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ORIGINAL RESEARCH

A Clinical Study on the Association of Sodium-Glucose Cotransporter 2 Inhibitors and Acute Kidney Injury Among Diabetic Chinese Population

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Purpose: To investigate the association of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and acute kidney injury in comparison to other classes of drugs.

Patients and Methods: A total of 4966 diabetes mellitus patients were investigated for developing Acute Kidney Injury (AKI) who were under prescription with the following class of drugs viz. SGLT2 Inhibitors, Dipeptidyl peptidase-4 (DDP4) inhibitors, Nonsteroidal anti-inflammatory drugs (NSAIDs), first-line drugs and anti-biotics. The primary outcome was based on the hospital encounter and Kidney Disease Improving Global Outcome (KDIGO) threshold values were used to assess the serum creatinine concentration. The secondary outcome was assessed based on the concentration level of serum creatinine after 90 days of hospital admission and evaluation of the KDIGO threshold values.

Results: The study observed that the risk of causing AKI for SGLT2 inhibitors was 5.59% which was comparatively low compared to other class of the investigated drugs (DPP4 inhibitors = 6.47%, antibiotics = 6.30%, first-line drugs = 6.82% and NSAIDs = 10.65%). The multivariate analysis observed that ibuprofen, celecoxib, indomethacin, insulin, cephalexin, and alogliptin were mostly associated with an increased rate of AKI. SGLT2 inhibitors have the lowest risk for developing AKI compared to other drugs and control.

Conclusion: AKI incidence is relatively low after initiation of SLGT2 inhibitors and concludes that regulatory warnings from certain health agencies about its risk for AKI on prescription are unwarranted.

Keywords: SGLT2 inhibitor, DPP4, acute kidney injury, NSAID, type-2 diabetes

Introduction

Acute kidney injury or acute renal failure (ARF) is caused due to the abrupt deterioration in kidney function.[1] It is characterized by an increased level of serum creatinine with or without a lesser urine pass.[2] The main function of the kidney includes clearing off endogenous waste products, acid-base balance, electrolytes, and endocrine function. The kidneys also regulate the excretion of almost all drugs, which, in turn, may lead to nephropathy.[3] Therefore, damaging the kidney may cause various life-threatening complications such as acidosis, body fluid imbalance, and multiple organ failure.[4] On the other hand, the mortality rate of patients admitted with AKI requiring dialysis support is more than 50%[5] and majority of cases being patients having diabetes mellitus who have infection in

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their kidney and urinary tract.[6] Diabetes mellitus patients also accounts for the majority of end-stage kidney disease. They are also distinguished by severe interstitial inflammation and the majority of the patients are at the risk for developing serious bacterial infections, which may often lead to renal tissue failure and AKI.[7]

Moreover, the adverse reaction of prescribed drugs for diabetic patients remains an underlying cause for acute kidney injury.[8] On the other hand, SGLT2 inhibitors are a class of anti-diabetic drugs that are used to treat type 2 diabetes mellitus.[9,10] This class of drugs inhibits the re-absorption of glucose in the kidney and lowers the blood sugar level.[11] There are also several prescriptions of such class that have been approved or many of them are presently under clinical trial.[12,13] For example, SGLT2 inhibitors such as canagliflozin are reported to enhanced blood sugar control and reduced the body weight and blood pressure of the patient.[14] However, there are certain safety warnings issued by Regulatory agencies about SGLT2 inhibitors regarding the risk of AKI after its initiation.[15–17] In fact, AKI is generally associated with a certain class of drugs such as NSAIDs and antibiotics. Therefore, our objective was to quantify based on a 90-day risk of AKI in older adults after initiation of SGLT2 inhibitors in routine clinical practice compared to other classes of drugs such as NSAIDs, DPP4 inhibitors, antibiotics, and first-line anti-diabetic drugs.

