Extraction of Drug Combination related to Liver Dysfunction

Akira Totoki[a,b], Suzuki Takahiro[a], Toshiyo Tamura[b], Katsuhiko Takabayashi[a]

[a] *Department of Medical Informatics and Management, Chiba University Hospital, Chiba, Japan*
[b] *Graduate School of Engineering, Chiba University, Chiba, Japan*

Abstract and Objective

Today a great number of drugs are used in clinical medicine and because of such vast amount we cannot possibly research adverse reaction for all combinations of medicines. Here we searched adverse reaction (liver dysfunction) induced by medication retrospectively through ALT (GPT) temporal data and prescription history files at Chiba University Hospital. There were 3,240 cases of liver dysfunction which appeared during hospitalization in all 84,437 cases. We checked prescription histories of those cases and extracted each medication just before ALT reached its peak and calculated their appearance rate of adverse reaction. Some of them showed higher frequency in the combinations than monotherapy. These results require immediate medical consideration of specialists, though the method might be effective to search for the complicated or more than a three drug combination causing liver dysfunction.

Keywords:

Adverse reaction, Drug combination

Background

Vast amounts of drugs are used in clinical medicine and research of combination between two medications which causes adverse reaction such as liver dysfunction have been tested in experiments as well as experience in clinical medicine. However complicated relations such as more than three drug combination have not been analyzed well.

Methods

At first, we checked ALT temporal data of all patients within a given period and divided all cases into two groups, one group were cases where liver dysfunction (group A) and the other were normal cases (group B). A given period is from one hundred days before admission to discharge. Patients with hepatocytic carcinoma or viral hepatitis were excluded. Group A consisted of cases where the value of ALT exceeded 45IU/L at least once during their hospitalization and it returned to a normal region before hospital discharge. The total of both groups were 65,317 cases, which are 74% of all cases. Next other cases were excluded; 1) ALT is already over the normal range before admission, 2) ALT keeps high range after discharge, 3) charge, 3) ALT goes above the normal range twice or more during hospitalization.

Secondly, we extracted medication during the same period from both groups and calculated the rate of appeared liver dysfunction.

Finally, we calculated the rate increment by using more drugs at the same time and extracted the combination which showed high increment. For instance, we found a combination of imipenem/cilastatinsodium, Midazolam and Flomoxefsodium. Among these three drugs, there are three combinations of two drugs. To find the high rate increment, we divided the appearance rate of three drug combination by those of the two drug combinations. In this case, the liver dysfunction appearance rate of three drug combinations is about 73% and the highest rate of two drug combinations is about 25%. Therefore, the rate increment resulted in about 2.9, indicating higher increment in three drug combination.

Results

We extracted medication as single drug and two, three and four drug combinations. Approximately 80 of three drug combinations showed more than 2 times higher appearance rate than two drug combinations, whereas there were few four drug combinations which showed such high rate increment compared to its three drug combinations.

Discussion and Conclusion

In this paper, we presented the method of searching for medication which can have closer relation to liver dysfunction when used together. The obtained results showed a high rate increment would belong to the following three cases. First cases are those which really have an adverse reaction. Second case are those often used with another drug or in a physiopathological state causing liver dysfunction .Third might not be a cause but a treatment in itself. In any case, it is necessary to accumulate information which can be reconsidered by doctors and pharmacists. This method achieved the purpose of extracting medication which closely relates to liver dysfunction, and we believe this method is useful and effective for searching evidence retrospectively.