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Repeated Administration of Newly Synthesized Aceclofenac Sustained Release Form Causes Agranulocytosis: Case Report of an Unforeseen Adverse Event during the Phase 1 Trial

Hui Jin, Renhua Zheng, BoHyung Kim and Sung-Vin Yim*
Department of Clinical Pharmacology, College of Medicine, Kyung Hee University Hospital, Seoul 130-701, Korea
*Correspondence: S. V. Yim; Tel: +82-2-958-9567, Fax: +82-2-958-9559, E-mail: ysvin@khu.ac.kr, ysvin@yahoo.co.kr

CASE REPORT

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Aceclofenac is a non-steroidal anti-inflammatory drug (NSAIDs) for inflammatory diseases. In this report, we report a serious adverse event (AE) occurred during the phase I clinical trial for a new sustained-release (SR) formulation of aceclofenac. There was a serious adverse event (AE), agranulocytosis, induced by aceclofenac SR form. An open-labeled, repeated-doses, randomized, crossover study was conducted at Kyung Hee University Hospital and 26 Korean healthy male volunteers were enrolled. All subjects received both aceclofenac SR 200 mg once daily and aceclofenac IR 100 mg twice daily for 4 days with 11 days washout period. After 11 days washout period, one subject showed a serious decrease in the segment neutrophil (267/mm^3) on a laboratory test prior to the reference drug administration in period 2. We first report a case of agranulocytosis, during a phase I clinical trial.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAIDs) which is widely used to treat painful inflammatory diseases, such as osteoarthritis.[1] In this study, we tested a new sustained-release (SR) formulation of aceclofenac (SamA pharmaceutical Inc., Suwon, Republic of Korea). There was a serious adverse event (AE) induced by aceclofenac SR form. We first report a case of agranulocytosis, during a phase 1 clinical trial.

An open-labeled, repeated-doses, randomized, crossover study was conducted at Kyung Hee University Hospital Clinical Research Institute (Seoul, Republic of Korea). Twenty six Korean healthy male volunteers were enrolled after obtaining written informed consent.

All subjects received both aceclofenac SR 200 mg once daily and aceclofenac IR 100 mg twice daily for 4 days, in each period by a random order, and two periods were separated by 11 days washout period. Blood samples were collected on the first day (for single dose pharmacokinetics) and on the fourth day (for steady-state pharmacokinetics) in each period. For safety assessment, vital sign, electrocardiogram and laboratory test were checked during the trial. For tolerability evaluation, the investigator monitored all the subjects through the inquiry, and recoded any AEs during the trial. The clinical trial was conducted according to the International Conference of Harmonization - Good Clinical Practice (ICH-GCP) and ethical standard established in the Declaration of Helsinki.

Total of 4 subjects withdrew from the trial. Two subjects (R14 and R17) were withdrawn due to AEs and two subjects (R07 and R16) withdrew voluntarily. Subject R14 showed a gastric discomfort and nausea, and subject R17 showed serious decrease in the segment neutrophil (267/mm^3).

Subject R17 was a healthy 28-year-old Korean male and he had received a test drug (aceclofenac SR 200 mg) for 4 days, in period 1, and there were no significant abnormities in the vital signs, ECG and laboratory test, during the period 1. After 11 days washout period, subject R17 showed a serious decrease in the segment neutrophil (267/mm^3) on a laboratory test prior to the reference drug administration in period 2, and no one gave attention to such results. When the investigator had recognized such serious event at the end of the period 2, subject R17 had already administered all the reference drugs (aceclofenac IR 100 mg twice daily). Fortunately, subject R17 did not show any

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Table 1. Subject R17's counts of WBC and segment neutrophil during the clinical trial

Period	Screening period	Period 1		Period 2		Follow up period	
date	day -12	day 1	day 5	day 16	day 20	day 23	day 26
WBC (mm^3)	6430	6690	5340	3820	2780	4280	6250
Seg. Neutrophil (%)	48.2	45.9	51.7	7	20.2	25.2	46.2
Seg. Neutrophil count (mm^3)	3099	3070	2760	267	561	1078	2887

other related symptoms, such as fever or serious infection, and segment neutrophil count have been recovered on subsequent serial CBC monitoring (Table 1). Such result was reported to Institutional Review Board and Korean Food and Drug Administration.

Several cases of drug induced agranulocytosis or neutropenia have been reported, which include diclofenac induced agranulocytosis.[2,3] Aceclofenac is a pro-drug of diclofenac,[1] and it may provide the possibility of the aceclofenac induced agranulocytosis.

Throughout our result, we could suggest a possibility that large dose of NSAIDs, such as aceclofenac, might suppress the bone marrow and induce agranulocytosis in susceptible subjects. Ho et al. demonstrated that NSAIDs suppressed the proliferation of bone marrow mesenchymal stem cells by arresting the cell cycle and inducing cell death.[4,5] Although there are no direct evidences that NSAIDs suppressed the bone marrow hematopoietic stem cells, Ho's studies supported the possibility that bone marrow hematopoietic stem cells may be suppressed by NSAIDs. In another perspective, regimen of aceclofenac may be associated with the occurrence of agranulocytosis. Although the subject received a reference drug for 4 days after agranulocytosis occurrence, the segment neutrophil count have been recovered to its normal range. In conclusion, rare, but serious AEs such as agranulocytosis, has been occurred in clinical trial and there would be a need for adequate monitoring of the blood count in aceclofenac pharmacotherapy.

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