Original Article
Yonsei Med J 2024 Feb;65(2):120-128
https://doi.org/10.3349/ymj.2023.0207
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Evaluation of the Regulatory Required Post-Authorization Safety Study for Propacetamol: Nested Case-Control and Case-Time-Control Studies

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Purpose: Following the withdrawal of propacetamol in Europe owing to safety issues, the regulatory authority of South Korea requested a post-marketing surveillance study to investigate its safety profile.

Materials and Methods: We conducted nested case-control and case-time-control (CTC) analyses of cases and controls identified for outcomes of interest, including anaphylaxis, thrombosis, and Stevens–Johnson syndrome (SJS), using the claims database of South Korea, 2010–2019. Risk-set sampling was used to match each case with up to 10 controls for age, sex, cohort entry date, and follow-up duration. Exposure to anaphylaxis, thrombosis, and SJS was assessed within 7, 90, and 30 days of the index date, respectively. We calculated odds ratios (OR) with 95% confidence intervals (CIs) using conditional logistic regression to assess the risk of outcomes associated with propacetamol.

Results: We identified cases of anaphylaxis (n=61), thrombosis (n=95), and SJS (n=1) and matched them to controls (173, 268, and 4, respectively). In the nested case-control analysis, the ORs for anaphylaxis and SJS were inestimable given the small number of propacetamol users during the risk period; meanwhile, the OR for thrombosis was 1.60 (95% CI 0.71–3.62). In the CTC design, the effect estimate was only estimated for thrombosis (OR 0.56, 95% CI 0.09–3.47).

Conclusion: In both nested case-control and CTC analyses, propacetamol was not associated with an increased risk of anaphylaxis, thrombosis, or SJS. The findings from this study, which used routinely collected clinical data, provide reassuring real-world evidence regarding the safety of propacetamol in a nationwide population to support regulatory decision-making.

Key Words: Propacetamol, real-world evidence, post-authorization safety, regulatory decision making, nested case-control study, case-time-control study

INTRODUCTION

Propacetamol is an injectable paracetamol prodrug that has been widely used for decades to treat emergency patients. However, despite its proven effectiveness and faster action than oral antipyretics,[1] the European Medicines Agency (EMA) with-

Received: June 5, 2023 **Revised:** September 8, 2023 **Accepted:** October 10, 2023 **Published online:** January 17, 2024
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*Sungho Bea and Dongwon Yoon contributed equally to this work.
•Dr. Shin received grants from the Ministry of Food and Drug Safety, the National Research Foundation of Korea, and pharmaceutical companies, including Yungjin Pharm, Pfizer, Celltrion, and SK Bioscience. No other relationships or activities have influenced the submitted work. The other authors have no potential conflicts of interest to disclose.

drew propacetamol from the market in 2009 due to concerns over serious hypersensitivity, injection site reactions, and thrombosis.[2] Accordingly, the Korean regulatory body demanded the establishment of a risk management plan, which incorporates both phase III trial and observational study using non-randomized real-world data (RWD) from routine clinical practices, as part of a post-marketing safety control to address the emerging safety concerns of propacetamol.

The safety of propacetamol has not been studied extensively, with most studies limited to propacetamol-induced hypotension, which is a well-perceived adverse event by physicians to manage the risks in patients.[3-5] However, there have been several case reports of serious hypersensitivity involving allergic dermatitis and Stevens–Johnson syndrome-like (SJS-like) pustulosis in Europe,[6-8] which have raised concerns about the safety of propacetamol. In light of the reported cases of propacetamol-induced hypersensitivity in Europe, the possibility of hypersensitivity-related adverse events cannot be ruled out, thereby requiring a timely assessment of these conditions from a Korean perspective. Moreover, as a previous study on the safety of propacetamol suggested a potential ethnic difference between Asia and Europe in terms of serious hypersensitivity and thrombosis,[9] a comprehensive evaluation of the safety concerns raised in a large population is needed.

Given that post-marketing safety surveillance using real-world data is imperative to overcome the limitations of efficacy and safety data derived from randomized controlled trials (RCTs), we aimed to evaluate the association between propacetamol use and three adverse events of interest, including anaphylaxis, thrombosis, and SJS, using nested case-control and case-time-control (CTC) designs.