Patients and Methods

Ethical Approval and Standards

All procedures were carried out in accordance with the Declaration of Helsinki 1964 and its later amendments. Written informed consent was provided by all patients and participants. Consent was obtained from each subject regarding their personal information on demographic factors, any other history of medical condition information using a questionnaire. The human subject research was approved by the Institutional Medical Ethics Committee of the Second Affiliated Hospital of Nantong University All protocols and procedures on the animal study were approved by the Hospital Ethical Research Committee.

Study Population and Data Source

In this study, we examined 4966 diabetes mellitus patients enrolled in The Second Affiliated Hospital of Nantong University, Nantong 226,001, Jiangsu, PR China between June 2017 to July 2019. These subjects were prescribed with SGLT Inhibitors, DDP4 inhibitors, NSAIDs, anti-diabetic first-line drugs, and antibiotics. The study includes only patients which are above 55 years and who had been active users of these drugs for at least one year and patients younger than 55 years were excluded from the study.

Main Exposures

Adults aged above 55 years or older who were prescribed with SGLT2 Inhibitors, DDP4 inhibitors, NSAIDs and antibiotics between June 2017 to July 2019 were categorized and investigated for the study. The prescription details such as date, dosage, and duration of prescribed drugs were recorded for each drug. Participants who received more than one SGLT2 inhibitors were excluded from the study. SGLT2 inhibitors' use was defined as the daily use of the drugs viz. canagliflozin, ipragliflozin, jardiance, and dapagliflozin. DDP4 inhibitors' use was defined as the daily use of the drugs viz. vildagliptin, alogliptin, and linagliptin. NSAID use was defined as use of the drugs viz. celecoxib, ibuprofen, indomethacin which were received for at least one or 2 doses. Patients who received more than 2 doses of NSAIDs were excluded. Diabetes patients using cephalexin and amoxicillin when required was defined as antibiotic use and the daily use of insulin and metformin was defined as the use of anti-diabetic first-line drug and metformin act as the control drug. All patients were recorded for the history of their drug usage track records and follow-up ended until the completion of the study.

Outcome

The primary outcome of the study was AKI based on the hospital encounter. KDIGO threshold values were used to define the serum creatinine concentration. Whereas the secondary outcome was based on the assessment of the hospital admission after 90 days and serum creatinine concentration was assessed for the KDIGO threshold.

Pharmacokinetics (PK) Study on the Mouse Model

Animal infection models in the pharmacokinetic evaluation serves an important role in preclinical assessments, dosing optimization and setting of confirming susceptibility breakpoints.

Its ultimate goal is to mimic them in humans which allows a robust PK study to discover the optimal drug

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exposures that lead to therapeutic success thereby minimizing the cost and duration of clinical trials. In this study, animal experiments were carefully performed according to the guidelines of the Care and Use of Laboratory Animals published by the National Institutes of Health[18] and was approved by the Institutional Ethical Committee of our Hospital. All animals were kept in a pathogen-free environment on a 12 h light/12 h dark cycle and had access to feed and water ad libitum. For evaluating the pharmacokinetic properties, Male ICR mice (20 ± 2 g, 5–6 weeks) were obtained from Shanghai laboratory animal center (Shanghai, China) and the mice, were kept in plastic pages (25 ± 2°C; 55 ± 5% humidity). They were adapted for 7 days with a free diet and distilled water. The diabetic mice were uniformly grouped based on the blood glucose levels. Pharmacokinetics-based analysis was carried out by administrating the male normal mice with each of the investigated class of drugs viz. SGLT2 inhibitors (canagliflozin, ipragliflozin, jardiance, dapagliflozin), DPP4 (vildagliptin, alogliptin, linagliptin), NSAID (ibuprofen, indomethacin, celecoxib), antibiotics (cephalexin, amoxicillin) and the two First-line drug (insulin and metformin) with a dosage of 3 mg each for 5 days. Drugs were dissolved in water, and administered using a 5-mL syringe with a 2-cm long gavage needle through the mouth to the mouth once daily for 2 weeks. For the pharmacokinetics analysis, 24 h after the last administration of the drugs, the mice were sacrificed and blood was withdrawn from the orbital vein, liver and kidney tissues and they were isolated after dissection for further analysis. The isolated tissues and plasma were initially treated with PBS solution and mixed with 100 mL each of acetonitrile and Methyl tert-butyl ether (MTBE) and centrifuged at 12,000 rpm for 15 mins. The supernatant was taken and collected in a tube and evaporated using a vacuum concentrator and the concentrations of the administered drugs were measured and analyzed with an HPLC equipped with a UV detector. The pharmacokinetics parameters such as Cmax, half-life, and area under the curve (AUC) for 24 hr were calculated.

