ORIGINAL RESEARCH

Acetaminophen administration and the risk of acute kidney injury: a self-controlled case series study

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Background: Acetaminophen (APAP) is frequently used for analgesia and is considered safer than nonsteroidal anti-inflammatory drugs (NSAIDs) for the kidneys. However, there is little epidemiological evidence of the association between APAP and acute kidney injury (AKI).

Objectives: To examine the association between APAP and AKI using the self-controlled case series (SCCS) method, which is a novel strategy to control between-person confounders by comparing the risk and reference periods in each patient.

Methods: We performed SCCS in 1,871 patients (39.9% female) who were administered APAP and subsequently developed AKI, by reviewing electronically stored hospital information system data from May 2011 to July 2016. We used conditional Poisson regression to compare each patient's risk and reference period. As a time-varying confounder, we adjusted the status of liver and kidney functions, systemic inflammation, and exposure to NSAIDs.

Results: We identified 5,650 AKI events during the 260,549 person-day observation period. The unadjusted incidences during the reference and exposure periods were 2.01/100 and 3.12/100 person-days, respectively. The incidence rate ratio adjusted with SCCS was 1.03 (95% confidence interval [CI]: 0.95–1.12). When we restricted endpoints as stage 2 AKI- and stage 3 AKI-level creatinine elevations, the incidence rate ratios were 1.20 (95% CI 0.91–1.58) and 1.20 (95% CI 0.62–2.31), respectively, neither of which was statistically significant.

Conclusion: Our findings added epidemiological information for the relationship between APAP administration and AKI development. The results indicated scarce association between APAP and AKI, presumably supporting the general physicians' impression that APAP is safer for kidney.

Keywords: acetaminophen, acute kidney injury, adverse drug event, self-controlled case series, hospital information system

Introduction

Acetaminophen (*N*-acetyl-*para*-amino-phenol [APAP]) is a frequently used pain killer. APAP is generally regarded as a safer drug with regard to kidney function compared to nonsteroidal anti-inflammatory drugs (NSAIDs), which are known to contribute to the development of acute kidney injury (AKI).[1] However, little is known about the association between APAP and AKI, especially for therapeutic dosing.

Previous case reports[2-4] and cohort studies[5,6] have suggested an association between supratherapeutic doses of APAP and AKI. To our knowledge, there is only one case series[7] that reported two AKI cases suspiciously induced by therapeutic-dose APAP. The causality in those cases remains unclear because the patients had taken other suspicious drugs in addition to APAP, and the drug-induced lymphocyte stimulation tests, which

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examined their hypersensitivity to APAP, were negative.[7] Looking at in vitro data, APAP in therapeutic doses is said to induce fibroblast proliferation, possibly resulting in kidney injury, but its clinical implications have not yet been proven.[8] Although there is quite limited epidemiological evidence for the association between therapeutic-dose APAP and AKI, guidelines,[9,10] textbook,[11] and even the National Kidney Foundation web page[12] describes its safer profile for the kidney, which is widely known among physicians.[13] In contrast, an official medical package leaflet published in Japan[14] stated that APAP is contraindicated in patients with severe renal impairment in order to prevent further renal damage, but no evidence has been shown to reinforce this contraindication.

Therefore, we believe that it is important to investigate any association between therapeutic dose APAP and AKI, to enhance better decision making for pain management. However, APAP is so widely used[13] that demographic variance of the target population is too large; many between-person confounding factors would exist if we intended to perform conventional retrospective methods. Hence, a contrivance in study design is required.

In this study, we aimed to demonstrate the possible association between the administration of therapeutic doses of APAP and the occurrence of AKI, using a recently introduced, retrospective, observational design named self-controlled case series (SCCS). As a model, SCCS can easily control for potential between-person confounding factors that do not change over time by comparing risk and reference periods within each individual.[15,16]

Methods
Study design and settings
This is an SCCS study using drug prescription and biochemical blood test data obtained from the hospital information system

(HIS) of a single facility. SCCS is a kind of case-series method developed recently.[15,16] The method compares incident rates during time periods with different risk statuses within each individual in order to estimate the incident rate ratio of risk factors.[17] SCCS can therefore avoid time-independent confounding factors occurring between study subjects by comparing "risk" and "reference" periods within individuals; thus, there is no need for a separate control group. This feature makes it easier to examine drug adverse events retrospectively using HIS, in which a suitable control group is difficult to find.[18] The pictorial representation of the design is shown in Figure 1.