MATERIALS AND METHODS

Data source

We used the Health Insurance Review and Assessment (HIRA) database of South Korea, which serves as a repository of the entire Korean healthcare utilization, encompassing diagnoses, prescriptions, and surgical procedures, from January 1, 2010, to December 31, 2019. The database ensures anonymity of the patients using de-identified keys. With a population coverage of over 50 million, the HIRA database captures information on personal characteristics and healthcare utilization based on reimbursed claims for inpatient, outpatient, and emergency department visits, including but not limited to diagnoses, procedures, length of hospitalization, prescribed drugs, day supply, dose strength, route of administration, and costs. All procedures and prescriptions were coded using domestic codes, and all diagnoses were coded using the Korean Standard Classification of Diseases, 7th revision, and a modified version of the International Classification of Diseases, 10th revision (ICD-10). Unless ineligible due to emigration or death, all citizens are continuously enrolled in the system, thereby providing a comprehensive record of healthcare utilization.[10]

Study population

We included all patients who were diagnosed with fever (ICD-10 code: R50, main indication for propacetamol) and prescribed propacetamol simultaneously between January 2010 and December 2019. The cohort entry date was defined as the first date of diagnosis and propacetamol prescription. Patients were excluded if they were under 18 years of age; had less than 365 days of baseline assessment period; had a history of predefined outcomes, such as anaphylaxis, thrombosis, or SJS; had hemolytic anemia or allergic contact dermatitis before 365 days of cohort entry; or had a pregnancy-related record during the study period. In the study cohort, patients were followed up from cohort entry until a diagnosis of individual outcomes, in-hospital death, or the end of the study period (Dec. 31, 2019), whichever occurred first.

Case-control selection

This population-based study aimed to investigate the association between propacetamol and three main outcomes: anaphylaxis, thrombosis, and SJS. All the analyses were performed separately for each outcome. We conducted both nested case-control and CTC analyses using the cases and controls identified for each outcome. These case-based designs were used due to the extremely rare incidence of outcomes in the general population and the time-varying nature of propacetamol use.

To ascertain the occurrence of each outcome, we identified cases of anaphylaxis, thrombosis, and SJS based on the primary or secondary position of the diagnosis between January 2011 and December 2019 in the HIRA database. For anaphylaxis, cases were identified as all patients diagnosed with either anaphylactic shock or an anaphylactoid reaction with an epinephrine. Thrombosis cases were defined as all patients diagnosed with phlebitis, thrombophlebitis, portal vein thrombosis, or other venous embolisms and thromboses. To improve the validity of thrombosis diagnosis, cases were excluded if a record of thrombosis diagnosis was changed to thrombosis due to cardiac and vascular prosthetic devices, implants, or grafts within 30 days of thrombosis diagnosis. For SJS, the cases consisted of all patients diagnosed with either SJS or toxic epidermal necrolysis. To minimize outcome misclassification, we excluded cases of SJS if the record of SJS changed to staphylococcal scalded skin syndrome, pemphigus, contact dermatitis, or nonbullous erythema multiforme within 30 days of SJS diagnosis.[11] The index date of each case was defined as the first date of diagnosis (Day 0). Two allergists reviewed the operational definitions of the cases (Supplementary Table 1, only online).

To select controls for each case, we used risk-set sampling to match the case with a random sample from the risk set, which yields odds ratios (ORs) that are identical estimators of hazard

ratios (HRs).[12] Up to 10 controls were matched on age (±365 days), sex, cohort entry (±180 days), and follow-up duration. The index date of the matched controls was assigned the same index date as their corresponding cases.

Exposure assessment

We classified cases and controls into propacetamol users and non-users based on the presence of a propacetamol prescription during the exposure assessment period. This period included the interval ranging from 1 day before the index date and pre-defined timeframes for each outcome. The duration of the exposure assessment period varied depending on the specific outcome being studied based on the pathophysiology and relevant previous studies. Anaphylaxis is an acute and severe reaction that generally occurs within minutes to hours of exposure to an antigen. However, delayed responses may also occur in some patients. Given the potential delayed response of anaphylaxis, we defined the exposure assessment period within 7 days from the index date for anaphylaxis (1–7 days period prior to the index date).[13] For thrombosis, the exposure assessment period was defined as within 90 days from the index date based on previous research (1–90 days period prior to the index date).[14] In terms of SJS, a previous study using the Japanese Adverse Drug Event Report database found that the majority of SJS cases occurs within 30 days after paracetamol use, a metabolite of propacetamol.[15] Other studies similarly support the plausible onset of SJS within 30 days.[16,17] Hence, we defined the exposure assessment period within 30 days from the index date for SJS (1-30 days period prior to the index date).

Potential confounders

We considered demographic and socioeconomic factors, as well as previous medical history and medication use, as potential confounders in this study. These potential confounders varied across each outcome and were assessed within 1 year prior to the index date, unless stated otherwise. Demographic and sociodemographic characteristics were assessed using the index date. Atopic diseases, mastocytosis, cardiovascular diseases, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, contrast medium, proton-pump inhibitors (PPIs), hypnotics, opioids, and neuromuscular blockers were included for anaphylaxis. Fractures, hysterectomy, oophorectomy, chronic obstructive pulmonary disease, dyslipidemia, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, autoimmune disease, renal disease, antipsychotics, antidepressants, oral contraceptives, and antiplatelets were included for thrombosis. Finally, cerebrovascular disease, autoimmune disease, renal disease, hepatic disease, diabetes, simple herpes, human immunodeficiency virus infection, NSAIDs, antibiotics, diuretics, and anti-seizure medications were included for SJS. The models were adjusted separately for these variables in the analysis of each outcome (Supplementary Table 2, only online).

