patients 2, 4, 5) compared with those with a normal pre-IVIg treatment Hb level.

In addition, we calculated the arithmetic mean haematocrit (Hct) level (physiologic range: male = 37–54%; female = 35–48%) across all cycles for each patient. Of ten patients, six had a normal Hct percentage level, while four showed a decrease of Hct 24 hours after the end of IVIg therapy. The respective pre-IVIg and 24-hour post-IVIg Hct values for these patients were as follows: patient 4 −35.6% and 30.5%; patient 7 −42% and 33.6%; patient 2 −31% and 27.9%; and patient 8 −33.7% and 31%). Notably, two of these four patients commenced IVIg therapy with an already low Hct level.

Discussion

In this preliminary clinical study, we analyzed variations in serum electrolyte, Hb and albumin levels in ten patients with AMBDs who, over the past 2 years, had received 133 cycles of IVIg (for a total of 399 infusions). Our aim was to better understand the possible clinical consequences of such changes, particu-

Table III. Arithmetic means, standard deviations and probability levels (p-values) of variations in serum hemoglobin (Hb) and albumin levels before, during and after 133 cycles of intravenous immunoglobulin (IVIg) therapy in 10 patients with autoimmune mucocutaneous blistering diseases[a]

Phase of IVIg therapy	Hb (g/dL)	p-Value[b]	95% CI	Albumin (g/dL)	p-Value[b]	95% CI
24h before	12.58 (± 1.76)[c]		10.95, 14.21	3.68 (± 0.28)[c]		3.42, 3.94
1st day	12.16 (± 2.02)[c]	0.115	10.29, 14.02	3.32 (± 0.31)[c]	<0.001[d]	3.03, 3.61
2nd day	11.68 (± 1.96)[c]	0.007[d]	9.86, 13.5	3.09 (± 0.28)[c]	<0.001[d]	2.82, 3.34
3rd day	11.64 (± 2.12)[c]	0.011	9.68, 13.6	3.12 (± 0.26)[c]	<0.001[d]	2.87, 3.37
24h after	11.62 (± 2.12)[c]	0.009[d]	9.66, 13.58	3.14 (± 0.24)[c]	0.0016[d]	2.91, 3.37
4wk after	13 (± 1.6)[c]	0.26	10.74, 15.2	3.8 (± 0.26)	0.4243	3.42, 4.16

a Physiologic ranges: Hb 12–16 g/dL; albumin 3.5–5.2 g/dL.

b Compared with levels 24h before therapy.

c Indicates the value is below the physiologic range or could be below the range when the standard deviation is taken into account.

d Statistically significant (Bonferroni adjustment, $\alpha = 0.01$).

larly with respect to the transience and severity of these changes, and whether any life-threatening situations developed.

Since no data in this area were available in the literature, we did not know if different methods of industrial preparation or purification of IVIg preparations, or different excipients contained in these products, may have influenced the observed changes. We did know that differences among various IVIg commercial preparations have been described in the literature, but how these differences would impact on safety, tolerability, or efficacy had not been well defined as there have been few comparative studies,[40] and, likewise, how these different preparations may have differentially affected serum electrolyte, Hb or albumin levels was not known. Therefore, we gave each patient receiving a particular IVIg preparation the same amount of that preparation in an attempt to eliminate, or at least reduce, the possibility that use of a specific preparation may have biased the observed effects on serum electrolyte, albumin and Hb concentrations.

We also documented patients' use of immunosuppressive therapy over previous months, prior to commencement of IVIg therapy, and all patients had normal serum electrolyte, Hb and albumin levels at commencement of IVIg therapy. Given that commonly used corticosteroids are able to modulate serum electrolyte balance[41] and that an immunosuppressant such as azathioprine can influence Hb values,[42] this observation confirms our finding that IVIg, except in very rare cases of underlying predisposing conditions, does not change serum electrolyte or Hb levels; if this was the case, a 'summation effect' on such levels would have been observed.