We identified people who were prescribed oral APAP from May 2011 to July 2016, by searching the HIS database of Kyoto University Hospital. The hospital is a tertiary general hospital with 34 divisions including internal medicine, surgery, emergency department, and psychiatry that take care of both the acute and chronic conditions of various diseases. The database covers all the patients who have ever consulted doctors working in the hospital. Its prescription database includes all outpatient and inpatient prescriptions in the hospital but does not include those written outside the hospital (eg, by general practitioners). From these potentially eligible patients, we excluded patients younger than 18 years at the beginning of the observation period, because our research scope was adult patients. In addition, we excluded patients on chronic dialysis therapy who would no longer be burdened by the initiation of renal replacement therapy (RRT). Similar to the prescription, our database does not include any treatment outside the hospital, such as at dialysis facilities. Furthermore, because acute blood purification in the hospital is recorded using paper documents, we could not extract the exact day of RRT. Therefore, we excluded patients whose estimated glomerular filtration rate (eGFR) value at the beginning of the observation was <7 mL/min/1.73 m[2], as
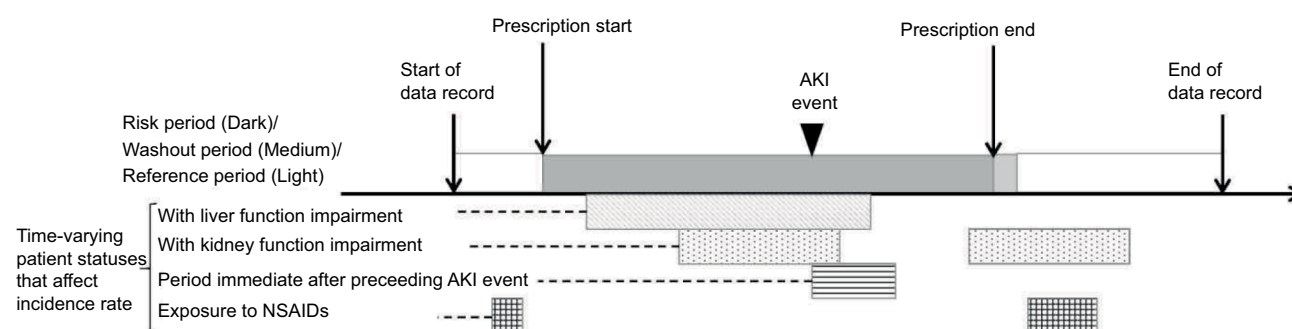

Figure 1 Pictorial representation of SCCS we used in our context of interest.
Notes: The method compares the incidence rates of risk and reference periods with an adjustment for variables affecting the incidence rate. Here, the risk is acetaminophen administration extracted from prescription data. In this study, we adjusted for exposure to NSAIDs, liver function impairment, kidney function impairment, and effects of preceding AKI event.
Abbreviations: AKI, acute kidney injury; NSAIDs, nonsteroidal anti-inflammatory drugs; SCCS, self-controlled case series.

calculated with MDRD formula for the Japanese population, because patients with an eGFR <7 mL/min/1.73 m^2 can be seen as end-stage renal disease (ESRD) patients.[19]

The inclusion flow diagram is shown in Figure 2. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R0290). The Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, on which committee approval is based, advised consent from patients was not required because we secondarily used existing patient data collected for clinical purpose. Patient recruitment was done with an adequately managed opt-out method, as required in aforementioned guideline: we disclosed documents showing their right to decline participation to patients. Personal information was handled using secure computers in accordance with the Guideline on the Personal Information Protection Law in Japan.

Exposure and risk period

We defined our exposure group as those patients who were administered APAP, as identified by data extracted from the HIS of Kyoto University Hospital in the aforementioned period. We used the Japanese drug code specific to oral APAP, which is identical to the Anatomical Therapeutic Chemical (ATC) Classification of D00217, in our database search queries. A risk period in SCCS ("exposed period" in this study) is a period during which the individuals are biologically considered to be at risk of the drug's adverse event of interest. We define the risk period here by the calendar days of APAP administration. If a patient was instructed to take APAP regularly, the corresponding days were considered to be the exposed period, assuming that all patients took all drugs when prescribed. If a patient was prescribed APAP to be taken on an as-needed basis, we assumed that he/she took the medication regularly three times a day and the corresponding periods were seen as the exposed period.