Statistical analysis

Sociodemographic characteristics and potential confounders among cases and controls are described as means and standard deviations for continuous variables, or frequencies and proportions for categorical variables. We compared these baseline characteristics using absolute standardized differences (values over 0.1 indicates potentially significant differences).[18] All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA). Statistical significance was set at $p<0.05$. This study was approved by the Institutional Review Board of Sungkyunkwan University (SKKU 2019-07-011-001), which waived the requirement for patient consent as only de-identified data were used.

Nested-case control analyses

We used a nested case-control design in the primary analysis to evaluate the association between propacetamol and each outcome (Fig. 1A). In this analysis, we calculated the ORs by comparing the propacetamol exposure ratios (users vs. non-users) between cases and matched the controls within pre-identified cohort (i.e., nested). We used a conditional logistic regression model to estimate the ORs (which are unbiased estimators of HRs using the risk-set sampling method) and the corresponding 95% confidence intervals (CI), adjusting for sociodemographic characteristics, cohort entry, previous medical history, and medication use for each outcome. We conduct two sensitivity analyses to verify the robustness of the primary findings. First, the exposure assessment period was varied to account for the instantaneous or insidious onset of each outcome: anaphylaxis (from 7 days in the main analysis to 3 or 14 days), thrombosis (from 90 days to 45 or 180 days), and SJS (from 30 days to 15 or 60 days). Second, in addition to evaluating the current use of propacetamol in the main analysis, we examined the association between recent and past use of propacetamol. Recent and past use of propacetamol were defined as 8–14 days and ≥15 days from the index date for anaphylaxis, 91–180 days and ≥181 days for thrombosis, and 31–60 days and ≥61 days for SJS, respectively.

CTC analyses

The conventional case-crossover design includes only individuals with cases, and compares their exposure status during the risk and control periods. Although this design implicitly adjusts for time-invariant confounders, it is susceptible to temporal trends in drug exposure. To address this limitation and minimize potential confounding by indication in the primary analysis, we used a CTC design in our secondary analysis.[19] In this analysis, we measured the ORs by comparing the propacetamol exposure ratios between risk period and control periods within individuals. We used identical case-control pairs from the primary analysis, and defined the risk period as–1–7 days, 1–90 days, and 1–30 days prior to the index date for anaphylaxis, thrombosis, and SJS, respectively. For each risk peri-

