The Risk of Acute Asthmatic Attacks Associated with Different Dosage Forms of Non-Steroidal Anti-Inflammatory Drugs: *a Self-Controlled Case Series Study*

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Conflict of Interest

All PMDA members involved in MIHARI Project have no dealings or transaction with any vendor, pharmaceutical companies or any other party which could result in benefit to us.

Abstract

➢Background: Our previous research in PMDA's MIHARI Project revealed that self-controlled case series (SCCS) could be applied for drug-safety evaluation with Japanese claims data. Although it is well known that any Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may cause asthmatic attack, few studies have evaluated the risk of asthmatic attack associated with different dosage forms of NSAIDs.
➢Objective: To evaluate the association between the incidence of acute asthmatic attacks and different dosage forms of NSAIDs using SCCS method.
➢Methods:
Design: SCCS.
Setting: The Japan Medical Data Center claims database included 1.2 million patients (as of 2012) was used for this research. Patients who experienced both exposure of NSAIDs and acute asthmatic attack were included.
Exposures: Risk period was defined as the duration of NSAIDs prescription. Washout period was defined as 7 days after the end of Risk period. Baseline period was period other than Risk or Washout periods. These periods were defined respectively for five different dosage forms (injection, oral, suppository, ointment/plaster and eye drop).
Main outcome measures: If inhalation procedure and prescription start of inhaled β2 agonists were recorded on the same day, it was defined as the date of occurrence of acute asthmatic attacks.
Statistical analysis: Conditional Poisson regression models were used to calculate Incidence Rate Ratio (IRR) and 95% Confidence Interval (CI) of acute asthmatic attacks in Risk or Washout periods relative to those in Baseline period for each different dosage form of NSAIDs.
➢Results: The IRR of acute asthmatic attacks in the Risk period was 50.93 (95% CI, 36.37-71.33) with injection, 26.37 (95% CI, 24.56-28.31) with oral, 27.05 (95% CI, 19.12-38.27) with suppository, 6.53 (95%CI, 5.35-7.96) with ointment/plaster and 1.94 (95%CI, 0.62-6.14) with eye drop forms of NSAIDs, respectively.
➢Conclusions: The risk of acute asthmatic attack with different dosages of NSAIDs could be ranked from high to low; in the following order, injection > oral ≈ suppository > ointment/plaster forms. There was no significant increased risk of asthmatic attack with eye drop forms of NSAIDs.

Background

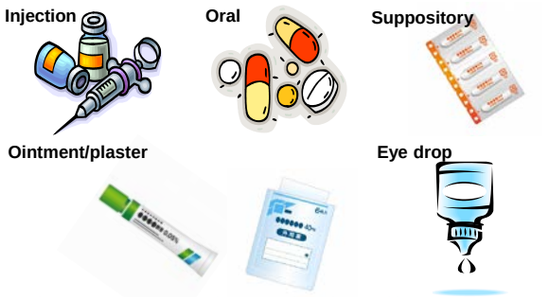
・Our previous research identified an increased risk for acute asthmatic attack in prescription period of any Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) by using that self-controlled case series (SCCS) methods with Japanese claims data.
・Although there are various dosage forms (injection, oral, suppository, ointment/plaster and eye drop) of NSAIDs in Japan, we have not evaluated the risk of acute asthmatic attack by different dosage form of NSAIDs in the previous research.

Objective

・To evaluate the association between the incidence of acute asthmatic attacks and different dosage forms of NSAIDs using the SCCS method.

Methods

➢Data source:
• Commercially available Japanese claims data provided from Japan Medical Data Center Co., Ltd (about 1.2 million patients)
➢ Data period: Jan 2012 to Dec 2012
➢ Study population:
– ***inclusion criteria***
• ≥ 3 months continuous follow-up (first 3 months are not included in observation period)
• The patients who experienced both exposure of any dosage form of NSAIDs and acute asthmatic attack over the observation period (exposed-case)
– ***exclusion criteria***
• Diagnosis of acute asthmatic attack or asthma at first 3 months of follow-up period
• Diagnosis of chronic obstructive pulmonary disease (COPD) at any time during the follow-up period
➢ Exposure:
• Any dosage form of NSAIDs prescription in claims data
• The dosage forms of NSAIDs in this research are as follow;