Endpoints and event measures

The primary endpoint was the occurrence of an AKI event. An AKI event was defined as serum creatinine elevation by ≥0.3 mg/dL in 2 days or ≥1.5 times in 7 days compared to the result of the most recent examination. These criteria were based on the definition of stage 1 AKI by the Kidney Disease Improving Global Outcomes Foundation.[20] Therefore, in this study, we included only periods in which the patients received blood examinations at least twice in 7 days, based on our method of defining AKI. The onset date of AKI was determined by laboratory data that satisfied the aforementioned criteria. Our blood examination database includes examination date and result but not the exact time
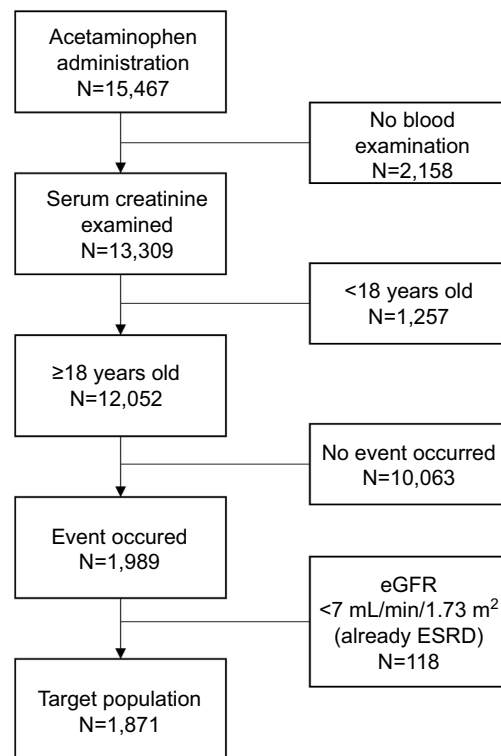

Figure 2 Inclusion flow diagram of the target population.
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

when the blood specimen was collected. In a precise sense, KDIGO defines stage 1 AKI as a serum creatinine elevation by ≥0.3 mg/dL in 48 h; however, in this study, we used two calendar days instead of 48 h because of the aforementioned limitation of data granularity.

We also examined the incidence of advanced AKI events as endpoints. Stage 2 AKI (defined as serum creatinine elevation of greater than or equal to twice the baseline level) and stage 3 AKI-level creatinine elevation (≥4.0 mg/dL, or greater than or equal to three times the baseline level) were selected. As mentioned earlier, we could not extract the exact date of RRT, hence we applied creatinine elevation condition only as a definition of severer AKI equivalent to stage 3 AKI.

Washout period

Serum creatinine, which is the key value defining AKI, is reported to elevate 24 and 48 h after kidney damage.[21] In addition, little is known about the lead time between APAP administration and the onset of kidney injury. Therefore, an AKI event could be detected shortly after the cessation of APAP exposure. In this study, we treated two calendar days after the cessation as a washout period, which had a different risk structure than the control period. We also modified the assumption for the length of the washout period with the sensitivity analysis described later.

Adjustment of time-varying confounders

As discussed earlier, SCCS can avoid between-person confounders that do not change over time, but we had to adjust time-varying variables that correlate to both the exposure and the occurrence of the event. Figure 3 shows the causal diagram of our context of interest. We identified several time-varying confounders: liver function impairment, kidney function impairment, systemic inflammation, and NSAIDs use. In addition, we adjusted the effect of AKI occurrence itself on subsequent events.

Liver function impairment

APAP has been shown to induce renal damage in patients with impaired liver function.[5] In addition, physicians may hesitate to prescribe APAP for patients with impaired liver function, due to its well-known hepatotoxicity. Therefore, liver function acts as a confounding factor that needs to be adjusted. We defined liver function impairment as the elevation of serum alanine aminotransferase to levels of more than double the upper limits of normal (ULN), or the elevation of alkaline phosphatase above its ULN, referring to the criteria of drug-induced liver injury.[22] We assumed liver function impairment to be transient and to occur independently of the kidney injury.

