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CASE REPORT

Combination Thrombolytic and Anti-Platelet Therapies in an Infant with Incomplete Kawasaki Disease and Coronary Aneurysms

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A 3-month-old infant was transferred to our facility with persistent fever and concerns for septic shock. A 2-D echocardiogram revealed multiple coronary aneurysms and axillary and coronary artery thrombi, and a diagnosis of incomplete Kawasaki disease (KD) was established. Aggressive therapies including intravenous immunoglobulins, enoxaparin, abciximab, aspirin, and alteplase were used to decrease the size of the coronary aneurysms and inhibit further thrombus formation. After minimal change in the size of coronary aneurysms and in thrombus formation, clopidogrel was added. Approximately 2 weeks after initiation of these therapies, a decrease in the coronary aneurysm size was noted with no signs of thrombus. This case documents successful use of thrombolytic and combination anti-platelet agents (i.e., clopidogrel, abciximab, and aspirin) in an infant with KD and cardiovascular sequelae.

KEYWORDS abciximab, alteplase, clopidogrel, incomplete Kawasaki disease, thrombosis

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INTRODUCTION

Kawasaki disease (KD) or mucocutaneous lymph node syndrome is an acute vasculitis that occurs primarily in childhood. Most patients are treated with intravenous immunoglobulins (IVIG) and aspirin (80 to 100 mg/kg/day in divided doses).[1] Initial goals of pharmacotherapy for KD include inhibiting the inflammatory response and preventing complications including coronary artery aneurysms, myocardial infarction, and ischemic heart disease. Approximately 15% to 25% of untreated patients with KD will develop cardiovascular complications including coronary artery aneurysms and coronary thrombosis.[2,3]

ABBREVIATIONS ADP, adenosine 5′-diphosphate; CK-MB, creatinine kinase-myoglobin; Col/ADP, collagen/adenosine diphosphate; Col/Epi, collagen/epinephrine; IVIG, intravenous immunoglobulins; KD, Kawasaki disease; LAD, left anterior descending artery; RCA, right coronary artery

There are no established guidelines for treating patients who develop coronary aneurysms and coronary thrombosis; a sparse amount of anecdotal data are available from case reports and case series.[4-14] We report a case of an infant with KD and multiple coronary artery aneurysms and thrombi who was successfully treated with a combination of thrombolytic and anti-platelet therapies including aspirin, abciximab, and clopidogrel.

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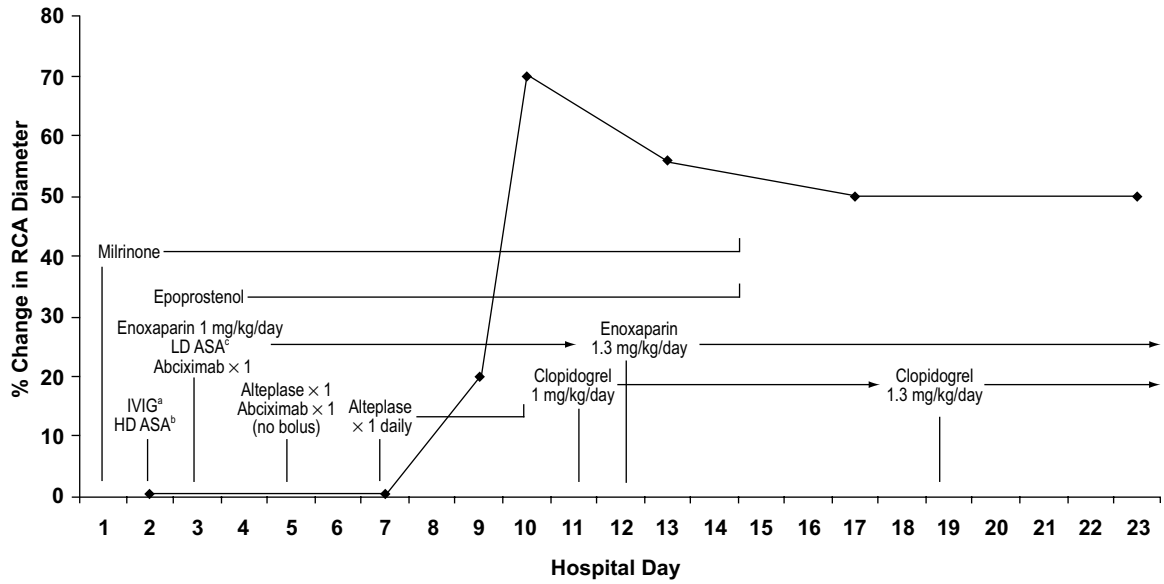