https://doi.org/10.3349/ymj.2023.0207

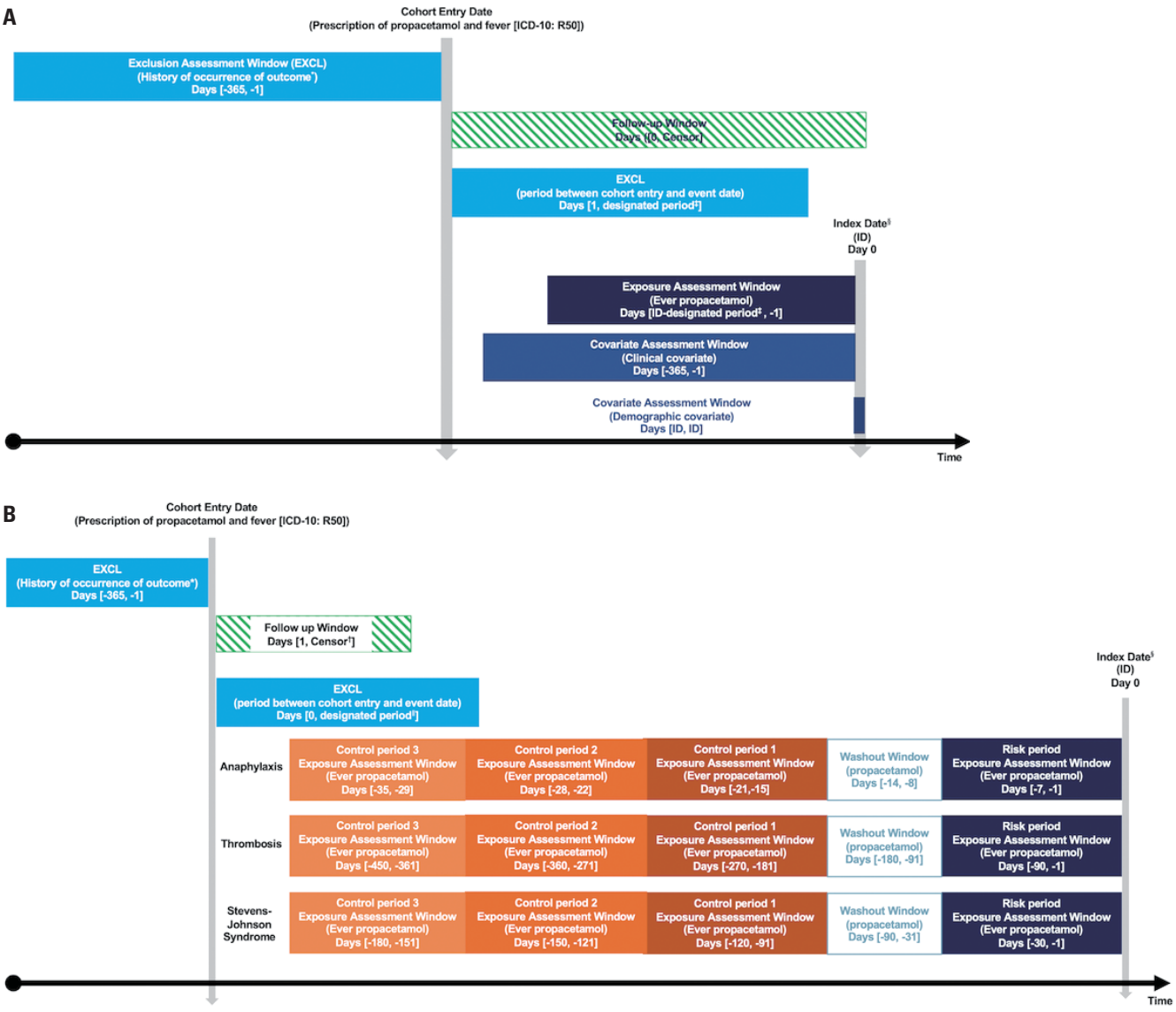

Fig. 1. Overall designs for the nested case-control and case-time control studies. (A) Nested case control design. (B) Case-time-control design. *Anaphylaxis, thrombosis, or SJS; †Censored at the earliest of incident outcome (anaphylaxis or thrombosis or SJS), death, end of the study period (Dec. 31, 2019); ‡7 days for anaphylaxis, 90 days for thrombosis, 30 days for SJS; §Controls risk-set matched on age, sex, date of cohort entry (±180 days), and duration of follow-up (from cohort entry to index date); ‖35 days for anaphylaxis, 450 days for thrombosis, and 180 days for SJS. EXCL, exclusion assessment window; ICD, International Classification of Diseases; ID, index date; SJS, Stevens–Johnson syndrome.

od, we set three consecutive control periods defined as 15–21 days, 22–28 days, and 29–35 days before the index date for anaphylaxis; 181–270 days, 271–360 days, and 361–450 days before the index date for thrombosis; and 91–120 days, 121–150 days, and 151–180 days before the index date for SJS. To avoid potential carryover effects, we adopted a wash-out period between the risk and control periods, which was 8–14 days, 91–180 days, and 31–90 days for anaphylaxis, thrombosis, and SJS, respectively (Fig. 1B).[20] We used conditional logistic regression to estimate the ORs and corresponding 95% CIs, adjusting for discordant pairs of potential confounders described in the primary analysis. For secondary analysis, three sensitivity analyses were conducted. First, we varied the risk and control periods for each outcome: 7 to 3 or 14 days, 90 to 45 or 180 days, and 30 to 15 or 60 days for anaphylaxis, thrombosis, and SJS, respectively. Second, we repeated all the analyses without adopting a washout period. Third, we varied the number of control periods for each outcome (from 3 to 1 or 5).

RESULTS

Among the 332856 patients who were prescribed propacetamol and diagnosed with fever (ICD-10: R50) during the study period, 192621 met the inclusion criteria. After case-control matching using risk-set sampling within the population, 61 cases of anaphylaxis were matched to 173 controls, 95 cases of thrombosis were matched to 268 controls, and one case of SJS