Statistical Analyses

SPSS Statistical Software 21.0 (SPSS Inc, USA) was employed for carrying out the statistical analysis. The patient's characteristics were evaluated based on the categories of the exposed. The characteristics of the patients were assessed based on the drug exposure and the crude incidence rates were calculated by dividing the observed number of outcomes by the sum of all person time within each exposure group. Mean values for continuous variables were calculated based on the frequency of drugs exposed compared using the Student's *t*-test. The odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression to analyze the association of the investigated drugs and acute kidney injury. A drug proportional hazard model was used for estimating the relative risk for AKI. Metformin – a first-line anti-diabetic drug was taken as the reference or the control.

Results

In this study, a total of 4966 diabetes mellitus patients in the age group between 55 and 75 who were prescribed with SGLT2, DDP4, NSAID, first-line drugs, and antibiotics drug were investigated. The mean age was 68.7 years for male and 71.4 years for females. SGLT2 inhibitors account for 32.52%. While other drugs such as DPP4 account for 18.55%, NSAID with 23.08%, antibiotic with 9.38% and first line with 16.47% drug users, respectively. The baseline characteristics of the patients who were exposed to such class of drugs and their usage information are presented in Table 1. One of the first-line drugs (metformin) acts as the control in the present study. At the time of follow-up, there were 1047 patients who were experiencing kidney injury during the first 3 months of the follow-up. However, during the secondary endpoint, 3919 patients were experiencing AKI. Altogether there were 4966 subjects at the end of the study.

The incidence rate of AKI at the end of the study varied from 5.38 for canagliflozin (SGLT2 inhibitor) to 11.22 for ibuprofen. Whereas the other SLGT2 inhibitors had an incidence rate of 5.42, 5.58, and 6.0, respectively, for ipragliflozin, jardiance and dapagliflozin. The statistical analysis from Table 2 also observed that NSAID such as ibuprofen, celecoxib, and indomethacin possessed the highest risk for acute kidney injury compared to other classes of drugs. In fact, NSAIDs account for 47.07% of cases of AKI of the total investigated population. The average percentage for the risk of causing AKI for SGLT2 inhibitors was 5.59% compared to 6.47% of DPP4, 6.30% of antibiotics, 6.82% of first-line drugs and 10.65% NSAIDs. The statistical analysis from Table 3 observed that NSAIDs viz. ibuprofen, celecoxib, indomethacin, insulin (first-line drugs), cephalexin (antibiotic), and alogliptin (DPP4) were mostly associated with an increased rate of AKI compared to control drug metformin. Ibuprofen, celecoxib, and indomethacin had a relatively increased rate of 2.41 (95% CI, 1.91–2.54),

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Table 1 Characteristics of the Drug Usage of the Type-2 Diabetes Patients