Kidney function impairment

Kidney function declines gradually over time,[23] and impaired kidney function is revealed to be the risk factor of AKI development.[24,25] In addition, patients with impaired kidney function are more likely to be prescribed APAP,[26] adhering to the recommendation of guidelines[27] and others discussed earlier.[9-12] Therefore, kidney function is also a time-varying confounder to be adjusted. In this study, we defined kidney function impairment to be an eGFR value of <60 mL/min/1.73 m^2 and subdivided them into four strata ($45 \leq$ eGFR <60 mL/min/1.73 m^2, $30 \leq$ eGFR <45 mL/min/1.73 m^2, $15 \leq$ eGFR <30 mL/min/1.73 m^2, and $7 \leq$ eGFR <15 mL/min/1.73 m^2).[28]
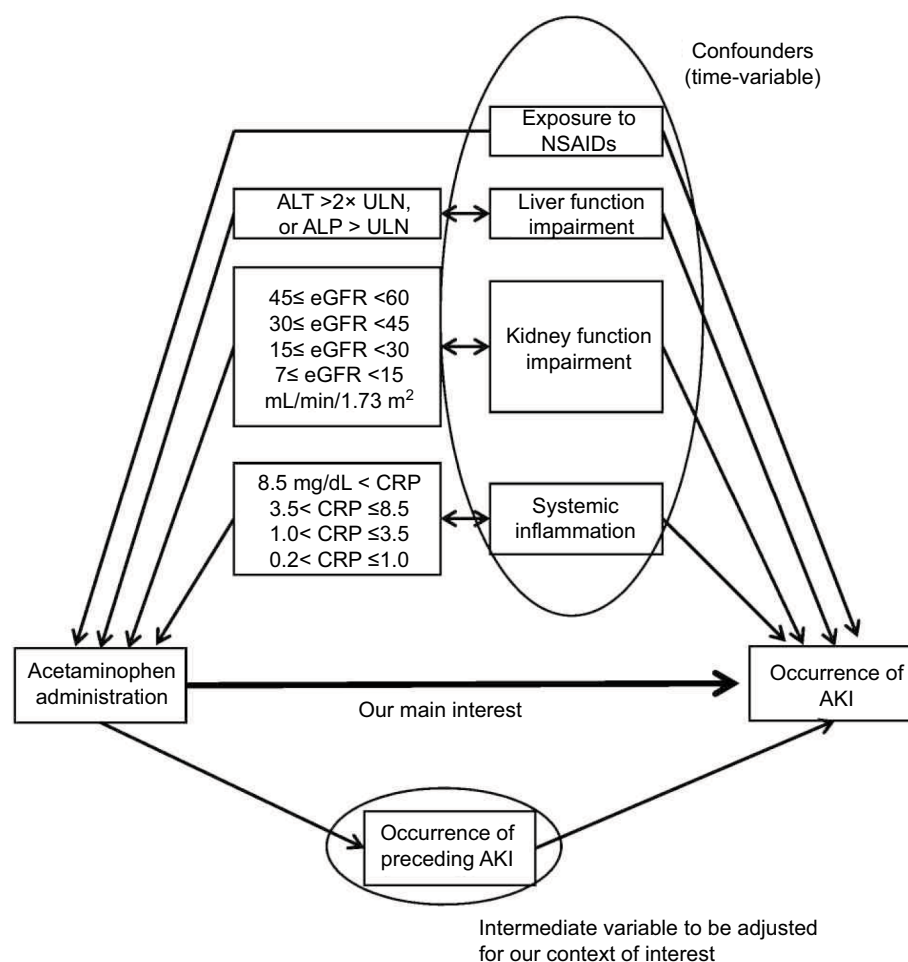

Figure 3 Causal diagram of our context of interest.
Note: We identified and adjusted four time-variable confounders and one intermediate variable shown here.
Abbreviations: AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; ULN, upper limits of normal.

Systemic inflammation

AKI occurs in 22.7% of hospitalized patients, especially those in a severely ill condition.[29,30] Clinically ill conditions are generally transient and such patients tend to need APAP as analgesic agents, hence, the general condition of the patient is a time-variable confounder. As an indicator of the patients' general condition, we used C-reactive protein (CRP) to represent the status of systemic inflammation. We assumed that a CRP value of >0.2 mg/dL indicated systemic inflammation because this value is the threshold in the Kyoto University Hospital laboratory. In addition, we subdivided systemic inflammation status into four strata, decided by the 50th, 75th, and 90th percentiles of the analyzed period sorted by the CRP value (0.2< CRP ≤1.0 mg/dL, 1.0< CRP ≤3.5 mg/dL, 3.5< CRP ≤8.5 mg/dL, and 8.5 mg/dL < CRP).

We assumed that aforementioned impaired liver and kidney functions and systemic inflammation status start at the point of the middle day in the blood examination interval. For example, when a patient satisfied impaired liver function criteria at the examination on May 5, while he/she did not satisfy the criteria at the examination just before on May 1, we assumed that his/her impaired liver function started at May 3.

NSAIDs' use

As discussed earlier, NSAIDs is well known to cause AKI. Both NSAIDs and APAP are analgesics; thus, a correlation in their administration may exist due to background conditions. Therefore, we treated NSAIDs' administration as a confounding factor. We used the Japanese drug code equivalent to the ATC drug code of M01AB, M01AC, M01AE, M01AG, and M01AH to determine the NSAIDs used. Similar to APAP administration, we defined a 2-day washout period.

Occurrence of AKI

We intended to examine the direct effect of APAP administration on AKI events, but the occurrence of AKI increases the incidence rate of subsequent AKI.[31] This means that an AKI event acted as an intermediate variable in our causal model. To the best of our knowledge, there is no firm knowledge about how long the preceding AKI affects the following ones. Therefore, we assumed a 7-day period after AKI (hereafter called the preceding AKI-affected period), to adjust for the effect of one AKI event on subsequent ones,[2] as shown in Figure 1.