One of the most important adverse effects of IVIg treatment reported in the international literature is the possibility that patients receiving this therapy can develop severe hyponatremia[34] or pseudohyponatremia.[33] The risk of morbidity and mortality following development of hyponatraemia is increased in patients with concomitant congestive heart failure.[43] Pseudohyponatremia increases risk of acute renal failure but only in patients with pre-existing renal insufficiency.[33] Two cases of dilutional (hypertonic) hyponatremia have been reported in patients treated with an IVIg preparation, with the mechanism of action in such cases having been ascribed to accumulation of the sucrose carrier in the preparation and subsequent drawing of water from the intracellular to the extracellular compartment.[34] However, other investigators have characterized the same phenomenon as a pseudohyponatremia resulting from increases in serum protein (hyperproteinemia) and lipids (hyperlipidemia) with a subsequent decrease in plasma water volume and Na^+ concentration.[35] Moreover, pseudohyponatremia would increase plasma viscosity with a consequent increased risk of thromboembolic events. Although we believe that these previous studies are inconclusive because they included only small patient samples, they nevertheless indicate that such thromboembolic events occur only in patients with underlying risk factors, such as advanced age, pre-existing severe renal or cardiovascular disease, severe hyperlipidemia, or bedridden status.[35,38,39]

Our findings are consistent with the results of the above-mentioned studies.[35,38,39] None of the patients in our study developed severe hyponatremia or pseudohyponatremia. Indeed, as shown in table II, no significant variations in serum Na^+ or Cl^- levels were seen during IVIg therapy and, therefore, no predictors of hyper/hyponatremia or hyper/hypochloremia were identified. Conversely, a statistically significant ($p = 0.0032$) variation in serum K^+ level was observed 4 weeks after completion of IVIg therapy but, again, this was not predictive of hyper/hypokalemia (mean serum K^+ level at this time point was 4.03 ± 0.38 mmol/L). Indeed, only one of the ten patients in the study exhibited persistent but very mild hypokalemia before, during and after IVIg therapy and this patient did not require supplementation because

his serum K^+ level was never <2.7 mmol/L (and therefore low enough to engender fear of grave complications). Mean serum Ca^{2+} levels exhibited mild fluctuations on the third day of therapy (9.0 ± 0.47 mg/dL; p = 0.2179 vs pre-IVIg value) and 24 hours after the last infusion (9.07 ± 0.44 mg/dL; p = 0.5332 vs pre-IVIg value). There was also a statistically significant variation in mean serum Ca^{2+} level 4 weeks after completion of IVIg therapy (9.47 ± 0.28 mg/dL; p < 0.001 vs pre-IVIg value) but this was clinically negligible (table II). We do not know whether these variations in serum calcium levels were related to IVIg therapy; in fact, we strongly believe that these fluctuations could have been related to adjuvant use of corticosteroid therapy and specific patient characteristics (e.g. three elderly women had osteoporosis).

The variations in serum Hb and albumin levels observed in this study showed that these parameters were more sensitive to IVIg than serum electrolytes. Indeed, IVIg contains erythrocyte-specific isoantibodies against A and B blood antigens, and two previous studies have noted that IVIg therapy may cause enhanced erythrocyte sequestration.[36,37] This occurs because immune complex-like moieties activate the complement C3b fraction and bind to erythrocyte complement receptor-1, thereby functioning as opsonins and inducing erythrophagocytosis, particularly in young patients.[36,37] Our investigation supports the findings of these two studies by showing that there is a mild decrease in Hb concentration with IVIg therapy, starting on the first day of therapy (mean serum Hb 12.16 ± 2.02 g/dL; p = 0.115 vs pre-IVIg value) and continuing until 24 hours after the last infusion (11.62 ± 2.12 g/dL; p < 0.009 vs pre-IVIg value) [table III]. This may be associated with a mild or moderate hemolysis with consequent anemia in patients with an underlying predisposing condition of low Hb level or high erythrocyte sequestration.[37] In fact, only one of our patients needed two blood transfusions because her serum Hb reached <8 g/dL and this patient had a pre-existing low Hb level.