Figure. Overview of pharmacotherapeutic interventions with corresponding percent change in right coronary artery (RCA) diameter from baseline versus hospital day.
[a] *IVIG = Intravenous immune globulin*
[b] *HD ASA = High dose aspirin (80 mg/kg/day)*
[c] *LD ASA = Low dose aspirin (5 mg/kg/day)*

CASE REPORT

A 3-month-old (5.5-kg) Caucasian male was admitted to our emergency department with fever and emesis. This infant was born at 39 weeks gestation with no complications. One month prior to this presentation, he was hospitalized twice for fever of unknown origin. In the emergency department, his physical exam was significant for a temperature of 99.3°F, heart rate of 173 beats per minute, respiratory rate of 28 breaths per minute, blood pressure of 50/30 mm Hg, and capillary refill of more than 4 seconds. The patient had a bluish discoloration of his extremities with evidence of periungual desquamation in his toes and fingers and cracked erythematous lips. However, there was no evidence of lymphadenopathy or conjunctivitis. Laboratory findings were significant for a white blood cell count of 28,000 cells/mm^3 (66% neutrophils, 9% bands), a platelet count of 381,000 cells/mm^3, C-reactive protein of 19 mg/L (6270 pmol/L), and Westergren erythrocyte sedimentation rate of 17 mm/hr.

The infant was given aggressive fluid resuscitation including 100 mL/kg of crystalloids and 5% albumin. Cultures were obtained and intravenous antibiotics were initiated. A peripheral blood culture was positive for *Staphylococcus epidermidis* species in two bottles. However, this culture was felt to be a contaminant, and antibiotics were discontinued on hospital day 3. A 2-D echocardiogram revealed dilated right and left coronary arteries (5 mm and 5.5 mm in diameter, respectively), normal ventricular function, mild mitral regurgitation, and right and left dilated iliac axillary aneurysms with thrombi noted in the left axillary artery. The infant was diagnosed with incomplete KD and was initiated on intravenous immunoglobulins (IVIG) 2 gm/kg (Polygam S/D, Baxter Healthcare Corp; Deerfield, IL) and aspirin 80 mg/kg/day po divided every 6 hours. In addition, cardiac markers including creatinine kinase-myoglobin (CK-MB) and troponin were also assessed as surrogate markers of heart function and were 6.1 units/L (reference range 0 to 3 ng/mL) and 0.03 ng/mL (reference range 0 to 0.39 ng/mL), respectively.

Other interventions were attempted on hospital day 3 (Figure). In light of his decreased peripheral perfusion and gangrenous extremities, milrinone (Primacor, Hospira, Inc.; Forest, IL) and epoprostenol (Flolan, GlaxoSmithKline; Research Triangle Park, NC) were initiated. Epoprostenol was begun at a dose of 1 ng/kg/

min and increased every hour by 0.5 ng/kg/min based on blood pressure. In order to decrease the progression of the coronary aneurysms, abciximab (ReoPro, Eli Lilly; Indianapolis, IN) and enoxaparin (Lovenox, Sanofi Aventis; Bridgewater, NJ) were initiated. Abciximab was begun at a dose of 0.25 µg/kg IV over 5 minutes and followed by a continuous infusion of 0.125 µg/kg/min over 12 hours. Enoxaparin was initiated at a dose of 1 mg/kg/dose SQ q 12 hours, and the dose was titrated based on target anti-factor Xa concentrations (0.5 to 1.0 unit/mL). At this time, the aspirin dose was decreased to 5 mg/kg po daily.

On hospital day 5, the cardiac markers significantly increased from baseline (CK-MB, 0.9 ng/mL; troponin, 0.89 ng/mL). With these results and the presence of the thrombus based on the echocardiogram, the patient was given alteplase (Activase, Genetech Inc; San Francisco, CA) at a dose of 0.05 mg/kg/hr over 6 hours. Clottable fibrinogen was monitored periodically during therapy, and the infant was given fresh frozen plasma or cryoprecipitate at the intensivist's discretion in the event of bleeding episodes. Additionally, a second dose of abciximab was given (0.125 µg/kg/min over 12 hours). No loading dose of abciximab was given due to concerns of increased bleeding when it is used in combination with alteplase.

