Japanese Red Cross Society

Transfusion Information

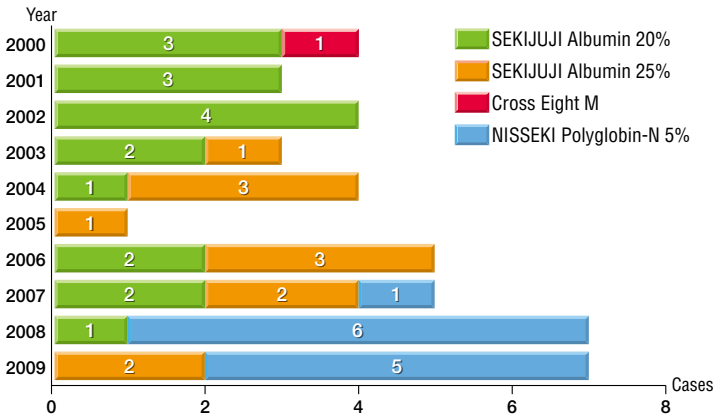
1101-127

Adverse reactions caused by plasma derivatives reported to JRC Blood Centers between 2000 and 2009

Japanese Red Cross Society manufactures and distributes plasma derivatives produced from domestic blood donations, which are: human serum albumin 20% and 25% (SEKIJUJI Albumin 20%, SEKIJUJI Albumin 25%), human coagulation factor VIII (hFVIII) (Cross Eight M), human immune globulin for IV injection (NISSEKI Polyglobin-N 5%), and anti-HBs human immune globulin "NISSEKI".
This issue of Transfusion Information shows the cases of suspected adverse reactions to plasma derivatives that have been reported by medical institutions to JRC Blood Centers since 2000.

Note: Regarding the names of the plasma derivatives, the old trade names are being used in this issue, since the cases were reported prior to the revision of the trade names.

Number of reports by year (number of reports from medical institutions)



In the decade from 2000 to 2009, 43 cases of adverse reactions were reported: 30 cases related to SEKIJUJI Albumin (18 cases for Albumin 20% and 12 cases for Albumin 25%), 1 case related to Cross Eight M, and 12 cases related to NISSEKI Polyglobin-N 5%. Although the number of reports on adverse reactions to SEKIJUJI Albumin varies from year to year, it remains at around 3 cases per year. As for Cross Eight M, only one case of dyspnea and fever was reported in 2000 and no adverse reactions have been reported since. Regarding NISSEKI Polyglobin-N 5%, introduced on the market in August 2006, one case was reported in 2007 but 5 or 6 cases have been reported annually from 2008 onwards.

Case reports on adverse reactions to human serum albumin products

SEKIJUJI Albumin 20%

Reported year	Number of cases	Adverse reactions
2000	3	Vomiting, hypotension
		Fever, itching
		Headache dull, malaise, sleepiness, oedema
2001	3	Flushed face
		Urticaria
		Chills, shivering, fever, disorientation
2002	4	Shock
		Fever, hypotension
		Chest pain, cough
		Anaphylaxis
2003	2	Hypertension, palpitations, vomiting
		Fever, acute renal failure
2004	1	Urticaria
2006	2	Shivering, chills, fever, rash
		Skin eruption, dyspnea, bradycardia
2007	2	Hypotension, facial pallor, respiratory depression
		Fever, rash
2008	1	Generalized redness, itching

SEKIJUJI Albumin 25%

Reported year	Number of cases	Adverse reactions
2003	1	Acute urticaria
2004	3	Anaphylactoid symptoms
		Anaphylaxis
		Fever, cardiac failure, arrhythmia
2005	1	Skin eruption, itching
2006	3	Pulmonary oedema
		Wheals
		Fever, vomiting, hypotension, chills
2007	2	Flushed face
		Hypotension
2009	2	Acute hepatitis (increase in GOT, GPT, ALP)
		Urticaria

More than half of the reports were for chills, fever, urticarial and other mild adverse reactions; however, more severe adverse reactions such as shock, anaphylactic (anaphylactoid) symptoms, circulatory disorders and pulmonary oedema caused by cardiac overload have also been reported.

Case report on adverse reactions to Cross Eight M

Reported year	Number of cases	Adverse reactions	Remarks
2000	1	Dyspnea, severe chills and shivering, fever	Administration of the drug on admission

Case reports on adverse reactions to NISSEKI Polyglobin-N 5%

Reported year	Number of cases	Adverse reactions, etc.	Indication (Primary diseases, complications, etc.)	Concomitant medication, etc.
2007	1	Hepatic function disorder	Kawasaki disease	Aspirin
2008	6	Chills, shivering, skin redness	Severe infection (treated in combination with antibiotics) (Acute promyelocytic leukemia (APL), chronic renal failure)	Antibiotics (with history of drug allergy)
		Aseptic meningitis	ITP	
		Urinary glucose positive*1	Kawasaki disease	
		Anaphylactic shock	Hypogammaglobulinemia (Lymphoma, diabetes mellitus)	
		Dementia, delirium	Polymyositis*2 (Diabetes mellitus)	
		Urinary glucose positive*1	Kawasaki disease	
2009	5	Skin eruption, hepatic function disorder	Kawasaki disease	Antibiotics
		Skin eruption, hepatic function disorder	Kawasaki disease	Antibiotics
		Anemia	Kawasaki disease	Aspirin
		Respiratory failure	Severe infection (treated in combination with antibiotics) (Unilateral multiple nephrolithiasis, hepatic function disorder, renal function disorder, atrial fibrillation)	
		Generalized redness, itching	Severe infection (treated in combination with antibiotics) (Fallot's tetralogy, mitral regurgitation, tricuspid regurgitation)	

Comparing the adverse reactions against indications, there were 3 cases of hepatic function disorders in Kawasaki disease.
There were also reports of severe adverse reactions, such as aseptic meningitis and anaphylactic shock.