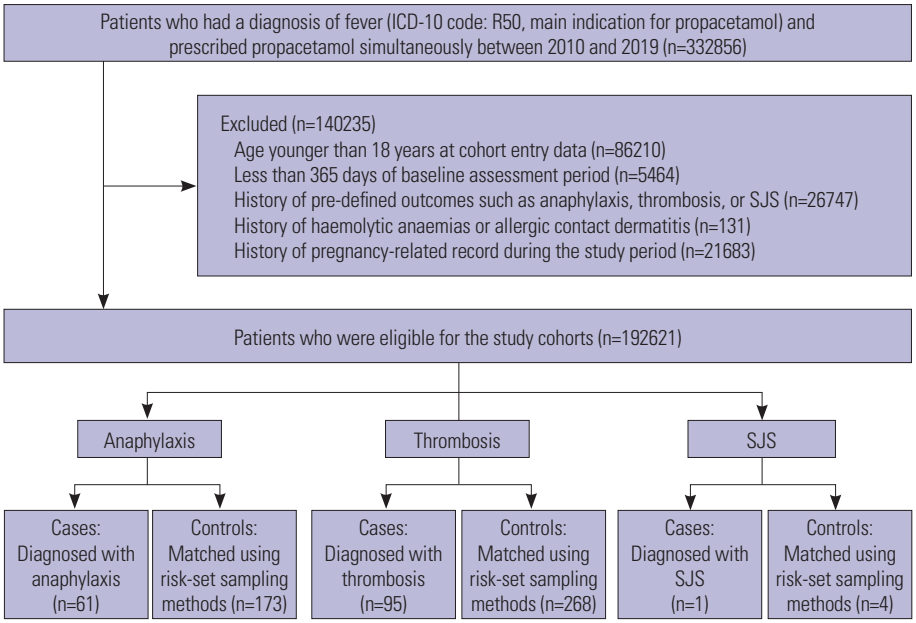

Fig. 2. Flowchart of the study population. ICD, international classification of diseases; SJS, Stevens–Johnson syndrome.

was matched to four controls (Fig. 2). At cohort entry, the mean age of patients with anaphylaxis was 41.4 (SD 16.0) years, while that of patients with thrombosis was 60.2 (17.2) years and SJS was 68 (SD N/A) years. More female than male patients had thrombosis (female: 55.8% vs. male: 44.2%) (Table 1).

In the nested case-control analysis, the OR for anaphylaxis could not be calculated due to the small number of users during the risk period. Similar results were found for SJS; one patient was not exposed to propacetamol during the risk period. Meanwhile, 16 (16.8%) patients with thrombosis and 19 (7.1%) patients in the matched control group received propacetamol during the risk period. However, no significant association was observed between thrombosis and propacetamol use (OR 1.60, 95% CI 0.71–3.62) (Table 2). The results of the sensitivity analysis were generally consistent with those of our primary nested case-control analysis (Supplementary Tables 3–5, only online).

In the CTC analysis, among the 59 patients with anaphylaxis, 1 (1.7%) received propacetamol during the risk period and 2 (1.1%) received it in at least one control period. The population of time-trend controls comprised 168 patients. Among them, 0 (0.0%) and 5 (1.0%) patients received propacetamol at least once during the risk and control periods, respectively. CTC ratios were not calculated as there were no discordant pairs in the case-crossover control of anaphylaxis. Similarly, in the SJS, CTC ratios cannot be calculated due to the lack of discordant pairs in both the case-crossover case and case-crossover control. However, among the 65 patients with thrombosis, 6 (9.2%) received propacetamol during the risk period and 10 (5.1%) received it in at least one control period. The population of time-trend controls comprised 141 patients. Among them, 8 (5.7%) and 18 (4.3%) patients received propacetamol at least once during the risk and reference periods, respectively. The CTC ratio was 0.56 (95% CI 0.09–3.47) (Table 3). Additionally, in the CTC design, no discrepancies were observed between the primary and sensitivity analyses (Supplementary Tables 6–8, only online).

DISCUSSION

This study found no evidence of an association between propacetamol use and an increased risk of anaphylaxis, thrombosis, or SJS. The safety of propacetamol was consistently observed in both the nested case-control and CTC analyses. Although nationwide population-based data were used, the frequency of propacetamol exposure during the risk period was extremely low. The results were generally consistent across the sensitivity analyses. Our findings provide evidence to support the decision-making regarding propacetamol in real-world settings, particularly for drugs that are included in the risk management plans by regulatory authorities.

However, few studies have investigated the safety of propacetamol. Most previous studies on propacetamol were conducted in a small number of patients and were limited to patient case reports.[7,21] Moreover, many studies have addressed topics such as skin sensitization of the healthcare team or pain at the injection site. However, there is insufficient evidence of serious adverse events, such as anaphylactic reactions, thrombosis, and SJS. A clinical trial of propacetamol showed similar rates of adverse events compared to dexibuprofen, but none of the adverse events of interest were reported in this study.[22] In a study using a spontaneous adverse drug reaction reporting database, most cases were non-serious adverse events, and thrombosis

https://doi.org/10.3349/ymj.2023.0207

Table 1. Baseline Characteristics of Anaphylaxis, Thrombosis, and SJS and Matched Controls