➢ Main outcome measures (Acute asthmatic attack):
•Combination 'Inhalation procedure' and 'Any inhaled β2 agonists prescription' in claims data
•If the inhalation procedure was performed concurrently with the prescription start of inhaled β2 agonists at the same day, we defined event occurred on that date.
➢ Periods definition:
– Risk period
• Period from start to end of NSAIDs prescription
• Include the prescription start date in the period
– Washout period
• 7 days after the end of NSAIDs prescription
– Baseline period
• Periods other than risk or washout periods

➢ Statistical analysis:
•Conditional Poisson regression models were used to calculate Incidence Rate Ratio and 95% Confidence Interval of acute asthmatic attacks in the Risk or Washout periods relative to those in the Baseline period.
•When we estimated the risk of one dosage form of NSAIDs in the case of a patient administrated with more than one dosage forms, the prescriptions of the other forms were ignored.

Results

Table1: Risk estimation of injection form (n = 174)

Periods	The number of events	Total Person-day	IRR*	95% CI**
Baseline period	151	44,728	1.00	—
Risk period	52	380	50.93	36.37 – 71.33
Washout period	31	1,918	5.56	3.74 – 8.27

Table2: Risk estimation of oral form (n = 3,171)

Periods	The number of events	Total Person-day	IRR*	95% CI**
Baseline period	2,215	782,373	1.00	—
Risk period	1,695	41,242	26.44	24.63 – 28.38
Washout period	294	35,666	3.30	2.92 – 3.74

Table3: Risk estimation of suppository form (n = 247)

Periods	The number of events	Total Person-day	IRR*	95% CI**
Baseline period	269	65,052	1.00	—
Risk period	38	368	27.13	19.17 – 38.39
Washout period	23	2,140	2.76	1.79 – 4.24

Table4: Risk estimation of ointment/plaster form (n = 1,867)

Periods	The number of events	Total Person-day	IRR*	95% CI**
Baseline period	2,347	480,843	1.00	—
Risk period	106	3,389	6.55	5.37 – 7.99
Washout period	127	22,276	1.19	0.99 – 1.43

Table5: Risk estimation of eye drop form (n = 180)

Periods	The number of events	Total Person-day	IRR*	95% CI**
Baseline period	260	47,241	1.00	—
Risk period	3	252	1.94	0.62 – 6.14
Washout period	10	1,704	0.97	0.51 – 1.85

➢ Risk of acute asthmatic attack associated with injection, oral, suppository and ointment/plaster forms of NSAIDs
• Compared with the Baseline periods, a risk of acute asthmatic attack in the Risk periods significantly increased in injection, oral, suppository and ointment/plaster forms (Tables 1 to 4).
• The risk could be ranked from high to low; in the following order, injection > oral ≈ suppository > ointment/plaster forms.

• These varying degree of risk might be reflect the amount of NSAIDs contained in each different dosage form or NSAIDs distribution throughout a body.
➢ Risk of acute asthmatic attack associated with eye drop form of NSAIDs
• There was no significant increased risk of asthmatic attack with eye drop form (Table 5).
• This lower risk of eye drop form could be explained by a low amount of NSAIDs contained in this form.
• Consistently with our result, precautions for the risk of acute asthmatic attack are not included in the package inserts of ophthalmic NSAIDs in Japan.
➢ Limitations of this research
• If asthmatic attack occurred in NSAIDs prescription on start date, it could not be denied that the event may have occurred before the usage of NSAIDs.
• When the risk of one dosage form was estimated in the case of a patient administrated with more than one dosage forms, the effect of the other dosage forms of NSAIDs was not considered.
• The simple SCCS method which was used in this research might not sufficiently adjust the effect of time-dependent factors, such as concomitant medication or acute respiratory infection.
• There was no information of usage of over-the-counter antiphlogistic analgetic containing NSAIDs in the claims data.

Conclusions

・Different dosage forms of NSAIDs could have varying degree of risk of acute asthmatic attack in the prescription periods.
・Medical professionals should recognize that any NSAIDs medication except for the eye drop form may be associated with the incidence of acute asthmatic attack.

* Incident Rate Ratio, ** 95% Confidence Interval