Risk Analysis of Drug Adverse Reaction: in Case of PPA

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The risk managements for marketing products are generally based on the risk assessment of adverse reactions. Sometimes, marketing medicines shows unwanted adverse reaction, because in pre-marketing safety data with limitations of patients numbers the adverse reaction with low prevalence rate can not be easily detected. The association between unwanted adverse reaction and marketing medicine can be studied by following types; case report, case series study, case-control study, cohort study.

In August, 2004, the KFDA banned the production and sale of cold remedies containing phenylpropanolamine(PPA), while US FDA requested drug companies discontinuing marketing products -containing PPA, in November, 2000. Both of regulatory decisions in USA and Korea were based on the case-control studies about an association between hemorrhagic stroke and PPA-containing appetite suppressants and cold remedies, respectively.

The regulatory history of PPA in USA and the comparative analysis of the case-control studies in USA and Korea on an association between hemorrhagic stroke and PPA are presented in this symposium.

1. Regulatory history of PPA in USA & Yale Hemorrhagic Stroke Project

Spontaneous case reports and published case series, accumulated from 1969 to 1991 in USA, suggested a possible association between PPA use and a increased risk of hemorrhagic stroke. Representatives of the manufacturers of products containing PPA and FDA staffs met in 1991 to plan a study that could further examine whether there was an association between PPA use and the risk of hemorrhagic stroke. An epidemiologic case-control study was determined to be the most feasible study design to evaluate the possible association between exposure to PPA and a rare outcome such as hemorrhagic stroke. The industry sponsors of the study selected investigators at Yale University School of Medicine to conduct the study.

The study, so called "Hemorrhagic Stroke Project", examined three questions: (1) Whether all users of PPA(including men and women 18 to 49 years old), compared with nonusers, had an increased risk of hemorrhagic stroke; (2) the possible association between PPA use and hemorrhagic stroke by type of exposure(appetite suppressants or cough-cold

product); and (3) among women aged 18 to 49 years, the possible association between first use of PPA and hemorrhagic. Case subjects (702) who were hospitalized with subarachnoid or intracerebral hemorrhage and had no prior history of stroke and were able to participate in an interview within 30 days of their event. For each case subject, two control subjects (1,367) with no stroke were identified (matched based on age, gender, and race).

The study reported taking PPA increases the risk of hemorrhagic in women and men may also be at risk. The increase in risk of hemorrhagic stroke was found for women using PPA for weight control in the 3 days after starting use of the drug, and for women using PPA as a nasal decongestant product in the first day of use. Although the risk of hemorrhagic stroke is very low, FDA recommended that consumers not use any products that contain PPA.

I. A Case – control study for evaluating an association between PPA and hemorrhagic stroke in Korean population

Although FDA's Nonprescription Drugs Advisory Committee recommended that PPA be considered not safe for over-the counter use, 9 of 14 committee members interpreted that it is inconclusive whether there is an association between PPA as decongestant and hemorrhagic stroke in the entire population (men and women). Furthermore, the prevalence of stroke is higher in old ages, however, Yale's study did not include patients over 50 years old. And it was unclear that there was no difference of risk of hemorrhagic stroke by PPA between American and Korean population. Therefore, a case-control study was performed to investigate the possible association between PPA as decongestants and hemorrhagic stroke in Korean population. Results were as follows;

1) There were 940 patients 30 to 84 years old who were hospitalized with hemorrhagic stroke in 33 hospitals; and two matched control subjects were 1,880 .
2) The use of cold remedies containing PPA was associated with a relative risk for hemorrhagic stroke of 3.86 in women. (; adjusted odds ratio)
3) In supplementary analysis about the relation between the exposure time to PPA and the risk of hemorrhagic stroke, the risk with the use of PPA 3 days before the occurrence of stroke was 5.36 times higher than the use of PPA 4-14 days before stroke in entire population. (; adjusted odds ratio)
4) Regarding the duration of exposure to PPA, taking PPA for more than 3 days showed higher risk (3.44) of hemorrhagic stroke in entire population.

The results suggested that PPA in cough and cold remedies be a possible risk factor for hemorrhagic stroke, especially in women.

KFDA concluded that this study was well designed and demonstrated that the association between PPA use as a cold remedies and an increased risk of hemorrhagic stroke was significant and was most striking in women. This study was the largest prospective case-control study ever conducted on hemorrhagic stroke and the first study showing the use of PPA as cold remedies associated with a risk for hemorrhagic stroke in

the world.

Finally, KFDA concluded that the benefits of the intended use of PPA do not outweigh the potential risk, therefore, KFDA requested the manufacturing companies removing PPA from all drug products.

Considering the case of PPA, the concern to find and report an adverse reaction of medicine is the first key element for risk analysis and also a well-designed case-control study is a good tool to evaluate an association between the use of drug products containing target ingredients and the risk.