Characteristics	Anaphylaxis			Thrombosis			SJS		
	Case	Control	aSD*	Case	Control	aSD*	Case	Control	aSD*
Total†	61 (100)	173 (100)		95 (100)	268 (100)		1 (100)	4 (100)	
Age‡, mean (SD), yr	41.44 (15.95)	39.54 (15.82)	0.120	60.23 (17.19)	57.44 (18.23)	0.158	68.00 (N/A)	67.50 (1)	0
Male sex	30 (49.18)	86 (49.71)		42 (44.21)	120 (44.78)		0 (0.00)	0 (0.00)	
Type of insurance			0.340			0.229			0
Health insurance	60 (98.36)	165 (95.38)		85 (89.47)	252 (94.03)		1 (100)	4 (100)	
Medical aid	1 (1.64)	8 (4.62)		10 (10.53)	16 (5.97)		0 (0.00)	0 (0.00)	
Residence			0.340			0.229			1.414
Metropolitan area	7 (11.48)	42 (24.28)		9 (9.47)	46 (17.16)		0 (0.00)	2 (50.00)	
Urban area	21 (34.43)	49 (28.32)		27 (28.42)	72 (26.87)		1 (100)	0 (0.00)	
Rural area	33 (54.10)	82 (47.40)		59 (62.11)	150 (55.97)		0 (0.00)	2 (50.00)	
Calendar year at cohort entry			0.547			0.530			N/A
2012	1 (1.64)	0 (0.00)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
2013	1 (1.64)	3 (1.73)		2 (2.11)	1 (0.37)		0 (0.00)	0 (0.00)	
2014	6 (9.84)	4 (2.31)		8 (8.42)	11 (4.10)		0 (0.00)	0 (0.00)	
2015	5 (8.20)	12 (6.94)		5 (5.26)	11 (4.10)		0 (0.00)	0 (0.00)	
2016	8 (13.11)	15 (8.67)		16 (16.84)	21 (7.84)		0 (0.00)	0 (0.00)	
2017	10 (16.39)	23 (13.29)		21 (22.11)	52 (19.40)		0 (0.00)	0 (0.00)	
2018	11 (18.03)	24 (13.87)		26 (27.37)	72 (26.87)		0 (0.00)	0 (0.00)	
2019	19 (31.15)	92 (53.18)		17 (17.89)	100 (37.31)		1 (100)	4 (100)	
Comorbidities‡									
Atopy dermatitis	33 (54.10)	77 (44.51)	0.193	N/A	N/A	N/A	N/A	N/A	N/A
Mastocytosis	0 (0.00)	0 (0.00)	0	N/A	N/A	N/A	N/A	N/A	N/A
Cardiac disease	5 (8.20)	5 (2.89)	0.233	N/A	N/A	N/A	N/A	N/A	N/A
Fracture	N/A	N/A	N/A	11 (11.58)	19 (7.09)	0.155	N/A	N/A	N/A
Spinal cord injury	N/A	N/A	N/A	0 (0.00)	0 (0.00)	0	N/A	N/A	N/A
Hysterectomy	N/A	N/A	N/A	0 (0.00)	0 (0.00)	0	N/A	N/A	N/A
Oophorectomy	N/A	N/A	N/A	0 (0.00)	0 (0.00)	0	N/A	N/A	N/A
COPD	N/A	N/A	N/A	15 (15.79)	19 (7.09)	0.276	N/A	N/A	N/A
Dyslipidemia	N/A	N/A	N/A	25 (26.32)	63 (23.51)	0.065	N/A	N/A	N/A
Hypertension	N/A	N/A	N/A	37 (38.95)	88 (32.84)	0.128	N/A	N/A	N/A
Coronary artery disease	N/A	N/A	N/A	12 (12.63)	21 (7.84)	0.159	N/A	N/A	N/A
Congestive heart failure	N/A	N/A	N/A	8 (8.42)	16 (5.97)	0.095	N/A	N/A	N/A
Cerebrovascular disease	N/A	N/A	N/A	15 (15.79)	29 (10.82)	0.147	1 (100)	1 (25.00)	2.449
Autoimmune disease	N/A	N/A	N/A	4 (4.21)	8 (2.99)	0.066	0 (0.00)	0 (0.00)	0
Kidney disease	N/A	N/A	N/A	14 (14.74)	15 (5.60)	0.306	1 (100)	0 (0.00)	0
Hepatic disease	N/A	N/A	N/A	N/A	N/A	N/A	1 (100)	2 (50.00)	1.414
Diabetes	N/A	N/A	N/A	N/A	N/A	N/A	1 (100)	1 (25.00)	2.449
Herpes simplex	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.00)	0 (0.00)	0
Comedications‡									
NSAIDs	60 (98.36)	160 (92.49)	0.284	N/A	N/A	N/A	1 (100)	4 (100)	0
Antibiotics	57 (93.44)	137 (79.19)	0.424	N/A	N/A	N/A	1 (100)	4 (100)	0
Contrast agents	14 (22.95)	42 (24.28)	0.031	N/A	N/A	N/A	N/A	N/A	N/A
PPIs	49 (80.33)	121 (69.94)	0.242	N/A	N/A	N/A	N/A	N/A	N/A
Somnifacients	13 (21.31)	34 (19.65)	0.041	N/A	N/A	N/A	N/A	N/A	N/A
Opioids	40 (65.57)	98 (56.65)	0.184	N/A	N/A	N/A	NA	NA	NA
Neuromuscular blockers	23 (37.70)	77 (44.51)	0.139	N/A	N/A	N/A	N/A	N/A	N/A
Antipsychotic agents	N/A	N/A	N/A	18 (18.95)	26 (9.70)	0.266	N/A	N/A	N/A
Antidepressants	N/A	N/A	N/A	26 (27.37)	53 (19.78)	0.180	N/A	N/A	N/A
Combined oral contraceptive pill	N/A	N/A	N/A	6 (6.32)	8 (2.99)	0.159	N/A	N/A	N/A