*1 Urinary glucose was detected after single-dose administration of 2g/kg body weight during the acute phase of Kawasaki disease and is thought to be attributed to maltose hydrate, the stabilizing agent added in NISSEKI Polyglobin-N 5%.

*2 Off-label use

Note: The two cases of urinary glucose positive were "not considered to be an adverse drug reaction" according to the reporting physician; nevertheless, they have been included in the table as cases reported by the medical institutions.

Progress in plasma derivatives manufactured by JRCS and the safety measures

Measures to ensure the safety of plasma derivatives include: an interview at the time of blood donation, nucleic acid amplification test (NAT), tests for infectious pathogens, and virus removal and/or inactivation during the production process. Although some cases with suspected viral infection caused by the administration of JRCS' plasma derivatives have been reported by medical institutions, a causal relationship has not been determined for any of the cases to date.

Jun. 1973	Started the distribution of SEKIJUJI Albumin 20 (human serum albumin, 20% 20 mL).
Jun. 1981	Started the distribution of anti-HBs human immune globulin "NISSEKI" (anti-HBs human immune globulin, 1000 units/5 mL).
Feb. 1983	Started the distribution of anti-HBs human immune globulin "NISSEKI" (anti-HBs human immune globulin, 200 units/1 mL).
Apr. 1984	Started the distribution of SEKIJUJI Albumin 20 (human serum albumin, 20% 50 mL).
Mar. 1992	Started the distribution of Cross Eight M 250, 500, 1000 (freeze-dried concentrated human blood coagulation factor VIII; 250 units, 500 units, 1000 units)
Nov. 1997	Introduced minipool NAT (500 sample-pool for HBV, HCV, HIV) for source plasma.
Apr. 1999	Added membrane treatment for virus removal in the production process of Cross Eight M (nanofiltration through a 35 nm pore size filter).
Jul. 1999	Added membrane treatment for virus removal in the production process of anti-HBs human immune globulin "NISSEKI" (nanofiltration through a 35 nm pore size filter).
Oct. 1999	Introduced minipool NAT (500 sample-pool for HBV, HCV, HIV) for all the donated blood (termination of NAT for source plasma).
Feb. 2000	Reduced the pool size of minipool NAT, from 500 to 50.
Mar. 2001	Implemented keeping a six-month inventory of the source plasma.
Aug. 2001	Started the distribution of SEKIJUJI Albumin 25 (human serum albumin, 25% 50 mL).
Aug. 2004	Reduced the pool size of minipool NAT, from 50 to 20.
Apr. 2005	Changed the pore size of the virus removal filter in the production process of Cross Eight M (from pore size 35 nm to 19 nm).
Aug. 2006	Started the distribution of NISSEKI Polyglobin-N 5% (2.5 g/50 mL).
Sep. 2006	Started the distribution of NISSEKI Polyglobin-N 5% (0.5 g/10 mL, 5 g/100 mL).
Aug. 2009	Discontinued the use of US bovine-derived ingredient for the incubation medium of mouse monoclonal antibody against hFVIII to be used for the purification process of Cross Eight M.
Aug. 2009	Changed the trade names of 5 plasma derivatives (change of trade names for the prevention of medication error).

Since plasma derivatives are produced by pooling blood plasma from tens of thousands of blood donors, it is essential to prevent contamination by viruses or other pathogenic agents. If pathogenic contamination occurs, it is extremely important to remove the contamination and eliminate infectivity.
JRC conducts NAT for HBV, HCV and HIV of the donated blood and discards the blood that tested positive. Furthermore, if infection is determined during the 6-month inventory holding of the source plasma, the relevant blood will also be discarded. In the production process, the preparation undergoes S/D treatment, pasteurization, virus removal filtration, and low pH incubation for virus removal and/ or inactivation and the final products are delivered after conducting NAT and confirming that all of the 3 viruses mentioned above as well as the HAV and human parvovirus B19 are negative.
At present, a certain proportion of the plasma derivatives used in Japan are imported products. JRC will continue to enhance the proper use of plasma derivatives and contribute to the promotion of domestic self-supply.

Requests for the reporting of adverse reactions

Regarding adverse reactions caused by plasma derivatives, the mechanism of their occurrence is still not fully understood. Moreover, since they are used in the treatment of serious illnesses, the distinction between the clinical course and the symptoms of adverse reactions may be difficult in some cases.
In order to determine the incidence of adverse reactions, you are requested to report any suspected cases of adverse reactions caused by plasma derivatives to the local JRC Blood Center.

Online Haemovigilance Information for Healthcare Professionals
URL http://www.jrc.or.jp/mr/english/

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* For more information, please contact the medical representatives of your local JRC blood center.