By hospital day 7, there was no change in the size of aneurysms or cardiac markers, and no resolution of the thrombus was noted. The patient was given a larger dose of alteplase – 0.1 mg/kg/hr as a continuous infusion over 6 hours. A 2-D echocardiogram showed approximately a 50% increase in the right coronary artery (RCA) diameter from hospital day 7 to 10 (Figure) and a thrombus detected in the left anterior descending (LAD) artery. During this time, three additional doses of alteplase (0.2, 0.25, and 0.5 mg/kg/hour infused over 6 hours) were given on days 8 through 10. On hospital day 10, the infant experienced bleeding from the lower extremities, which caused the infusion to be discontinued prematurely and the infant to be treated with cryoprecipitate.

Following alteplase therapy, no detectable changes in the thrombi were noted. The patient was started on clopidogrel (Plavix, Bristol-Myers Squibb Co; New York, NY) 1 mg/kg/day po daily on hospital day 9 in addition to enoxaparin and low dose aspirin (Figure). The dose was prepared immediately prior to administration by crushing a 75-mg tablet in water to qs to a final concentration of 15 mg/mL. On hospital day 9, a baseline Platelet Function Analyzer (PFA-100; Dade Behring) was used to monitor the efficacy of antiplatelet therapy and revealed a collagen/epinephrine (Col/Epi) closure time of 149 seconds (reference range, < 175 seconds) and collagen/adenosine diphosphate (Col/ADP) closure time of 55 seconds (reference range, < 105 seconds). An additional platelet function assay test was performed a week later and revealed a Col/Epi closure time of > 243 seconds and Col/ADP of 86 seconds. The dose of clopidogrel was increased by about 50% (Figure).

After two weeks in the pediatric intensive care unit, the patient continued to have poor perfusion to his lower extremities and developed dry gangrene of his digits. Both vascular and plastic surgery specialists were consulted. However, they felt that the patient's digits would auto-amputate and recommended no surgical interventions. As a result, epoprostenol and milrinone were discontinued, and the patient was transferred to the general patient ward. Follow-up echocardiograms on hospital days 17 and 23 revealed stabilization of the RCA and other coronary aneurysms with no additional evidence of thrombi (Figure). The patient was discharged on enoxaparin 1.3 mg/kg SQ twice daily, clopidogrel 1.5 mg/kg po daily, and aspirin 5 mg/kg po daily. Approximately 2 years later, the patient has stabilization of coronary aneurysms and continues on aspirin. Further details of this patient case are not available at this time.

DISCUSSION

Cardiovascular complications represent the most significant sequelae in patients with KD. These sequelae manifest themselves through a number of complications including myocardial infarction and ischemic heart disease. As a result, KD is now regarded as the leading cause of acquired heart disease in children in developed countries.[2,3] Unlike the coronary thrombosis that occurs in adults with atherosclerosis, the pathophysiology of coronary thrombosis associated with KD is not well

understood.[1,6] Some have proposed that these cardiovascular manifestations are a result of the overwhelming inflammatory response and necrosis in coronary arteries.[6,15]

Treatment of cardiovascular complications in patients with KD has not been well described. When administered in the acute phase of KD, IVIG has been shown to prevent coronary artery abnormalities.[16] However, up to 5% of patients develop coronary aneurysms despite treatment with IVIG.[17] No prospective trials have been performed and no guidelines have been established for the treatment of children with KD and coronary disease. some of the therapies that have been attempted in patients with coronary aneurysms with thrombosis or myocardial ischemia are noted in the Table. Most patients have been treated with combination thrombolytic therapy, anticoagulation, and anti-platelet therapies.[4-14] The majority of patients receiving these therapeutic interventions had thrombus resolution and/or a decrease in size of their aneurysms. In many of these cases, the eradication of the thrombus was attributed to intracoronary thrombolytic therapy.[8-10,12,13]