Table 1. Baseline Characteristics of Anaphylaxis, Thrombosis, and SJS and Matched Controls (continued)

Characteristics	Anaphylaxis			Thrombosis			SJS		
	Case	Control	aSD*	Case	Control	aSD*	Case	Control	aSD*
Antithrombotic agents	N/A	N/A	N/A	55 (57.89)	93 (34.70)	0.478	N/A	N/A	N/A
Diuretics	N/A	N/A	N/A	N/A	N/A	N/A	1 (100)	1 (25.00)	2.449
Anticonvulsants	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.00)	1 (25.00)	0.816
CCI‡			0.403			0.490			2.449
0	37 (60.66)	114 (65.90)		32 (33.68)	147 (54.85)		0 (0.00)	2 (50.00)	
1	13 (21.31)	39 (22.54)		35 (36.84)	76 (28.36)		0 (0.00)	0 (0.00)	
2	3 (4.92)	15 (8.67)		11 (11.58)	27 (10.07)		0 (0.00)	1 (25.00)	
≥3	8 (13.11)	5 (2.89)		17 (17.89)	18 (6.72)		1 (100)	1 (25.00)	

SJS, Stevens–Johnson syndrome; aSD, absolute standard deviation; COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; CCI, Charlson Comorbidity Index.
Data are presented as mean (SD) or n (%).
*When the absolute standardized difference was <0.1, it was considered balanced; †Case-control was matched using age (±1 year), cohort entry date (±180 days), follow-up date; ‡Age, comorbidities, medication use, and Charlson Comorbidity Index were evaluated within 1 year of the index date.

Table 2. Association between Treatment with Propacetamol and Anaphylaxis, Thrombosis, and SJS in Nested Case-Control Design

Adverse events*	Patients		OR (95% CI)	
	Cases	Controls†	Crude	Adjusted‡
Anaphylaxis	61 (100)	173 (100)		
Propacetamol use	2 (3.28)	0 (0.00)	N/A	N/A
Propacetamol non-use	59 (96.72)	173 (100)	Reference (1.00)	Reference (1.00)
Thrombosis	95 (100)	268 (100)		
Propacetamol use	16 (16.84)	19 (7.09)	2.66 (1.30–5.41)	1.60 (0.71–3.62)
Propacetamol non-use	79 (83.16)	249 (92.91)	Reference (1.00)	Reference (1.00)
SJS	1 (100)	4 (100)		
Propacetamol use	0 (0.00)	0 (0.00)	N/A	N/A
Propacetamol non-use	1 (100)	4 (100)	Reference (1.00)	Reference (1.00)

SJS, Stevens–Johnson syndrome; CI, confidence interval; OR, odds ratio.
Data are presented as n (%).
*The risk period measurement varied for each adverse event: 7 days for anaphylaxis; 90 days for thrombosis; 30 days for SJS; †Up to 10 controls were matched on age (±365 days), sex, cohort entry (±180 days), and follow-up duration; ‡Demographic and socioeconomic factors, as well as previous medical history and medication use, were considered potential confounders in this study.

Table 3. Association between Propacetamol Use and Anaphylaxis, Thrombosis, and SJS in CTC Design

	Propacetamol use		OR (95% CI)		CTC ratio (95% CI)
	Risk period	Control period	Crude OR	Adjusted OR*	
Anaphylaxis†					N/A
CCO cases	1 (1.69)	2 (1.13)	1.73 (0.10–30.76)	0.89 (0.02–32.79)	
CCO controls	0 (0.00)	5 (0.99)	N/A	N/A	
Thrombosis‡					0.56 (0.09–3.47)
CCO cases	6 (9.23)	10 (5.13)	1.86 (0.65–5.26)	0.68 (0.15–3.04)	
CCO controls	8 (5.67)	18 (4.26)	1.38 (0.57–3.36)	1.21 (0.43–3.42)	
SJS§					N/A
CCO cases	0 (0.00)	0 (0.00)	N/A	N/A	
CCO controls	0 (0.00)	0 (0.00)	N/A	N/A	