Sensitivity analysis

To confirm our results, we performed sensitivity analyses. First, we stratified patients by their gender. Next, we modified these assumptions in our analysis: the preceding AKI-affected period (1, 3, and 14 days) and washout period for APAP administration (1, 7, and 14 days).

We also calculated the incidence rate ratio of APAP administration with the model including potentially nephrotoxic agents known to cause kidney damage. These drugs could be associated with the development of AKI, but administration of these drugs, except NSAIDs, does not directly correlate to that of APAP because of the difference in their effects. Therefore, they do not necessarily act as confounding factor. The list of drugs is shown in Table S1.[32]

Statistical analysis

All analyses used R Version 3.2.1 software,[33] and the results are presented with 95% confidence intervals (CIs) when appropriate. We used conditional Poisson regression to compare each patient's risk and reference periods with Generalized Nonlinear Models package.[34] A two-sided P-value of <0.05 was considered statistically significant.

Results

Patient characteristics in this study are shown in Table 1. We included 1,871 patients, and 39.9% of the target population was female. The average age at the beginning of the observation was 63.3 years, and the average observation length was 139 days. The average exposure period of APAP administration was 16 days. In our population, 48.6% of patients had eGFR values >60 mL/min/1.73 m^2 at the time of first blood examination, while in 32.3% of patients, the eGFR was between 30 and 60 and, in 19.1% of patients, the eGFR was between 7 and 29. As explained earlier, patients whose eGFR value was <7 mL/min/1.73 m^2 were excluded.

Table 2 shows the unadjusted incidence of AKI stratified by the aforementioned factors and incidence rate ratios adjusted with SCCS. There were 5,650 AKI events (33.1% of them were first time AKI) that occurred during the 260,549 person-days of observation period. Among them, 4,584 AKI

Table 1 Patient characteristics of included patients (n=1,871)

Characteristics	Value
Age, mean (± standard deviation)	63.31 (±15.90)
Female gender (number of patients, %)	747 (39.9)
Baseline eGFR (number of patients, %)	
≥60	909 (48.6)
30–59	604 (32.3)
8–29	358 (19.1)
Observation length (days, interquartile range in parenthesis)	139.3 (57–174)
Exposure length (days, interquartile range in parenthesis)	16.06 (4–18)

Abbreviation: eGFR, estimated glomerular filtration rate.

Table 2 Unadjusted incidence and adjusted incidence rate ratio of AKI in periods with each risk status

Risk status	AKI occurred (times)	Period length (person-day)	Incidence (unadjusted/ 100 person-day, 95% CI)	Incidence rate ratio (adjusted with SCCS, 95% CI)	P
Exposure to acetaminophen					
No acetaminophen administration	4,584	228,036	2.01 (1.95–2.07)	Reference	
With acetaminophen administration	939	30,053	3.12 (2.93–3.33)	1.03 (0.95–1.12)	0.49
Washout periods (2 days)	127	2,460	5.16 (4.32–6.11)	1.05 (0.87–1.27)	0.59
Time-varying confounders					
NSAIDs use					
No NSAIDs administration	4,877	229,009	2.13 (2.07–2.19)	Reference	
With NSAIDs administration	681	30,096	2.26 (2.10–2.44)	1.27 (1.14–1.41)	<0.01
NSAIDs washout period (2 days)	92	1,444	6.37 (5.17–7.76)	1.24 (0.99–1.55)	0.07
Status of systemic inflammation					
CRP ≤0.2 mg/dL	401	72,712	0.55 (0.50–0.61)	Reference	
0.2< CRP ≤1.0 mg/dL	568	60,822	0.93 (0.86–1.01)	1.87 (1.62–2.15)	<0.01
1.0< CRP ≤3.5 mg/dL	1,224	60,897	2.01 (1.90–2.12)	3.63 (3.17–4.15)	<0.01
3.5< CRP ≤8.5 mg/dL	1,469	39,907	3.68 (3.50–3.87)	6.25 (5.45–7.16)	<0.01
8.5 mg/dL < CRP	1,988	26,211	7.58 (7.27–7.91)	11.7 (10.2–13.5)	<0.01
Renal function					
Without renal function impairment (eGFR ≥60)	402	116,739	0.34 (0.31–0.38)	Reference	
45≤ eGFR <60 mL/min/1.73 m^2	351	43,311	0.81 (0.73–0.90)	7.10 (5.91–8.53)	<0.01
30≤ eGFR <45 mL/min/1.73 m^2	874	39,889	2.19 (2.05–2.34)	32.2 (27.0–38.5)	<0.01
15≤ eGFR <30 mL/min/1.73 m^2	1,754	31,522	5.56 (5.31–5.82)	143 (119–173)	<0.01
7≤ eGFR <15 mL/min/1.73 m^2	2,269	29,088	7.80 (7.49–8.11)	309 (252–379)	<0.01
Liver function					
Without liver function impairment	3,006	165,586	1.82 (1.75–1.88)	Reference	
With liver function impairment	2,644	94,963	2.78 (2.68–2.89)	1.13 (1.05–1.22)	<0.01
Time elapsed from the latest AKI event					
≥8 days	3,330	235,748	1.41 (1.37–1.46)	Reference	
≤7 days	2,320	24,801	9.35 (8.99–9.72)	1.01 (0.95–1.08)	0.68

