

## Increased risk of adverse events when changing intravenous immunoglobulin preparations

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### SUMMARY

Intravenous immunoglobulin (IVIG) therapy has represented a major advance in the treatment of patients with primary immune deficiency disorders. In September 2000 a new IVIG formulation, Intragam P, was introduced into clinical use. Intragam P is prepared by delipidation of pooled plasma followed by an ion exchange chromatography step to eliminate immunoglobulin aggregates. It is then pasteurized for 10 h at 60°C for viral inactivation before storage at pH 4.25 in 10% maltose. We report initial clinical experience with this new preparation. The details of adverse reactions of patients who received the new preparation were gathered shortly after it became apparent there was a change in IVIG formulation. Seven of 49 patients receiving Intragam P spontaneously reported adverse effects, which were temporally related to infusions. Subsequently, all seven patients have been able to tolerate the product with prophylactic use of antihistamines and paracetamol. This case series indicates that long-term tolerance of an older IVIG product does not necessarily equate to tolerance to a newer product, even if technically superior. Caution should be exercised when changing IVIG products, as they are not biologically equivalent.

**Keywords** adverse effects immune deficiency Intragam Intragam P IVIG

### INTRODUCTION

Intravenous immunoglobulin (IVIG) therapy has been a significant advance in the management of patients with primary immune deficiency disorders. The availability of high-quality IVIG preparations in the early 1980s allowed restoration of physiological levels of IgG in the blood of hypogammaglobulinaemic patients. This has resulted in a significant reduction in morbidity and mortality in patients with primary immune deficiency disorders [1].

Prior to September 2000, most patients requiring IVIG in Australasia were receiving Intragam: an IVIG product prepared from pooled plasma from volunteer donors in Australia and New Zealand. Intragam was manufactured by Cohn fractionation followed by suspension in 10% maltose at pH 4.25. The manufacturing process was similar to that of Gamimune N (Cutter). Intragam was manufactured by the Commonwealth Serum Laboratories (CSL) in Melbourne and had had an excellent safety record since its introduction in 1988. No cases of hepatitis C transmission have

been recorded. Serious reactions were rare. Minor side-effects were seen in 0.5–10% of patients but were managed easily by premedication with paracetamol or non-sedating antihistamines [2–4]. Most patients were able to tolerate Intragam without premedication after the first few infusions.

In 1996 CSL modified the manufacture of its IVIG preparation. The new formulation, named Intragam P, is also made from pooled plasma from volunteer donors, which is then subjected to dilipidation. Subsequently, an anion exchange chromatographic purification procedure is undertaken to reduce immunoglobulin aggregates and has the added advantage of removing IgA. A pasteurization step was introduced to enhance viral inactivation. Like Intragam, Intragam P contains 10% maltose and is suspended at pH 4.25. High performance liquid chromatography (HPLC) studies undertaken by CSL have shown that Intragam P contains fewer immunoglobulin aggregates, suggesting a lower likelihood of adverse reactions. CSL studies also demonstrated a superior viral inactivation profile to Intragam.

Intragam P was trialled in an open label study in 1996. It was well tolerated without major adverse reactions in 35 patients with primary humoral immune defects in Australia and New Zealand. Patients were not premedicated prior to infusions. Intragam was phased out and Intragam P was introduced into routine clinical

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use in Australia in August 2000 and in New Zealand in September 2000. In this report we describe significant adverse effects associated with the initial use of Intragam P in Auckland, New Zealand.

## PATIENTS AND ADVERSE REACTIONS

### Background

In September 2000, a total of 49 patients was receiving Intragam for primary humoral immune deficiency disorders in Auckland (pop 1.1 million). It was well tolerated and no patients required prophylactic antihistamines or paracetamol routinely. When Intragam P was introduced, neither patients nor physicians were aware there had been a change in IVIG formulation. Therefore patients did not receive premedication and the rates of infusion were not modified. Seven patients spontaneously reported adverse reactions to the new product (Table 1). All seven had previously tolerated Intragam without difficulty.

Their symptoms are described below. There was one life-threatening complication. Subsequently, all seven patients have been able to tolerate Intragam P after premedication with paracetamol and antihistamines. Patients H1 and C1 were on home therapy. All others were receiving Intragam as out-patients.