Drugs	SGLT 2 Inhibitors, n (%)				DPP4 Inhibitors, n (%)			NSAID, n (%)			First Line, n (%)		Antibiotics, n (%)	
	Canagliflozin	Ipragliflozin	Jardiance	Dapagliflozin	Vildagliptin	Alogliptin	Linagliptin	Ibuprofen	Indomethacin	Celecoxib	Insulin	Metformin	Cephalexin	Amoxicillin
Pop (n)	418	314	409	474	337	318	266	404	334	408	406	412	245	221
Percent	8.42	6.32	8.24	9.54	6.79	6.4	5.36	8.14	6.73	8.21	8.17	8.3	4.93	4.45
Age (Years)	75.35	74.12	72.56	68.89	73.54	74.31	67.32	74.32	66.45	69.36	69.32	73.87	75.54	72.45
Hypertension	203 (48.56)	153 (48.88)	185 (45.45)	209 (44.09)	174 (51.63)	147 (46.23)	132 (49.62)	181 (44.8)	161 (48.2)	219 (53.68)	186 (45.81)	205 (49.76)	120 (49.98)	97 (43.89)
Diabetic Retinopathy	15 (3.59)	9 (2.88)	14 (3.44)	25 (5.27)	12 (3.56)	14 (4.4)	12 (4.51)	16 (3.96)	14 (4.19)	14 (3.43)	17 (4.19)	12 (2.91)	9 (3.67)	9 (4.07)
COPD	11 (2.63)	8 (2.56)	10 (2.46)	30 (6.33)	10 (2.97)	11 (3.46)	10 (3.76)	12 (2.97)	8 (2.4)	10 (2.45)	19 (4.68)	8 (1.94)	7 (2.86)	12 (5.43)
Diabetic neuropathy	12 (2.87)	7 (2.24)	13 (3.19)	8 (1.69)	15 (4.45)	16 (5.03)	5 (1.88)	11 (2.72)	12 (3.59)	12 (2.94)	9 (2.22)	15 (3.64)	8 (3.27)	7 (3.17)
Hypoglycemia	25 (5.98)	18 (5.75)	17 (4.18)	14 (2.95)	17 (5.04)	12 (3.77)	14 (5.26)	21 (5.2)	23 (6.89)	18 (4.41)	21 (5.17)	22 (5.34)	9 (3.67)	11 (4.98)
Congestive heart failure	21 (5.02)	14 (4.47)	22 (5.41)	11 (2.32)	11 (3.26)	19 (5.97)	12 (4.51)	18 (4.45)	14 (4.19)	14 (3.43)	18 (4.43)	13 (3.16)	12 (4.8)	8 (3.62)
Pulmonary vascular disease	29 (6.94)	18 (5.74)	23 (5.65)	19 (4.01)	14 (4.15)	10 (3.14)	15 (5.64)	21 (5.2)	19 (5.69)	13 (3.19)	11 (2.71)	17 (4.13)	10 (4.08)	13 (5.88)
Liver disease	6 (1.44)	8 (2.56)	18 (4.42)	21 (4.43)	9 (2.67)	15 (4.72)	6 (2.26)	14 (3.47)	12 (3.59)	17 (4.17)	12 (2.96)	14 (3.4)	8 (3.27)	9 (4.08)
Malignancy- To replace	8 (1.91)	10 (3.19)	7 (1.72)	12 (2.53)	12 (3.56)	7 (2.21)	7 (2.63)	9 (2.23)	8 (2.4)	12 (2.94)	8 (1.97)	23 (5.58)	14 (5.71)	6 (2.71)
Chronic Lung Disease	18 (4.31)	15 (4.79)	23 (5.65)	24 (5.06)	15 (4.45)	21 (6.6)	11 (4.14)	19 (4.7)	9 (2.69)	14 (3.43)	18 (4.43)	8 (1.94)	6 (2.45)	10 (4.52)
Cancer	27 (6.46)	19 (6.07)	19 (4.68)	29 (6.12)	10 (2.98)	16 (5.03)	14 (5.26)	23 (5.69)	8 (2.4)	21 (5.14)	27 (6.65)	27 (6.55)	7 (2.86)	12 (5.43)
Previous UTI	12 (2.87)	9 (2.88)	16 (3.93)	24 (5.06)	12 (3.56)	7 (2.2)	7 (2.63)	18 (4.46)	11 (3.29)	14 (3.43)	22 (5.42)	10 (2.43)	9 (3.61)	5 (2.26)
Pace Maker	10 (2.39)	11 (3.51)	11 (2.7)	12 (2.53)	9 (2.67)	9 (2.83)	8 (3.01)	13 (3.22)	14 (4.19)	13 (3.19)	13 (3.2)	16 (3.88)	5 (2.04)	9 (4.07)
Stroke	12 (2.87)	9 (2.88)	16 (3.93)	24 (5.1)	11 (3.27)	8 (2.52)	6 (2.26)	16 (3.96)	10 (2.99)	8 (1.96)	16 (3.94)	12 (2.91)	13 (5.31)	7 (3.18)
Atrial Fibrillation	9 (2.15)	5 (1.6)	13 (3.19)	12 (2.53)	6 (1.78)	6 (1.89)	7 (2.63)	12 (2.97)	11 (3.29)	9 (2.21)	9 (2.22)	10 (2.43)	8 (3.27)	6 (2.71)