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; SCCS, self-controlled case series.

events occurred during 228,036 person-days of the unexposed to APAP period, while 939 events occurred during 30,053 person-days of the exposed period and 127 events did during 2,460 person-days of washout period. The adjusted incidence rate ratio of AKI under the condition of APAP administration was 1.03 (95% CI: 0.95–1.12), and that of the washout period was 1.05 (95% CI: 0.87–1.27). Among time-varying confounders, the incidence rate ratios of systemic inflammation, kidney function impairment, liver function impairment periods, and use of NSAIDs were statistically >1.0. In particular, during the exposure to NSAIDs, the incidence rate ratio was 1.27 (95% CI: 1.14–1.41). However, that of the periods immediately after the preceding AKI event did not show statistical significance.

Table 3 shows the incidence rate ratios under the condition of defining endpoints as stage 2 AKI- and stage 3 AKI-level creatinine elevations. When we define stage 2 AKI as the endpoint, the number of AKI events was 545 and the number of patients that satisfied the inclusion criteria was 399. The incidence rate ratio of APAP administration was

1.20 (95% CI: 0.91–1.58). When we define stage 3 AKI-level creatinine elevation as the endpoint, 108 AKI events occurred in 91 patients. The incidence rate ratio was 1.20 (95% CI: 0.62–2.31).

Finally, we performed sensitivity analyses, as shown in Table 4. When we stratified patients by gender, the incidence rate ratio of APAP administration was 1.03 (men) and 1.01 (women). When we modified the assumptions as to the preceding AKI-affected period and length of the washout period, the incidence rates were ~1.01–1.03 under all assumptions. When we added potentially nephrotoxic agents into the model, the estimated incidence rate ratio was 1.04.

Discussion

We conducted a SCCS study to examine the potential association between APAP administration at therapeutic doses and the occurrence of AKI. Our results showed that the incidence rate of AKI, in the period that patients were prescribed APAP, was slightly higher than in the period in which they were not prescribed APAP, with the conditions of controlling

Table 3 Incidence rate ratio of AKI under the condition of defining events – stage 2 and stage 3 AKI-level creatinine elevation

End point definition	AKI stage 2	P	AKI stage 3	P
Number of patients	399		91	
AKI occurred (times)	545		108	
Incidence rate ratio of AKI in acetaminophen administration period (95% CI in parenthesis)	1.20 (0.91–1.58)	0.19	1.20 (0.62–2.31)	0.59
Incidence rate ratio of AKI in Washout period (95% CI in parenthesis)	1.26 (0.66–2.39)	0.48	0.76 (0.10–5.87)	0.79

Abbreviations: AKI, acute kidney injury; CI, confidence interval.

Table 4 Incidence rate ratio of AKI with modified assumptions: result of sensitivity analysis

Analysis	Incidence rate ratio of AKI in acetaminophen administration period (95% CI)	P	Incidence rate ratio of AKI in washout period (95% CI)	P
Main analysis	1.03 (0.95–1.12)	0.49	1.05 (0.87–1.27)	0.59
Only male (1,124 patients)	1.03 (0.93–1.15)	0.53	1.04 (0.82–1.33)	0.73
Only female (747 patients)	1.01 (0.88–1.16)	0.92	1.05 (0.78–1.42)	0.73
Preceding AKI-affected period				
1 day	1.03 (0.95–1.12)	0.49	1.05 (0.87–1.27)	0.59
3 days	1.03 (0.95–1.12)	0.52	1.05 (0.87–1.26)	0.64
14 days	1.03 (0.95–1.12)	0.47	1.07 (0.88–1.29)	0.50
Length of washout period				
1 day	1.03 (0.95–1.12)	0.47	1.15 (0.91–1.47)	0.25
7 days	1.02 (0.94–1.11)	0.38	0.94 (0.83–1.07)	0.38
14 days	1.01 (0.93–1.10)	0.76	0.89 (0.80–1.00)	0.05
Including potentially nephrotoxic agents into the model	1.04 (0.96–1.13)	0.36	1.06 (0.88–1.28)	0.55

Abbreviations: AKI, acute kidney injury; CI, confidence interval.

for kidney function, liver function, severity of systemic inflammation, and exposure to NSAIDs as time-varying confounders. However, the difference was not statistically significant over the null hypothesis that APAP administration was not associated with the development of AKI.