Serum albumin levels also displayed this type of variation (and perhaps to a slightly greater extent) in our study. There was a progressive decrease in mean albumin level from the first day of therapy (3.32 ± 0.31 g/dL; p < 0.001 vs pre-IVIg value) to 24 hours after the last infusion (3.14 ± 0.24 g/dL; p = 0.0016 vs pre-IVIg value) [table III]. Thus, albumin levels may vary during IVIg therapy. Indeed, in our study, serum albumin decreased to <1.8 g/dL in four patients, who required supplementation with human albumin infusions. This confirms the outcomes of two previous observations[29,32] which emphasized the critical role of albumin in patients receiving IVIg therapy, although the reason for the reduction in albumin during IVIg therapy remains unknown. These investigators hypothesized that the observed effect could be due to the increase in immunoglobulin concentration, which would consequently increase systemic protein levels and create an oncotic pressure imbalance that could result in peripheral edema. Conversely, other investigators have shown that this reduction might be due to inhibition of FcRn, which binds not only IgG but also albumin, protecting both from degradation and extending their lifespan.[21,44-46] Thus, saturation of FcRn might enhance both endogenous IgG and albumin catabolism.[21,44-46] We believe that both are very probable mechanisms. In addition, we believe a potential dilutional effect of IVIg might play an important role in triggering these clinical relevant events, since two of the ten patients in our study displayed a relevant decrease in Hct, although all other hemodilution parameters (e.g. serum electrolytes, complete blood count, and urine specific gravity) were normal before, during, and after IVIg therapy.

It would be very useful to establish objective criteria for evaluating who is susceptible to changes in Hb or albumin, but this is difficult. We suggest that patients may be at greater risk of developing decreases in serum Hb and/or albumin levels if they present with one of the following underlying conditions prior to starting IVIg therapy:

1. Malnutrition. In such cases, a diet rich in protein would be recommended.
2. Pre-existing low levels of albumin. This could be due to defective synthesis of albumin secondary to systemic diseases, such as cirrhosis of the liver, or to extravascular protein loss resulting from, for example, the nephrotic syndrome, protein-losing enteropathy, lymphatic blockage or mucosal disease, congestive heart failure, or acute or chronic inflammation.
3. Pre-existing low levels of hemoglobin. Possible causes include previous chronic anemia due to decreased red cell production, increased red cell destruction (hemolysis) and blood loss.
4. Pre-existing hemodilution.

Conclusion

We conclude from our study that although serum electrolyte values must be meticulously monitored in patients receiving IVIg therapy, changes in these parameters do not represent a real clinical threat. Patients in our study did not experience any symptoms as a result of changes in serum electrolyte levels because the observed fluctuations were transient and physiologic, and disappeared within 24–48 hours of the end of treatment. Furthermore, the variations in electrolyte levels had no consequences in terms of treatment. With respect to serum Hb and albumin levels, it is understood that in patients treated with IVIg, changes in these parameters may reach critical values below the physiologic range necessitating infusion of blood or human albumin. However, our study showed that these events are very rare, are observed only within the 24-hour period following the last infusion and occur

only in patients with a pre-existing low concentration of Hb or albumin before commencement of IVIg therapy. Furthermore, short-term follow-up performed 4 weeks after the end of the IVIg cycle revealed no statistically significant changes in serum Hb or albumin requiring additional therapy (table III).

In conclusion, we suggest that patients taking IVIg therapy very rarely develop severe pathologic conditions that require intervention as a result of disturbances in serum electrolyte, Hb, or albumin levels. Thus, our results reinforce and extend the notion that IVIg is a safe therapy, as has been reported by previous authors.[47-49] Our interesting findings should be confirmed in a larger case series or, if possible, in randomized controlled trials.

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