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Table 2 AKI Outcome During the Primary and Secondary Endpoints Caused by Different Types of the Investigated Drugs

Drug Class	SGLT 2 Inhibitors				DPP4 Inhibitors			NSAIDs			First-Line Drugs		Antibiotics	
Drugs	Canagliflozin	Ipragliflozin	Jardiance	Dapagliflozin	Vildagliptin	Alogliptin	Linagliptin	Ibuprofen	Indomethacin	Celecoxib	Insulin	Metformin	Cephalexin	Amoxicillin
New Pop (n)	418	314	409	474	337	318	266	404	334	408	406	412	245	221
Events During the 90 days	66	58	57	73	79	91	56	124	106	112	58	69	50	48
Events at secondary end	201	211	220	225	237	273	228	433	391	421	290	261	283	245
Total endpoint	267	269	277	298	316	364	284	557	497	533	348	330	333	293
Total Percent	5.38	5.42	5.58	6	6.36	7.33	5.72	11.22	10.01	10.72	7.01	6.64	6.71	5.9

2.32 (95% CI, 2.12–2.68), and 2.29 (95% CI, 2.05–2.65) respectively. There was not much difference in risk of AKI among the four SGLT2 inhibitors and linagliptin and vildagliptin (DPP4 inhibitors). In most of the drug users, the association of AKI remained significant even after the adjustment for multivariate analysis. The overall result indicates that NSAIDs drug users possessed a higher chance of developing AKI. While SGLT2 inhibitors have the lowest risk for developing AKI (Table 3). On the other hand, based on the pharmacokinetics analysis, the administration of the investigated drugs (3mg/kg) to the normal mice, the maximum plasma concentration could be reached 1–3 hrs followed by time-dependent elimination (Table 4). In most of the cases, the concentration of drugs peaked at 3h in the kidney and liver which is preceded by time-dependent excretion. The mouse model study also observed that the distribution of all the investigated drugs in the kidney and liver varied widely. The Tmax which was determined from the drug concentration in kidney and plasma was 0.5h for ipragliflozin, vildagliptin, celecoxib and metformin, 1h for canagliflozin, jardiance, dapagliflozin, alogliptin, linagliptin, ibuprofen, indomethacin, insulin, cephalexin, and amoxicillin. The half-life t/2 was the longest for celecoxib (4.5h) in the kidney, and shortest for insulin (1.4 h) in plasma (Table 5).

Discussion

In the present population-based study of type-2 diabetes patients, it is observed that patients with SGLT2 inhibitor were associated with a lower risk for AKI compared with other diabetic drugs such as DPP4 inhibitors, first-line drugs, NSAIDs, and antibiotics. The study provides assurance about the safety of SGLT2 inhibitors as currently prescribed in routine diabetic care for patients. In fact, SGLT2 inhibitors were once thought to be very effective for the treatment of type-2 diabetes mellitus that usually target the SGLT2 transporter in the proximal convoluted tubule and avert the reabsorption of filtered glucose which results in glucosuria.[19,20] In this study, 4966 (between 55 and 75 years old) patients were sorted out based on the drug users of SGLT2, DDP4, NSAID, first-line drugs, and antibiotics. The study also consists of a comprehensive investigation of the overview of these drugs that may be associated with acute kidney injury. During the first 90 days or 3 months of the hospital admission, 1047 patients were experiencing AKI and 3919 patients were experiencing AKI at the end of the study. The investigation noticed that the risk of developing AKI differs among the