After confirmation of the coronary aneurysms and thrombus, our patient was initiated on abciximab, enoxaparin, and aspirin. Williams et al. have shown that abciximab in combination with IVIG and aspirin led to a significant decrease in aneurysm size compared with IVIG and aspirin alone (41% ± 19% versus 17% ± 27%, P = .003).[18] In addition, glycoprotein IIb/IIIa receptor inhibitors in combination with anticoagulation and anti-platelet therapy have been used in patients with KD and myocardial infarction and coronary thrombosis with promising results.[5,6] On hospital day 5, there appeared to be no change in the size of coronary aneurysms or the thrombus, so our patient received a second dose of abciximab and was begun on alteplase. Four subsequent doses of alteplase were given on hospital days 7 through 10 (Figure), but no appreciable change in the aneurysm size or in the presence of the thrombus was noted. Unlike the previous cases presented in the Table, intracoronary alteplase was not considered. This therapy is extremely invasive and technically difficult to perform in young infants, and some have noted success without the use of intracoronary thrombolysis.[11]

On hospital day 11, clopidogrel was added to aspirin and enoxaparin at a dose of 1 mg/kg orally daily, which was based on the usual adult dose of 75 mg/day.[19] As a thienopyridine derivative, clopidogrel affects platelet activation by irreversibly inhibiting adenosine 5'-diphosphate (ADP). With decreased concentrations of ADP there is a decreased activation of the glycoprotein IIb/IIIa complex necessary for the interaction between platelet and thrombus formation.

The Council on Cardiovascular Disease in the Young recommends that children with multiple coronary aneurysms or giant coronary aneurysms (more than 8 mm in diameter) be initiated on anticoagulation therapy with warfarin or low-molecular-weight heparins in combination with aspirin.[1] However, this panel recognizes that combination anti-platelet therapy may be needed for patients with multiple coronary aneurysms as in the patient we present. After a literature review, we found 3 cases of patients with KD who were on combination therapy with inhibitors of ADP platelet-aggregation (Table).[4-6]

Etheridge and colleagues provide details of a 4-month-old infant with multiple coronary aneurysms and a thrombus in the RCA.[6] This patient's therapy began with a continuous infusion of heparin and abciximab for 12 hours and discharged home on warfarin and low-dose aspirin. An echocardiogram performed 24 hours after abciximab and heparin therapy revealed no change in the size of the aneurysms or thrombi. However, 6 weeks after abciximab administration, the patient had resolution of thrombi and aneurysms and was transitioned to ticlopidine and aspirin maintenance therapy. It must be noted that this patient did not have elevation of cardiac markers and was not treated with systemic thrombolytic therapy as in our patient. O'Brien and colleagues describe a 7-month-old infant with LAD giant coronary aneurysm and thrombus who also failed to respond to thrombolytic and anticoagulation therapy.[4] After 3 weeks of ticlopidine and aspirin the thrombus resolved.

These two cases, in addition to our case, provide evidence that combination anti-platelet therapies with or without systemic thrombolytic therapy may be needed to resolve or stabilize aneurysm size and eliminate coronary

Table. Summary of Treatment Modalities in Pediatric Patients with Kawasaki Disease with Coronary Thrombosis or Myocardial Infarction

Reference	Demographics	Coronary involvement	Treatment of Thrombosis	Outcome	Maintenance Anti-Platelet and Anticoagulation Therapy
O'Brien[4]	7 mo male	LAD, GA with large thrombus	Alteplase 0.5 mg/kg/hr CI for 19 hr, streptokinase 1,500 units/kg IV bolus and 1,500 units/kg/hr CI for 48 hr	No resolution of thrombus after thrombolytic therapy	Ticlopidine (8 mg/kg bid), ASA (20 mg daily)
Peduzzi[5]	3 mo female	Multiple aneurysms in all vessels and AMI	Eptifibatide CI for 72 hr (dose not reported)	Developed inferior wall myocardial infarction	Clopidogrel and warfarin (doses not reported)
Ethreridge[6]	4 mo female	RCA, LCA, LAD aneurysms with thrombus in the proximal RCA	Abciximab 0.25 mg/kg IV bolus and 0.125 mcg/kg/hr CI for 12 hr, heparin CI, ASA (80-100 mg/kg/day)	Resolution of thrombus upon discharge	Warfarin (to obtain INR 2.5-3.0) and ASA (5 mg/kg/day) for 6 wks; then ASA (5 mg/kg/day) and ticlopidine (5 mg/kg/day)
Tomita[7]	2 mo female	LCA, RCA, LAD aneurysms with thrombus in left circumflex artery and RCA	Alteplase 0.25 mg/kg IV bolus and 0.18 mg/kg/hr CI for 5.5 hr, urokinase 500,000 units/day CI and heparin CI for 15 days, dipyridamole (2.5 mg/kg/day), warfarin (0.1 mg/kg/day)	Developed complete occlusion of RCA	Warfarin (0.5 mg/kg/day), ASA (4 mg/kg/day), and dipyridamole (2.5 mg/kg/day)
Tsubata[8]	7 mo male	LAD, RCA, LCA aneurysms with thrombi in LAD and RCA	Alteplase 0.05 mg/kg IV bolus and 0.5 mg/kg/hr CI for 1 hr, intracoronary alteplase 0.09 mg/kg x 1 in LAD and RCA, heparin CI, ASA and dipyridamole (doses not reported)	Resolution of thrombus following intracoronary alteplase	ASA, dipyridamole (doses not reported)
Horigome[9]	3 mo male	GA LCA with thrombus in LAD	Urokinase 5,000 units/kg IV tid, heparin CI, and warfarin for 7 days, intracoronary alteplase 0.09 mg/kg x 1 and 0.14 mg/kg x 1	Resolution of thrombus following intracoronary alteplase therapy	Not provided
Katayama[10]	13 mo male	Occlusion in proximal, anterior LAD with AMI	Intracoronary urokinase 5,000 units/kg x 3 doses, 7,000 units, heparin CI for 7 days	Resolution of thrombus	Warfarin and ASA (doses not reported)