### Patients

Patient H1 (age 26 years) has X-linked hyper-IgM syndrome (XHIM, HIGM1) and was receiving 60 g of IVIG every 3 weeks [5]. He received his first dose of Intragam P in September 2000 and became unwell after the first 50 ml of his infusion. By the end of the infusion he began vomiting and was pyretic (fever 38.5°C). Three hours later he developed a skin rash and had swelling and aching of his upper and lower limb joints. The following day, serum sickness was diagnosed and he was prescribed 40 mg of prednisone daily, which was reduced to 10 mg over 7 days. There was prompt resolution of the joint and skin symptoms with treatment. The joint symptoms returned within 48 h of discontinuing prednisone, necessitating a second course. Again there was prompt resolution of symptoms.

Three weeks after his dose of Intragam P, he received 60 g of the former IVIG formulation, Intragam, without adverse effects. Five weeks after his first Intragam P dose patient H1 became disoriented, febrile and pyrexial. Blood and CSF cultures revealed *Neisseria meningitidis*. High-dose penicillin G was administered

and he made a full recovery. Subsequent administration of smaller doses (12 g) of Intragam P alone were associated with mild serum sickness symptoms. However after 4 months he was able to tolerate 36 g of Intragam P, provided it was given in combination with 24 g of Intragam. His dose has been gradually increased and he is now able to tolerate 56 g of Intragam P monthly.

Patient S1 (age 51) has common variable immune deficiency (CVID) complicated by bronchiectasis and chronic sinusitis. She receives 27 g of IVIG every 4 weeks. Two hours after receiving her first dose of Intragam P she felt lethargic, had severe myalgias and remained unwell for 10 days. A similar reaction occurred after a second infusion. With the use of loratadine and paracetamol 2 h prior to the infusion, there was some reduction in the severity and duration of symptoms. Combining Intragam with Intragam P further alleviated her symptoms. Subsequently she received 12 months of treatment with Intragam. When Intragam stocks were depleted, she was gradually weaned onto Intragam P over 3 months successfully.

Patient C1 has chronic sinusitis and bronchiectasis as a consequence of IgG subclass deficiency. After the first dose of Intragam P he felt lethargic. Two weeks after receiving Intragam P he felt unwell and developed numbness and tingling in his hands. Nerve conduction tests were consistent with a peripheral neuropathy. There has been improvement of his paraesthesiae over subsequent months. He has tolerated further doses of Intragam P uneventfully with premedication.

Patient G1 had myalgias and fever, which began 4 h after the first dose of Intragam P. He has subsequently received the product with loratadine and paracetamol prophylaxis without adverse effects. Patient W1 vomited the end of each Intragam P infusion and had myalgias and headaches for 3 days after each infusion. He has tolerated Intragam P with paracetamol prophylaxis.

Two children, patients J1 and R1, developed angio-oedema of the hands after infusion of Intragam P. These reactions abated with promethazine treatment. Subsequently, they have received Intragam P without difficulty without promethazine prophylaxis.

## DISCUSSION

It is unusual for an entire population of immune-deficient patients to receive a single preparation of IVIG. This attests to the safety and tolerability of Intragam, since its introduction to Australasia in 1988. Patients receiving Intragam did not require paracetamol or antihistamine prophylaxis. As it is collected from local volunteer donors, the antibodies derived are likely to reflect the prevalence of pathogens in New Zealand, which may be an advantage for immune-deficient patients.

When Commonwealth Serum Laboratories changed its manufacturing process, the entire immune deficient population was switched simultaneously to a different IVIG formulation. Following introduction of Intragam P, there was a marked increase in spontaneously reported adverse effects. Fourteen per cent (7/49) of primary immune deficient patients who received the preparation spontaneously reported side-effects; significantly more than previous reports of adverse reactions with Intragam [2,3]. This is also higher than the rates reported for other IVIG preparations in North America and Europe [6–10]. Given that the introduction of the new preparation occurred without the knowledge of either patients or clinicians, it is unlikely there was biased perception and reporting of adverse symptoms associated with the new IVIG preparation.