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Table 3 Associations Between AKI and the Investigated Class of Drugs

Drug	Classification	Endpoint Diagnosis with 1047 Outcome		Secondary Diagnosis with 3919 Outcomes	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Metformin (Control)	First line	1	1	1.0 (Reference)	1.0 (Reference)
Indomethacin	NSAID	2.81 (2.32–2.94)	2.29 (2.05–2.65)	2.45(2.09–2.54)	2.63 (2.41–2.72)
Vildagliptin	DPP4 inhibitors	1.23 (0.97–1.32)	1.18 (0.92–1.35)	1.20 (0.72–1.38)	1.07 (0.95–1.45)
Canagliflozin	SGLT 2 inhibitors	0.85 (0.67–1.21)	1.06 (0.68–1.34)	0.89 (0.61–1.25)	1.06 (0.91–1.42)
Cephalexin	Anti-biotic	2.17 (1.78–2.37)	1.52 (1.31–2.16)	1.56 (1.27–1.92)	1.82 (1.31–2.25)
Ibuprofen	NSAID	3.14 (2.87–3.74)	2.41 (1.91–2.54)	2.68 (2.21–3.03)	2.36 (1.84–2.93)
Jardiance	SGLT 2 inhibitors	0.87 (0.69–1.12)	0.76 (0.58–1.18)	0.83 (0.68–1.14)	0.85 (0.67–1.18)
Linagliptin	DPP4 inhibitors	0.97 (0.68–1.32)	0.86 (0.72–1.46)	0.87 (0.72–1.21)	1.23 (0.73–1.65)
Ipragliflozin	SGLT 2 inhibitors	0.78 (0.61–1.08)	0.86 (0.69–1.31)	0.84 (0.69–1.16)	0.95 (0.62–1.45)
Amoxicillin	Anti-biotic	1.73 (1.16–1.85)	1.36 (1.06–1.54)	1.17 (0.88–1.43)	1.34 (1.07–1.82)
Insulin	First line	2.26 (1.95–2.64)	2.36 (1.81–2.87)	2.42 (1.25–2.61)	2.73 (2.28–2.90)
Alogliptin	DPP4 inhibitors	1.83 (1.75–2.16)	1.43 (1.31–2.04)	2.27 (1.08–3.12)	2.85 (2.26–3.07)
Celecoxib	NSAID	2.95 (2.68–3.25)	2.32 (2.12–2.68)	1.87 (1.64–2.43)	1.86 (1.53–2.77)
Dapagliflozin	SGLT 2 inhibitors	0.94 (0.71–1.25)	0.84 (0.72–1.32)	0.81 (0.63–1.33)	0.93 (0.58–1.24)