Table. Summary of Treatment Modalities in Pediatric Patients with Kawasaki Disease with Coronary Thrombosis or Myocardial Infarction (cont.)

Reference	Demographics	Coronary involvement	Treatment of Thrombosis	Outcome	Maintenance Anti-Platelet and Anticoagulation Therapy
Burtt[11]	7 mo male	Aneurysms in LAD, RCA, and LCA with AMI	Streptokinase 10,000 units/kg IV x 2 doses, heparin CI	Resolution of thrombus and reperfusion of anterior wall	Warfarin (dose not reported)
Cheatham[12]	5 yr male	Occlusion in circumflex branch and LAD with thrombus in LAD with AMI	Intracoronary urokinase (Unknown dose), heparin CI	Resolution of thrombus and reperfusion of cardiac tissue	Warfarin and dipyridamole (doses not reported)
Kato[13]	9 children (7 male and 2 female) Median age 2 yr (range, 1.1-8.4 yr)	2 with AMI, 7 patients with massive thrombus in coronary aneurysms	Heparin 100 units/kg IV prior to PTCR, intracoronary urokinase 60,000 units/kg x 1 dose (repeat dose if needed-max of 10,000 units/kg), heparin CI for 12-24 hr	Decrease in size or resolution of thrombus in 6 of 9 patients	ASA (dose not reported)
Terai[14]	2 mo male	RCA and LCA aneurysms with mural thrombi in RCA	Urokinase CI IV 2,000-10,000 units/kg/day and heparin CI for 51 days	No change in RCA and LCA aneurysms or thrombi in RCA	ASA (10 mg/kg/day)
PR	3 mo male	RCA, LCA, LAD, R and L iliac axillary aneurysms with thrombus in L axillary and proximal/distal LAD	Abciximab 0.125 mcg/kg/hr CI for 12 hr x 2 doses, enoxaparin SQ (1 mg/kg/dose q 12 hr), ASA (5 mg/kg/day), alteplase CI for 5 doses (0.05-0.5 mg/kg/hr)	Thrombus resolution; Stabilization in aneurysm size	ASA (5 mg/kg/day), clopidogrel (1.8 mg/kg/day), enoxaparin SQ (1.3 mg/kg/dose q 12 hrs)

AMI, acute myocardial infarction; ASA, aspirin; CI, continuous intravenous infusion; GA, giant coronary aneurysm (> 8 mm in diameter); IV, intravenous; LAD, left anterior descending coronary artery; LCA, left coronary artery; PR, present case report; PTCR, percutaneous transluminal coronary revascularization; RCA, right coronary artery; SQ, subcutaneous

