Immediate adverse reactions of intravenous immunoglobulins

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Abstract

Intravenous immunoglobulin is the IgG plasma fraction prepared from thousands of do-nors. It is used in the treatment of many clinical conditions. Most adverse reactions that re-sult from its infusion are considered to be mild and self limited. We aimed to examine our local experience of immediate adverse reactions to Intravenous immunoglobulin. The charts of patients who received Intravenous immunoglobulin at King Khalid University Hospital from January 2003 to Dec 2005 were reviewed looking for new symptoms or signs that they developed during infusion or shortly afterwards.

Twenty five patients, out of 284, developed immediate adverse reactions to Intravenous im-munoglobulin infusions. All of these reactions were mild to moderate and responded to symptomatic therapy. Fever was the most common reaction. Patients with primary immu-nodeficiency had relatively less adverse reactions as compared to those with autoimmune conditions.

Intravenous immunoglobulin may be considered a relatively safe drug. However, patients should be monitored for the development of adverse reactions, most of which are easy to control.

Introduction

Intravenous immunoglobulin (IVIG) is a plasma product prepared from the serum of thousands of donors and is primarily composed of the IgG fraction [1]. IVIG has many clinical indications, but it is generally given for 2 major purposes; first as a replacement therapy for patients with primary or secondary immunodeficiency in a dose of 0.4-0.6 gm/Kg, and second as an immunomodulatory agent for patients with certain autoimmune conditions in a dose of 1-2 gm/kg. The consumption of IVIG has been increasing over the past 2 decades mainly because of the expanding number of indications where it was found to be useful [2,3].

IVIG is considered a relatively safe drug. However, ad-verse reactions are being observed as larger numbers of patients are treated with higher doses [4]. These reactions can be mild, like low-grade fever, flushing, or headache; moderate, like urticaria, wheezing, or aseptic meningitis; or severe, like severe respiratory distress, or hypotension [4]

Fortunately, most adverse reactions observed and re-ported in the literature are mild and self limited [5]. The adverse reactions that result from IVIG infusion can occur immediately during the infusion or shortly afterwards or can be delayed up to 72 hours post-infusion.5 The types of these adverse reactions and their frequency are highly variable among different reports and the data available is limited. We are reporting here our local experience of adverse reactions to IVIG at King Khalid University Hospital, an 850 bed tertiary teaching center, retrospectively over a period of 3 years.

Methods

The medical records of patients who received IVIG in the period from January, 2003 to December 2005 were obtained using the hospital computer system. We found 305 patients who received IVIG over the specified period. Among them, 284 patients had their charts available for review. These charts were reviewed individually looking for new symptoms or signs that developed in the patients during or shortly after receiving IVIG (about 2 hours). We also obtained information regarding the total number of infusions each patient received, the amount of each dose, duration of infusion, and whether the patient was pre-medicated with paracetamol, anti-histamine, steroid, or different combinations of these medications.

The IVIG brand used during the study period was Octagam®. In most of our patients IVIG was infused according to the manufacturer's recommendations. This study was done in accordance with the requirements of the ethical committee at the College of Medicine and King Khalid University Hospital.

Results

Twenty five (8.8%) patients had new signs or symptoms recorded in their charts during IVIG infusion or within 2 hours afterwards. Fourteen patients were males and 18 were children (<18 years). The adverse reactions occurred in 26 (1.4%) infusions out of 1754 infusions received by the 284 patients over the study period (one patient had 2 reactions in 2 separate infusions).A list of these patients with the indication for each infusion, the adverse reaction and whether the patient was pre-medicated or not is shown in Table 1.

Table 1. A list of patients who had adverse reactions from IVIG infusions

No.	Age (y)	Sex	Indication	Adverse reaction	Pre-medication
1**	0.3	F	PID	fever	all
2	45	F	ITP	fever	none
3	3	F	ITP	fever	none
4	9	M	ITP	headache	none
5	12	M	ITP	fever & vomiting	none
6	63	F	GBS	fever	none
7	16	M	GBS	fever	none
8	1.5	M	GBS	fever	paracetamol
9	3	M	GBS	fever	none
10	14	M	GBS	fever	none
11	5	M	GBS	fever	paracetamol

