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Case Report

A Rare Side Effect of IVIG: Diarrhea

IVIG Tedavisinin Nadir Bir Yan Etkisi: İshal

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ABSTRACT

Intravenous immunoglobulin (IVIG), which is primarily immunoglobulin G (IgG), is used in the treatment of many diseases. While it is generally well tolerated, some adverse effects may be seen in different systems during IVIG treatment. The adverse effects of IVIG infusion are typically mild and related to the infusion rate. The formation of the immunoglobulin aggregates that lead to the activation of the complement system can be prevented by decreasing the infusion rate, and mild adverse effects may be overcome. In rare cases, however, severe life-threatening adverse effects may develop, such as anaphylaxis, cardiac dysrhythmia, bronchospasm, changes in consciousness, aseptic meningitis, colitis and thromboembolism. We report here on a case diagnosed as unclassified antibody deficiency that developed a clinical picture of “diarrhea” due to IVIG treatment. The treatment was switched to the subcutaneous application (SCIg), and diarrhea was prevented.

Keywords: *IVIG, diarrhea, adverse effect, pediatric patients, diarrhea*

ÖZET

Öncelikle immünoglobulin G (IgG) olan intravenöz immünoglobulin (İVİG), birçok hastalığın tedavisinde kullanılmaktadır. Genellikle iyi tolere edilse de İVİG tedavisi sırasında farklı sistemlerde bazı yan etkiler görülebilmektedir. İntravenöz immünglobulin infüzyonunun yan etkileri tipik olarak hafiftir ve infüzyon hızı ile ilişkilidir. İnfüzyon hızı azaltılarak kompleman sisteminin aktivasyonuna yol açan immünoglobulin agregatlarının oluşumu önlenebilir ve hafif yan etkiler giderilebilir. Ancak nadir durumlarda anafilaksi, kardiyak aritmi, bronkospazm, bilinç değişiklikleri, aseptik menenjit, kolit ve tromboembolizm gibi hayatı tehdit eden ciddi yan etkiler gelişebilir. Burada sınıflandırılmamış antikor eksikliği tanısına yönelik İVİG tedavisi alan ve yan etki olarak “ishal” tablosu gelişen; sonrasında ise tedavide subkutan immunglobolin uygulamasına (SCIg) geçilerek ishal tablosu önlenen bir olguyu sunuyoruz.

Keywords: *IVIG, yan etki, primer immun yetmezlik, çocuk hasta, ishal*

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INTRODUCTION

Intravenous immunoglobulin (IVIG) was licensed in 1981 for the treatment of primary antibody deficiencies and has been used in the treatment of many diseases over the last 40 years (1,2). Standard IVIG preparations are obtained from 5000-10000 donor plasma and contain a variety of antibodies that are formed by the donors due to natural infections and immunization (2). Immunoglobulin G (Ig G) is the main compound, although it may contain a modest amount of immunoglobulin A (IgA) and different stabilizers (Maltose, sucrose, glucose, proline and glycine) (1). Intravenous immunoglobulin is generally well tolerated, although adverse effects can be seen in rare cases that are typically mild – most frequently fever, shivering, fatigue, headache, myalgia and arthralgia. A temporary decrease in the infusion rate or pausing the infusion for 15–30 minutes is generally enough to end the adverse effects (3,4). Among the intermediate adverse effects are headache, dyspnea, vomiting and chest pain, while severe adverse effects, such as anaphylaxis, cardiac dysrhythmia, bronchospasm, changes in consciousness, aseptic meningitis, colitis and thromboembolism, have been reported (3). Adverse effects are classified as "immediate reaction," "delayed reaction" and "late reaction" according to the manifestation of symptoms, such as within the first six hours, after six hours to one week, and after one week, respectively (3). The most common late adverse effect is headache, while rare late adverse effects include transfusion-related acute lung damage, colitis, dermatological adverse effects and infectious diseases. Late adverse effects due to IVIG treatment are generally systemic and may manifest weeks or even months after the infusion (2, 3).

The risk factors of the patient should be evaluated early in the course, and the administration of the infusion at a slower rate, depending on the adverse effect, and planning premedication may prevent their development. Switching the application site from intravenous to subcutaneous may decrease these negative effects to a minimum when especially systemic adverse effects are encountered. We report here on a case diagnosed with non-specified antibody deficiency that developed a clinical picture of "diarrhea" due to IVIG treatment. The treatment was switched to the subcutaneous application (SCIg), and diarrhea was prevented.

Case Report

A 7-year-old male patient was being followed-up at the pediatric immunology outpatient clinic for three years for unclassified antibody deficiency. The case, whose parents were healthy, was diagnosed with primary immune deficiency (PID) while being evaluated for frequent lower respiratory tract infections. A physical examination of the patient revealed a body weight in the 3–10 percentile and height in the 25–50 percentile and was otherwise unremarkable aside from pectus carinatum. Genetic analysis was performed but revealed no mutation. The laboratory findings of the patient are presented in Table 1. A significant reduction in the frequency of infections was seen in the patient, who had been receiving IVIG for the last three years. While there were no adverse effects in the first year of the treatment, diarrhea with more than 10 excessively watery stools, starting 24 hours after IVIG treatment and lasting for 10 days, was observed after the first year. No pathological finding was noted in the stool examinations performed to evaluate diarrhea, which resulted in isonatremic severe dehydration and required hospital admission. A total of seven clinical pictures of diarrhea were seen in the case, all of which developed after IVIG infusion. Invariably, the start time of the diarrhea was hour 24 after the completion of the IVIG infusion and was observed to last for almost 10 days each time. Detailed stool microscopy, stool cultures and acute phase reactants were studied during each hospital admission, and all were negative and within the normal ranges. Infection markers were negative. The treatment was changed to preparation with a different stabilizer with a decreased infusion rate and the administration of anti-inflammatory premedication. However, the picture of diarrhea could not be prevented. Intravenous immunoglobulin preparations causing diarrhea in our patient are listed in Table 2. Subsequently, the total dose of IVIG was divided into four doses to be administered subcutaneously in four weekly administrations. The patient was monitored for 48 hours after the subcutaneous application of the drug. No reactions were seen after the SCIg application. After weekly SCIg treatment for three months, treatment was converted to recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIg) treatment. The patient has been followed-up on the fSCIg treatment for the last six months. The severe diarrhea picture was controlled first by SCIg and followed by fSCIg with no additional adverse effects. The consent of the patient's parents was obtained for this study.