thrombi. O'Brien and colleagues speculate two possible explanations for the effectiveness of these specific anti-platelet agents.[4] First, inhibition of the ADP pathway on the glycoprotein IIb/IIIa complex may inhibit the likelihood of new thrombus formation or further development of the current thrombus. Next, inhibitors of ADP platelet-aggregation have been shown to release tissue plasminogen activator.[20] Our patient was initially treated with abciximab on the third and fifth day of hospitalization. Etheridge et al. noted that abciximab may have delayed efficacy in resolution of aneurysms and thrombi.[6] However, the combination of clopidogrel and aspirin shortly following abciximab and thrombolytic therapy may have shortened the time to elimination of the coronary thrombi and stabilization of aneurysms in our patient compared to Etheridge and colleagues.[6] In addition, there is an increasing body of evidence that combination anti-platelet therapy may be needed in some adult patients who are at high risk. The combination of clopidogrel and aspirin versus aspirin alone has been shown to be more effective in reducing the number of vascular events in patients with acute coronary syndrome who do not have evidence of ST-segment elevation.[21] Thus, future research should define the role of combination anti-platelet therapies in children with KD and coronary disease.

Based on the limited efficacy data of clopidogrel in children, we adjusted the doses of clopidogrel using platelet aggregation studies with the PFA-100. The PFA-100 is an instrument designed to assess hemostasis occurring from drug-induced platelet dysfunction and platelet defects. There is a growing body of evidence that platelet aggregation studies can help predict recurrent cardiovascular events in patients who may have resistance to anti-platelet therapies such as clopidogrel.[22,23] In fact, in 2005 the American College of Cardiology recommended that platelet aggregation studies may be performed in high risk patients following percutaneous intervention therapy and that the dose of clopidogrel should be optimized if suboptimal platelet inhibition is noted.[24] The PFA-100 is one of several platelet aggregation instruments currently available. As clopidogrel results in inhibition of the ADP pathway, the PFA-100 assesses the closure time associated with Col/ADP. Several studies have provided data to support the PFA-100 to assess the closure time and efficacy of clopidogrel dosing.[25-26] A week after initiation of clopidogrel, the PFA-100 a revealed a Col/ADP closure time of 86 seconds (reference range < 105 seconds). Based on this value, the dose was increased to 1.5 mg/kg/day. Although the use of a platelet aggregation instrument to optimize anti-platelet therapy is not widely recognized, we employed this technology to adjust our patient's dose given the serious nature of his aneurysms and thrombosis and given concerns for inconsistency in the dosage formulation.

Recently Li et al. published a multicenter, prospective, randomized trial comparing the pharmacodynamics of clopidodgrel in ranging doses versus placebo in 73 children less than 24 months of age who had heart disease and were at risk for thrombosis.[27] Using light-transmission aggregometry, the authors noted that 0.2 mg/kg/day of clopidogrel in children achieved similar anti-platelet activity as 75 mg in an adult. Future studies are needed to confirm these results. A Phase 3 study evaluating 0.2 mg/kg/day of clopidogrel in neonates and children with cyanotic heart disease is currently underway with an estimated completion date of 2010.[28] This study may help to further clarify the dosing of clopidogrel in this population.

One important consideration in our patient was the difficulty in oral administration of clopidogrel. There are currently no data available on an extemporaneous formulation for clopidogrel. Data from the Plavix package insert suggest that clopidogrel is insoluble in water.[19] Previous reports of clopidogrel in pediatric patients have described preparation of clopidogrel doses using individual dosing capsules prepared by the pharmacy or administering the nearest half, one-third, or one-fourth tablet.[29-30] Due to the age of the infant and the dose prescribed, we prepared the formulation immediately prior to administration by crushing the 75-mg tablet in water to a final concentration of 15 mg/mL. Clopidogrel is relatively acidic and concerns have been raised about administration of an oral extemporaneous formulation. However, no problems were noted in our patient. Other attempts have been made to prepare an extemporaneous suspension. Camara and colleagues provided details of an extemporaneous formulation used for a

desensitization protocol.[31] However, no data on stability of an extemporaneous solution has been published.

CONCLUSION

This case documents the first report of a combination anti-platelet regimen including abciximab, clopidogrel and thrombolytic therapy in an infant with KD and coronary aneurysms with thrombosis. A growing body of evidence suggests that combination anti-platelet therapy may prevent or possibly delay the development of thrombus formation in patients with KD and coronary aneurysms. Future trials should focus on combination anti-platelet therapies in preventing and treating patients with significant cardiovascular sequelae. In addition, this report highlights the continued need for extemporaneous formulations of medications like clopidogrel in pediatric patients.

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