12	1.5	M	GBS	fever	paracetamol
13	0.6	F	KD	fever	paracetamol
14	2	M	KD	fever	paracetamol
15	7	F	KD	fever	none
16	0.9	M	KD	fever	paracetamol
17	8	M	KD	fever	none
18	25	F	Autoimmune Hemolytic Anemia	fever	none
19	63	F	SLE	fever	none
20	27	F	SLE	nausea	paracetamol steroid
21	36	F	SLE	fever	none
22	30	M	Rapidly progressive glomeru-lonephritis	fever	none
23	5	M	Intractable epilepsy	fever	all
24	1	M	Acute demyelinating encephalitis	fever	none
25	11	F	Brachial Neuritis	fever, vomiting & headache	None

*all, indicates: paracetamol, anti-histamine, and steroids. PID: primary immunodeficiency. ITP: immune throm-bocytopenic purpura. GBS: Guillain-Barre syndrome. KD: Kawasaki disease. SLE: systemic lupus erythematosus.
**Patient # 1 had 2 reactions of fever after 2 separate infusions.

All reactions were mild to moderate and resolved with symptomatic therapy. Fever was the most common reaction and occurred in 23 patients, followed by nausea and vomiting in 3 patients and headache in 2. Patient number 25 (Table 1) could have had aseptic meningitis.

For patients with primary immunodeficiency (PID), ad-verse reactions occurred in 2/242 (0.83%) infusions, both were in one patient out of 18 (5.6%). On the other hand, for patients who received IVIG as an immunomodulatory agent, adverse reactions occurred in 24/1512 (1.5%) infu-sions, that is in 24/266 (9%) patients.

Paracetamol was used as a pre-medication prior to 78 in-fusions, antihistamines prior to 26 infusions, and steroids prior to 24 infusions. This includes all infusions whether associated with an adverse reaction or not. Sometimes, different combinations of these medications were used. Steroids were sometimes given as part of the treatment of the original disease and not meant to be a pre-medication to IVIG.

Discussion

The frequencies of immediate and delayed adverse reac-tions reported in the literature are fairly common but for-tunately mostly mild and self limited [5]. The rate of immediate adverse reactions we found in our patient population, which is 8.8% of patients received IVIG or 1.4% of the number of infusions, is comparable to many other reports.

Chen et al. from the University Health system consortium in the USA reported a rate of adverse reactions in 11% of patients who received IVIG with fe-ver being the most common reaction [6]. A similar rate was reported by Lee et al from New Zealand [7]. Also, Sing-Grewal et al recently reported a rate of 10.3% of immediate reactions in Australian children corresponding to 3.5% of infusions, with headache being the most com-mon [8]. More closely, a report from Jordan by Al-Wahadneh et al. indicated that 14.5% of patients had ad-verse reactions to IVIG [9]. Headache was the most common in the latter study as well.

The lower rate of adverse reactions we found in patients with PID as compared to other patients receiving IVIG for immunomodulatory purposes was observed in earlier studies. Brenan et al., reported 111 reactions in 13,508 infusions (0.8%) in a prospective study over 12 years in patients with PID[10]. In the contrary, one study from Iran reported a much higher rate of reactions which was 12.35% of infusions in patients with PID [11]. Tcheurekdjian et al. reported even a higher rate of imme-diate reactions in those patients, up to 17% of infusions [12]. Overall, most of the reactions noticed in the 3 latter studies were mild and resolved within 24 hours.

Fever was by far the most common adverse reaction re-corded in our study. This is consistent with the report of the FDA's MedWatch passive surveillance system.5 In few occasions fever may have been related to the disease itself which might be hard to distinguish. A very common reaction toIVIG reported in the literature is headache [8,13,15]. It mostly occurs as a delayed reaction and more in patients with history of migraine. We had comparatively few patients recorded to have headache during in-fusion. This may partly be due to the relatively poor recording of such an event in some patients' charts. We have not found thrombotic or renal complications in our patients.

Pre-medicating patients with paracetamol, anti-histamine, or steroid is thought to be useful for certain patients who develop adverse reactions to IVIGinfusion depending on the type of reaction.4 However, there are no well controlled studies as far as we know to support this notion. In our study, it was not possible to investigate whether pre-medicating patients helps in preventing or ameliorating some adverse reactions because of the limited number of patients and the retrospective nature of this study.

Our study has several limitations; most important is that the accuracy of our data depended on the accuracy and completeness of the notes of the physician and nurse who supervised the IVIG infusion. Though every effort was spent to collect the data as completely as possible, some information may have been missed by us during this process. This may be expected in such retrospective study. The number of patients with adverse reactions was limited as well.

Finally, our report covers an under-studied issue in Saudi Arabia and else where and may be a useful contribution to a subject that needs to be studied further in a more controlled fashion. The collaboration of the efforts of multiple centers in this regard is very much needed.

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