Table 1. Laboratory findings

Parameters	Patient	Normal values for age
Complete blood count White blood cells, cells/ml Neutrophils, cells/ml Lymphocytes, cells/ml	 9140 3910 3890	 6000-17500 1500-8500 2300-5600
Pre-infusion immunoglobulin values IgG, mg/dl IgA, mg/dl IgM, mg/dl IgE, ku/L	 327 98,8 39.5 1.7	 715±181 47.72±18.33 94.41±40.34 0-100
Immunoglobulin values* IgG, mg/dl* IgA, mg/dl IgM, mg/dl IgE, ku/L	 813 150 40 1.7	 715±181 47.72±18.33 94.41±40.34 0-100
Lymphocyte subsets CD3+ Cells, cells/ml (% of lymphocyte) CD4+ Cells, cells/ml (% of lymphocyte) CD8+ Cells, cells/ml (% of lymphocyte) CD19+ Cells, cells/ml (% of lymphocyte) NK Cells, cells/ml (% of lymphocyte)	 2917/mm3 (75%) 1556/mm3 (40%) 1361/mm3 (35%) 778/mm3 (20%) 195/mm3 (5%)	 1400–4500 700–2000 500–1400 400–1500 100–700
Spesific antibodies Anti Hbs IgG	 Negative	
C3 C4	110 mg/dl 22 mg/dl	73-180 12-39

*with IVIG replacement

DISCUSSION

The frequency of adverse effects has been reported to be 1–81% in cases undergoing IVIG treatment, although the adverse effects of IVIG infusion are typically mild and related to the rate of infusion. In rare cases, severe life-threatening adverse effects, such as anaphylaxis, can be seen (1,2,5). Diarrhea due to IVIG has been identified among the early adverse effects of IVIG but has been reported only rarely and has been associated with complement activation by immunoglobulin aggregates or the stabilizers in the preparation (5). The presence of the prekallikrein activator and kallikrein in the immunoglobulin preparations and increased IL-6, TNF α and thromboxane B2 levels have also been put forward as causes of adverse effects (1,2,5).

Table 2. Intravenous immunoglobulin preparations causing diarrhea in our patient

	Preparation 1	Preparation 2	Preparation 3
Preparation	5%, liquid	5%, liquid	%10, lyophilized
Stabilizer	D-sorbitol	Maltose	Glycine
Amount of IgA (microgram/mL)	<3.1	<200	<140
Osmolality (mOsm(kg)	325 ± 4.8	310-380	240-300
Sodium content (mEq/ml)	<3.2 mEq/ml	<30 mEq/ml	-
pH	5.6±0.1	5.1-6.0	4.6–5.1

Premedication with antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs may substantially decrease the severity and incidence of the adverse effects associated with IVIG, and prehydration with normal saline has also been used to prevent adverse immunoglobulin-induced effects (1). The product was changed to a preparation containing a different stabilizer, administered at a decreased infusion rate, with the administration of anti-inflammatory premedication, although the picture of diarrhea could not be prevented. Conversion to SCIg from IVIG seems to be an effective approach to decreasing immunoglobulin-induced adverse effects in patients with previous experience of severe adverse effects or those who are at high risk of development of adverse effects (1,2,6). The SCIg or fSCIg treatment option can thus be chosen in cases experiencing severe systemic adverse effects. The IVIG-induced clinical picture of diarrhea was initially prevented by SCIg application and followed by fSCIg treatment in the case presented here. The association between IVIG and necrotizing enterocolitis (NEC) was evaluated in a newborn with hemolytic anemia in a study by Josep Figueras et al. (7). The development of NEC in cases with severe autoimmunity on high doses of IVIG was emphasized, which it was suggested could be decreased by slow infusion. While the present case had no autoimmunity and the IVIG dose was not high, diarrhea development could not be prevented by slow infusion. Based on the findings of the case presented here, it can be stated that the clinical picture of diarrhea is not as–

sociated with high dose, rapid infusion or autoimmunity. Interestingly, IVIG has been used successfully for treating autoimmune and inflammatory diseases as an immunomodulator and anti-inflammatory agent, while Rogatien et al. (8) demonstrated that IVIG regulated bowel homeostasis in an animal model in which diarrhea was developed.

In conclusion, severe adverse effects complicate the treatment of conditions, such as PID, in which IVIG replacement is mandatory. Diarrhea in IVIG treatment has been reported rarely in the literature. fSCIg may be considered a safe option in cases with systemic adverse effects, such as diarrhea since such effects are reported less in SCIg treatment.

Conflict of Interest / Çıkar Çatışması

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