SJS, Stevens–Johnson syndrome; CCO, case-crossover; CI, confidence interval; CTC, case-time-control; OR, odds ratio.
Data are presented as n (%).
*Demographic and socioeconomic factors, as well as previous medical history and medication use, were considered potential confounders in this study; †Exposure to propacetamol was assessed 1–7 days before the index date, a total of three control periods were set after washout window, and each period was set to 7 days (-15 to -21 days, -22 days to -28 days, -29 days to -35 days); ‡Exposure to propacetamol was assessed 1–90 days before the index date, a total of three control periods were set after washout window, and each period was set to 90 days (-181 to -270 days, -271 days to -360 days, -361 days to -450 days); §Exposure to propacetamol was assessed 1–30 days before the index date, a total of three control periods were set after washout window, and each period was set to 30 days (-91 to -120 days, -121 days to -150 days, -151 days to -180 days).

https://doi.org/10.3349/ymj.2023.0207

was reported with a very low frequency.[9] Similarly, in our study, the limited number of patients treated with propacetamol and experiencing adverse events of interest presented a challenge in assessing the ORs. Taken together, despite using the national claims data, the low exposure to propacetamol prior to the occurrence of the adverse events of interest suggests the safety of propacetamol against these events.

In 2009, the EMA withdrew propacetamol due to the potential risks of serious hypersensitivity reactions, thrombosis, and injection site reactions.[2] In our previous research exploring regional variations in propacetamol-related adverse events between Asia and Europe, we found a correlation between the use of propacetamol and thrombosis, as well as contact dermatitis/eczema in Europe, but not in Asia.[9] Although, the present study did not identify any association between the use of propacetamol and thrombosis, thrombosis showed the highest frequency among adverse events of interest during the risk period. However, as a subtype of thrombosis, phlebitis may be related to injection site reactions owing to the nature of the formulation as an injection.[23] Taken together, these findings provide evidence that supports the safety profile of propacetamol in relation to the risk of thrombosis among Asians, while also implying the potential existence of regional disparities in adverse events of propacetamol.

To the best of our knowledge, this study is the first in Korea to utilize RWD for regulatory decision-making. Advances in the quality, quantity, and diversity of RWD, integrated with statistical analytical methods used to mitigate bias such as confounding bias, misclassification bias, and time-related bias, have offered an opportunity to leverage RWD to present an understanding of drug safety and effectiveness. Taking advantage of this new opportunity, regulatory authorities, including the Food and Drug Administration of the United States and the EMA, utilize RWD to add elaboration to their decisions.[24,25] RCTs are widely accepted as the gold standard of evidence, and it is often necessary to generate evidence using RWD when RCTs cannot be performed or when there is insufficient motivation for sponsors to conduct them, such as in cases where there is a conflict of interest.

This study had several limitations. First, since randomization was not performed, bias due to unmeasured confounding factors may have occurred. However, the results were less likely to be affected by bias as we used various statistical methods (i.e., matching and adjusting) and sensitivity analyses. Second, the use of propacetamol before the adverse reactions of interest may have been due to protopathic symptoms. However, the results remained consistent when the risk period varied. Moreover, similar results were observed in both the nested case-control and CTC designs, demonstrating the robustness of this study. If the use of propacetamol was associated with protopathic symptoms, the OR of adverse events would have been high. Nevertheless, no significant OR was observed in this study, and the effect of protopathic bias was expected to be small. Third, the misclassification of outcomes may have affected the results of our study. However, since our outcomes were severe adverse events, they were very unlikely to be misclassified. Moreover, to improve the validity of the diagnosis, patients with a diagnosis and prescription for medication (epinephrine) were included. Fourth, due to the inherent limitation of claims data, establishing a precise temporal relationship between outcomes and exposures on the same date was challenging. Thus, we restricted exposure assessment periods before the index date (Day 0). This cautious approach may have led to a potential exposure misclassification in our findings. Finally, given the rare conditions of pre-defined outcomes in nature, the number of cases was relatively small, which precluded the calculation of statistically significant ORs. Therefore, caution is needed when interpreting the results of our study.

In both the nested case-control and CTC designs, no evidence was found to support an increased risk of anaphylaxis, thrombosis, or SJS following propacetamol use. Additionally, despite the use of a nationwide claims database, the exposure to propacetamol during the risk period was extremely low, indicating its safety. Using routinely collected clinical data, we can address drug safety issues and support decision-making processes.

AVAILABILITY OF DATA AND MATERIAL

Data used in this study are obtainable by services provided by the Uppsala Monitoring Centre, but restrictions may apply to the availability of these data, which were used under the license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with the permission of Uppsala Monitoring Centre.

ACKNOWLEDGEMENTS

This study was supported by a grant from Yungjin Pharm.

This research was supported by the SungKyunKwan University and the BK21 FOUR (Graduate School Innovation) funded by the Ministry of Education (MOE, Korea) and National Research Foundation of Korea (NRF).

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https://doi.org/10.3349/ymj.2023.0207