**Table 1.** Patients and adverse reactions to Intragam P

Patient, age, gender	Disorder	Adverse Reaction	Batch numbers
H1, 26 M	XHIM	Serum sickness	0013, 0014
S1, 51, F	CVID	Myalgias, lethargy	0013, 0014
C1, 23, M	IgG sub.	Neuropathy	0013, 0014
W1, 23, M	XLA	Vomiting	0013, 0014
G1, 38, M	CVID	Fever, myalgias	0013, 0014, 0022
J1, 7, M	SCID/BMT	Angio-oedema	0022
R1, 9, M	XLA	Angio-oedema	0026, 0029

XHIM: X-linked hyper-immunoglobulin M syndrome; CVID: common variable immune deficiency; XLA: X-linked agammaglobulinaemia; SCID/BMT: severe combined immune deficiency/bone marrow transplant. IgG sub.: IgG subclass deficiency.

The basis for the increased rate of adverse reactions is not clear. Most of the adverse reactions have been serum sickness-like, suggesting the presence or formation of immunoglobulin aggregates. Nevertheless, HPLC studies have shown Intragam P contains fewer IgG aggregates than Intragam. Therefore formation of immune complexes *in vivo* may be the most likely explanation for many of these reactions. Although an increased incidence of adverse reactions has been noted in patients suffering from cryoglobulinaemia, this was not relevant to any of the patients in this series [11]. Patients H1 and S1 experienced amelioration of adverse symptoms with concomitant Intragam. The explanation for beneficial effect of Intragam in alleviating the adverse effects of Intragam P is unclear. Possibilities include solubilization of immune complexes formed by Intragam P or the presence of neutralizing antibodies to cytokines or vasoactive agents.

Review of batch numbers of Intragam P indicated that this was not a batch-related problem (Table 1). The two children (patients J1 and R1) who received batches 0022, 0026 and 0029 suffered angio-oedema. Most of the adult patients who reacted adversely received batches 0013 and 0014 (Table 1).

The severe reaction experienced by patient H1 may have been a consequence of the higher dose of IVIG (1 g/kg) needed for XHIM. His high levels of serum IgM (>6 g/l) may have also contributed to immune complex formation. This case illustrates that severe reactions can occur in patients who do not have an overt sepsis and have tolerated IVIG for many years [12]. In spite of his severe immune deficiency, he has not previously or subsequently suffered invasive bacterial infections. His bacterial meningitis may have been a result of the prolonged course of prednisone needed for his serum sickness reaction. It should be noted that serum sickness may further impair lymphocyte function [13].

Several IVIG preparations are available in the United States and Europe [8,14]. Patients established on one preparation may be changed to another for either economic reasons or availability factors [15]. This case series illustrates the need for caution when patients are switched from one IVIG preparation to another, as there may be an increased risk of adverse reactions. Patients on home therapy should receive the first few infusions of the new IVIG preparation in hospital. Patients who have been able to tolerate a previous IVIG preparation without problems may benefit from paracetamol and non-sedating antihistamines for the first few infusions.

It would also be prudent for the new preparation to be infused at a slower rate than the older preparation. If immune complexes form *in vivo*, slower infusion rates may allow clearance of these aggregates before activation of other effector pathways such as the complement cascade occurs. Similarly, IVIG preparations have been shown to induce cytokines and other biologically active molecules [16]. Slower rates of infusion may allow these molecules to be cleared before producing adverse reactions.

In recent years, many IVIG preparations have had a viral inactivation step incorporated into their production. This has resulted in modification of the manufacturing process for IVIG preparations. It is important that changes in the manufacture of IVIG products are communicated to prescribing physicians so precautions can be instituted. These observations also highlight the importance of both pre- and post-marketing surveillance after the introduction of new IVIG products. Some adverse events such as those described here may not be identified in small

pre-marketing studies prior to the introduction of new IVIG preparations.

These cases illustrate that tolerance to an older IVIG preparation does not guarantee that a newer technically superior product will be equally well tolerated. These observations support recently expressed concerns that IVIG preparations cannot be regarded as being biologically equivalent [15].

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