The analgesic action of APAP is not fully understood, while its hepatotoxicity is well acknowledged.[35] Several researchers have indicated that cyclooxygenase-3 might be a target enzyme of APAP,[36,37] while other in vivo data have suggested that another metabolite, named AM404, was the key factor in the mechanism of APAP as an analgesic agent.[38]

There are several case reports reporting that an APAP overdose causes AKI.[2-4] Previous reviews have suggested that renal insufficiency occurs in 1–2% of patients after an APAP overdose.[39] Another cohort study from Taiwan showed that the overall risk of developing AKI was about twice as high in patients with APAP intoxication,[6] discussing that AKI may be caused by N-acetyl-p-benzoquinoneimine (NAPQI), which is a toxic intermediate metabolite of APAP[40] produced in excess by the saturation of normal metabolic pathways in the liver. Hence, their results are difficult to apply to the effects of APAP at therapeutic doses.

So far, there are mixed opinions about the association between therapeutic dose APAP and AKI. To our knowledge,

there is no observational study examining the association between them. In the present study, we utilized SCCS with the adjustment of time-varying confounders to extract reliable associations from an easily available HIS data, which contains prescription and blood examination results. APAP is a relatively inexpensive drug to compensate costly clinical research; therefore, we believed that it was important to pursue less costly but statistically validated methods.

SCCS was originally developed for evaluating association between vaccinations and their adverse effects[15] and is now commonly used for the purpose.[41] Recently, researchers have investigated the associations between drug administration and some events by this method using existing electronically stored databases, with examples including antipsychotic drugs and myocardial infarction[42] and thiazolidinediones and fracture.[43] One study investigated the association between antidepressants and hip fracture using both SCCS and conventional case–control method and concluded that SCCS could perform more accurately than case–control methods,[44] indicating that SCCS is potentially valuable for our research purposes.

Our main analysis secondarily showed that the incidence rates of AKI associated with systemic inflammation, kidney function, liver function, and NSAIDs' use were

significantly higher than reference. These results were compatible with previous reports, indicating that the analysis program for our SCCS model was properly developed. The effect of preceding AKI events did not show statistical significance in spite of existing knowledge, but this result can be explained by the variable's correlation to kidney function impairment.

Our data showed that the incidence rate of AKI associated with APAP administration was 1.03 times higher than the reference and was 1.05 times higher in the washout period. Point estimates were slightly >1.0, but it did not show statistical significance. Not showing statistical significance does not directly mean the absence of a relationship between APAP and AKI, but considering the distribution of the 95% CI, it could be supposed to be scarce or ignorable. In contrast to the aforementioned case report[7] and the in vitro data[8] indicating that therapeutic dose APAP could cause AKI, our result was consistent with the well-known physicians' impression. At least, considering a previous report,[1] which showed that the AKI risk with NSAIDs' use is 60% higher than reference, and our present data showing the association of NSAIDs' use with AKI, we could conclude that the clinical importance of the association between APAP use and AKI is weaker than that of NSAIDs.

When we set the event as advanced AKI events, the point estimates of the incidence rate ratios were higher than that of the base case model, but they also did not show statistical significance. Though the number of patients was small and CI became wider, the difference in the incidence rate of severer AKI, part of which can be seen as severe kidney injury as requiring RRT, associated with APAP administration, could be supposed to have little clinical importance.

From the sensitivity analyses, which modified assumptions in the base case model, we obtained almost similar incidence rate ratios, indicating the robustness of our findings. Including potentially nephrotoxic agents into our model also did not show apparent change in the results. This result may be explained by the little correlation between administration of APAP and these drugs. However, it must be considered that we included all drugs grouped together on account of the difficulty in data handling when including each drug separately into the model.

AKI can sometimes be a lethal condition,[45] and it is also well known that those who recovered from AKI can progress to chronic kidney disease,[46] which is a major risk factor for cardiovascular diseases. AKI can lower patients' quality of life,[47,48] and therefore, prevention of AKI is very important. From our results, the clinical importance of the association

between APAP and AKI seems unremarkable, or at least smaller than that of NSAIDs and AKI. Considering the side effects of other pain-killing treatment options, using APAP is a reasonable choice when physicians intend to preserve patients' kidney function.

