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ULINASTATIN TREATMENT FOR KAWASAKI DISEASE

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Purpose Is ulinastatin administration an effective treatment for Kawasaki disease? We investigated the ulinastatin administration and other factors that might influence the duration of fever and C-reactive protein (CRP) in the children sufferin g from Kawasaki disease. *Method* We planed multi-center and retrospective study. We investigated 80 patients in the 12 institutions from March 1998 to May 2001. Three patients were excluded because of a readministration of high-dose gamma glob u lin. 44 female and 33 men were treated by high-dose gamma globulin: a single administration of 2g/kg or ulinastatin administration with high-dose gamma globulin. Ulinastatin was infused 5000/kg x 3 per day intravenously when the patients has high tempe r at ure. Their age was 2.8 +/- 2.4 years old. 43 patients were treated by high-dose gamma globulin and 31 patients were treated by high-dose gamma globulin with ulinastatin. We analyzed a correlation between the duration of fever and CRP, and following f ac tor s; age, sex, maximum CRP, maximal white blood cell count, minimal albumin concentration, minimal hemoglobin concentration and treatment protocols, by multiple regression analysis. *Result* The duration of fever and CRP from the start of t rea tmen ts were 41 +/- 39 hours and 8.8 +/- 5.4 days. Maximal CRP value was 10.0 +/- 7.2 mg/dl. The duration of fever significantly correlated with age and minimal albumin concentration (regression coefficient were 4.57 and -19.1; $p<0.02$ and $p<0.03$, re spect ively). The duration of CRP was significantly correlated with age (regression coefficient was 1.05; $p<0.0003$). Neither the duration of fever nor CRP was correlated with treatment protocols with or without ulinastatin. *Conclusion* The a dditio nal ulinastatin treatment with high-dose gamma globulin do not influence the duration of fever and CRP in our cases.

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A NEW THERAPY FOR KAWASAKI DISEASE -EFFECTIVENESS OF ULINASTATIN THERAPY-

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Over the past two decades, intravenous immunoglobulin (IVIG) therapy has become established as a standard therapy for Kawasaki disease, but still has some problems. First, there are some cases resistant to initial high dose IVIG therapy. Although such cases are often successfully treated with additional IVIG therapy, a few cases are still resistant. Second, IVIG is costly and not without risk of adverse reactions, including transmission of infectious agents. Considering these problems, we think that an alternative therapeutic approach to Kawasaki disease is needed. Kawasaki disease is an inflammatory disease that causes panvasculitis, including coronary artery. Polymorphonucleocytosis in the early stage of the illness suggests the implication of neutrophils in the pathogenesis of Kawasaki disease. Urinary trypsin inhibitor (ulinastatin, UTI) is derived from human urine, and inhibits the neutrophil elastase activity. Ulinastatin has been shown to have a clinical application for the treatment of inflammatory diseases such as pancreatitis, systemic inflammatory response syndrome, and acute respiratory distress syndrome. We conducted an original therapeutical regimen using ulinastatin for Kawasaki disease. From March 1999 to June 2001, sixty cases were received ulinastatin therapy, forty-one cases (68 %) responded to ulinastatin alone, while nineteen cases (32 %) needed additional IVIG therapy. Only two cases (2%) showed an ectatic coronary changes (3.5 mm and 4.8 mm in diameter, respectively) of the left anterior descending branch. We concluded that our new therapy for Kawasaki disease using ulinastatin is at least as effective as IVIG therapy and less expensive and less risky.

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PHARMACOKINETIC AND SAFETY EVALUATION OF A PEDIATRIC FORMULATION OF PENTOXIFYLLINE FOR TREATMENT OF ACUTE KAWASAKI DISEASE

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PURPOSE: Pentoxifylline (PTX) may decrease coronary artery damage in Kawasaki Disease (KD) by inhibiting TNF-α production. This study evaluated the safety and pharmacokinetics (PK) of a new pediatric oral syrup preparation of PTX as an adjunct to intravenous immunoglobulin and aspirin in the treatment of KD in children. **METHODS:** Six patients were enrolled/cohort (Cohorts A, B, C, and D- 10, 15, 20, and 25 mg/kg/day; divided TID). TNF-α levels (Days 1 and 6) were evaluated by ELISA. Six PK sera collected around the first dose were measured by HPLC and evaluated by non-compartmental analysis for PTX and its active metabolite (M-I). **RESULTS:** The most common adverse events were vomiting and fever, each reported in 5 of 18 patients. No toxicities were dose-related. For Cohorts A and B, the mean age $\pm$ SD was 33 $\pm$ 21 months. The median baseline TNF-α level was 9.51 pg/mL. Of 8 patients with day 6 TNF-α levels, six had an average decrease in TNF-α of 28%. The PTX mean areas under the plasma concentration versus time curve (AUC, a measure of drug exposure) were 559 (range, 216-1886) and 1786 (range, 286-9199) ng*hr/mL, and the M-I mean AUCs were 950 (range, 363-1826) and 3162 (range, 1069-12055) ng*hr/mL for Cohorts A and B, respectively. The overall apparent clearances (Cl/F) were 5.9 (range, 1.7-15.9) and 2.8 (range, 0.9-17.5) L/hr/kg. The M-I/PTX ratio was 1.7 and 1.8 in Cohorts A and B, respectively. No evidence of accumulation or saturation of absorption was noted. **CONCLUSIONS:** PTX was well tolerated. Gastrointestinal symptoms may have been due to high dose aspirin, PTX, or the combination of the two medications. The pharmacokinetic parameters were highly variable and similar to those seen in other populations. After analysis of Cohorts C and D, we will determine the optimal dose of PTX in KD.