Limitations

There were several limitations to our study. First, unobserved confounding factors may still exist, including both those arising from the limitations of the dataset and those having intrinsically uncontrollable features. For example, we could not include the major time-varying conditions, such as post-cardiac surgery state and sepsis, due to the limitation of our dataset, which could not sufficiently acquire the existence of such conditions. In addition, the indication for APAP administration may act as an intrinsically uncontrollable time-varying confounding factor. We cannot distinguish AKI caused by APAP from AKI due to a background poor clinical condition that resulted in APAP administration. As described in the "Methods" section, those time-varying factors that correlate to APAP administration and affect the risk of AKI development can result in the observed incidence rate ratios being larger or smaller than the real value. From the clinical viewpoint, such confounders generally increase the proportion of APAP administration and also increase the incidence of AKI because severe conditions require pain control and result in high incidence of AKI. Therefore, a calculated incidence rate ratio with only observed confounders, in which APAP administration period contains more patients with unobserved confounder increasing incidence rate, shows larger values than real incidence rate ratios. Considering that our main result already showed little association between APAP and AKI, this problem may have little impact on our result, even though the possibility of an unexpected effect still remained.

Second, we used a dataset from a single facility and, therefore, potential sampling bias may exist. Third, this study restricted observation periods to those periods in which patients received blood examinations at least once in 7 days. That is to say, our results cannot directly be applied to patients who do not need such frequent blood examinations. Last, we could not fully collect APAP administration (eg, taking over-the-counter drugs). This bias can lead to erroneous estimation of the incidence rate ratio, but its effect may be small. This is because Japanese health insurance covers APAP prescription for almost all diseases, so the target population could get an APAP prescription at lower cost than buying over-the-counter drugs.

Conclusion

Using prescription and biochemical blood test data from HIS, we performed SCCS to compare the incidence rate of AKI between periods in which patients were and were not exposed to therapeutic dose APAP. We found that the incidence was slightly higher during a period with APAP administration as a point estimate; however, the difference was not statistically significant. General physicians often recognize that APAP is relatively safe for the kidneys; however, it has not been demonstrated in epidemiological data. Even though it is not necessarily a statistically precise interpretation, our research epidemiologically added supporting information to the general physicians' impressions.

Data sharing

It is difficult for authors to share data we used, because our data contain personal identifier, prescription data, and blood examination data, which Japanese legal regulation regards as sensitive personal information not to be freely disclosed.

Acknowledgments

Author contributions

SH and TT contributed to the research idea and study design. SH contributed to the data acquisition. SH and HY analyzed the data. KY and NK contributed to the statistical analysis. SH and HY contributed to the article writing. TM and HT contributed to the mentorship. MY and TK contributed to the supervision. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 The list of potentially nephrotoxic agents we used in sensitivity analysis

Potentially nephrotoxic agents	ATC code
Antidepressants/mood stabilizers	
Amitriptyline	N06AA09
Doxepin	Not approved in Japan
Fluoxetine	Not approved in Japan
Lithium	N05AN01
Antihistamines	
Diphenhydramine	D04AA32
Doxylamine	Not approved in Japan
Antimicrobials	
Acyclivir	D06BB03
Aminoglycosides	J01G
Amphotericin B	A01AB04
Beta-lactam	J01C, J01D
Foscarnet	J05AD01
Ganciclovir	J05AB06
Pentamidine	P01CX01
Quinolones	J01M
Rifanpin	J04AB02
Sulfonamides	J01EE01
Vancomycin	A07AA09
Antiretrovials	
Adefovir	J05AF08
Cidofovir	Not approved in Japan
Tenofovir	J05AF07, J05AF13, J05AR03, J05AR09, J05AR17, J05AR18
Indinavir	J05AE02
Benzodiazepines	N05BA, N05CD, N05CF
Calcineurin inhibitors	
Cyclosporine	L04AD01
Tacrolimus	L04AD02
Cardiovascular agents	
Angiotensin-converting enzyme inhibitors	C09A, C09B
Angiotensin receptor blockers	C09C, C09D
Clopidogrel	B01AC04
Ticlopidine	B01AC05
Statins	C10AA, C10BA
Chemotherapeutics	
Carmustine	L01AD01
Semustine	Not approved in Japan
Cisplatin	L01XA01
Interferon-alpha	L03AB01, L03AB05, L03AB06, L03AB09, L03AB10, L03AB11, L03AB12, L03AB15
Methotrexate	L04AX03
Mitomycin-C	L01DC03
Contrast dye	V08A
Diuretics	
Loops	C03CA
Thiazides	C03AA
Triamterene	C03DB02
Proton pump inhibitors	
Lansoprazole	A02BC03
Omeprazole	A02BC01
Pantoprazole	Not approved in Japan
Others	
Allopurinol	M04AA
Gold therapy	M01CB
Haloperidol	N05AD01
Pamidronate	M05BA03
Phenytoin	N03AB02, N03AB52
Quinine	P01BC01
Zoledronate	M05BA08

Abbreviation: ATC, Anatomical Therapeutic Chemical.