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GABEXATE MESILATE (FOY) AS A NEW ADDITIONAL THERAPY TO HIGH DOSE INTRAVENOUS GAMMAGLOBULIN FOR HIGH RISK KAWASAKI DISEASE

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Objective: Although high dose gammaglobulin (IVGG) associated with aspirin became the standards in the therapy for Kawasaki disease (KD), the coronary complications still occur about 10 percent of all KD patients. We report five cases of KD successfully treated with FOY which is recently found to be effective in SIRS by suppressing the production of inflammatory cytokines in addition to IVGG and aspirin. Methods: We gave FOY in five KD cases aged 7 mo. to 3 y/o admitted consecutively in January to April 2001 in our hospital with informed consent. Four patients were at high risk group who needed to be given IVGG total dose of 2g/kg and one patient was at low risk group. FOY was given intravenously to all patients with continuous dose in 1-2mg/kg/hr.Results: FOY was effective in decreasing each body temperature, white blood cell counts, and CRP. Four cases were cured with FOY without the coronary complications. The coronary complications occurred in only one case who had admitted on 9th day and the dilatation of the coronary was seen on the day of admission, however even in this severe case with early coronary dilatation, no progress was seen after treatments. FOY showed no side effects in all five cases.Conclusions: We believe FOY in addition to IVGG and aspirin was effective in our all five cases. Although further case controlled studies are needed, FOY could be expected to be a new additional therapy for preventing the coronary complications of KD.

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EFFECT OF PLASMA EXCHANGE IN KAWASAKI DISEASE REFRACTORY TO HIGH DOSE INTRAVENOUS GAMMAGLOBULIN THERAPY

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Background: In Kawasaki disease (KD), administration of intravenous gammma-globulin (IVGG) reduced frequency of coronary artery lesion (CAL) from 25% to 8%. However, approximately 500 children still develop CAL every year in Japan. We evaluated the efficacy and safety of plasma exchange (PE) for children with KD intractable to IVGG therapy. **Patients and Methods**: Among 255 children with KD treated with initial IVGG, 119 children were identified at high risk for CAL according to the increases in fractional changes (FC) of white blood cell count, neutrophils, and CRP between baseline and 1 to 2 days after IVGG treatment. Seventy-five were administered additional IVGG, and finally 50 of them were underwent the PE therapy in 3 consecutive days. All the children were serially monitored for the development of CAL by echocardiography during the course of the disease until days 28-30. The incidence of CAL was compared among the children treated and those untreated with PE. **Results**: The demographic differences between the treated and untreated children were not significant on admission. The PE therapy was safely performed without any adverse reactions, and has completed in each child. Out of 50 children treated PE, only 10 (20.0%) had CAL, including temporary dilatation in 7, persistent CAL in 1, and giant aneurysms in 2 children. In contrast, 24 children (40.7%) among 69 without PE were affected with CAL, including giant aneurysm in 5 ($P < 0.0004$). **Conclusions**: We suggested that PE therapy performed within 10 days after the onset of the disease should be effective and safe for the children with KD intractable to the IVGG therapy. The PE therapy may be applied as soon as possible when the fractional increases in inflammatory markers after the initial IVGG are determined.

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EFFECTS OF INTRAVENOUS GAMMMAGLOBULIN THERAPY COMBINED WITH DEXAMETHASONE FOR THE INITIAL TREATMENT OF ACUTE KAWASAKI DISEASE

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We studied effects of intravenous gammmaglobulin therapy (IVGG) combined with dexamethasone (DEX) for the initial treatment of acute Kawasaki disease(KD). Prospectively studied 33 KD patients received total of 2g/kg IVGG for consecutive 4-5days plus 0.3mg/kg DEX for consecutive 3days (group 1). Retrospectively studied 33 KD patients received standard IVGG therapy (2g/kg IVGG for consecutive 4-5days)(group 2) were compared to analyze the efficacy and safety of the new regimen. There were no differences in age, sex, body weight, duration of illness, or given doses of gammmaglobulin between those two groups. Clinical no responders to the initial treatment received additive IVGG treatment. Informed consent was obtained from children's parents before therapy. No serious adverse effect was noted in both groups. The duration of high fever after the start of initial treatment in group1(1-12 days) was shorter than in group 2 (1-16 days)($p=0.07$, by Mann-Whitney U-test). Two patients in group 1 and two patients in group 2 developed small coronary aneurysms. Although further analysis using larger numbers of patients are necessary to confirm the efficacy of this new regimen, we preriminaly demonstrated that IVGG combined with DEX in the initial treatment of acute KD was safe and may shorten the duration of fever .