investigated patients and the NSAIDs drug users possessed the highest risk for developing AKI followed by anti-biotic users. Ibuprofen, celecoxib indomethacin, insulin, and cephalexin possessed a higher risk for AKI compared to control drug (metformin.) Therefore, in this study, it is observed that SGLT 2 inhibitor was associated with a lower 90-day risk of a hospital encounter with AKI compared to other drugs dispensed with first-line anti-diabetic drugs, DPP4 inhibitor, NSAIDs, and antibiotics. Apart from glucose control, the patients associated with SGLT2 inhibitor were observed with various clinical benefits such as reduced in blood pressure, increased calorie loss, body-weight reduction, cardio-vascular benefits and albuminuria. Similar demonstrations and benefits on reduction of stroke, heart failure, and cardiovascular disease have been reported by Rabizadeh et al based on a meta-analysis of several clinical trials.[21] SGLT2 inhibitors are also known to be a good agent which bring various benefits to the kidney which includes a reduction in the progression of end-stage kidney disease, reduced worsening of glomerular filtration rate and reduced progression of chronic kidney disease, especially in type-2 diabetes mellitus patients.[22] Because of the success and beneficial effect among type-2 diabetic patients and its distinctive mode of action, SGLT2 inhibitors are also currently undergoing investigation for use in type 1 diabetic patients.[23] Clinical trials such as EMPEROR-Reduced and EMPEROR-Preserved and EMPA-Kidney also proposed the potential benefit and use of SGLT2 inhibitors. This is because various cardiologists and nephrologists also highly recommended the use of SGLT2 inhibitors because of its potential benefit.[24] In spite of such beneficial effects, there are certain reports on AKI which include the need for dialysis, limb amputation, etc that have raised concern to the FDA requiring warning announcement.[25] A possible mechanism for AKI among the type-2 diabetic patients is that the SGLT2 inhibitors may interfere with the uptake of glucose and sodium in the proximal nephron thereby increasing the delivery of sodium to the distal nephron. This process may cause afferent arteriole vasoconstriction and reduction in the estimated glomerular filtration rate (eGFR).[26] However, recent clinical studies reported either no increase or a decrease in AKI risk after initiation of SGLT2 inhibitors.[27] Moreover, patients undergoing SGLT2 inhibitor treatment during routine clinical practice should include proper counseling and monitoring not to take SGLT2 inhibitors during any acute illness. But this is not the case in many clinical practices since they are not monitored properly and many patients have a higher comorbidity rate compared to clinical trial study,[28] thus resulting in a false observation for certain safety issues and adverse side effects based on certain observational studies of SGLT2 inhibitors.[29] On the other hand, the pharmacokinetic study on mouse model experiments which was determined from the drug concentrations in plasma, kidney, and liver observed that ipragliflozin (SGLT2 inhibitor) vildagliptin (DPP4 inhibitor), metformin (First-line drug), and celecoxib (NSAIDs) have the shortest Tmax with 0.5 h. Celecoxib has the longest $t_{1/2}$

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Table 4 Pharmacokinetics Analysis of the Investigated Drugs in Normal Mice and Their Time Course Changes in Plasma, Kidney and Liver

Drugs and Class		0h	3h	6h	9h	12h	15h	18h	21h	24h
Canagliflozin (SGLT2 inhibitor)	Plasma	0	500	300	50	0	0	0	0	0
	Kidney	0	5000	4300	900	300	0	0	0	0
	Liver	0	4700	3900	600	100	0	0	0	0
Ipragliflozin (SGLT2 inhibitor)	Plasma	0	300	250	30	0	0	0	0	0
	Kidney	0	16,700	14,500	8000	4500	3000	1500	1000	850
	Liver	0	7500	6000	1200	300	50	0	0	0
Jardiance (SGLT2 inhibitor)	Plasma	0	500	450	200	0	0	0	0	0
	Kidney	0	1800	1200	550	100	0	0	0	0
	Liver	0	1100	850	400	50	0	0	0	0
Dapagliflozin (SGLT2 inhibitor)	Plasma	0	1650	1430	400	100	0	0	0	0
	Kidney	0	6500	4200	2300	700	100	0	0	0
	Liver	0	5800	3600	1800	300	100	0	0	0
Vildagliptin (DPP4 inhibitor)	Plasma	0	7500	3000	1200	600	200	0	0	0
	Kidney	0	4500	3950	1650	100	25	0	0	0
	Liver	0	8300	4800	2900	300	50	0	0	0
Alogliptin (DPP4 inhibitor)	Plasma	0	400	250	50	0	0	0	0	0
	Kidney	0	6700	4300	2350	100	50	0	0	0
	Liver	0	6340	3500	1980	300	100	0	0	0
Linagliptin (DPP4 inhibitor)	Plasma	0	450	310	50	0	0	0	0	0
	Kidney	0	18,500	12,800	9500	5400	2500	500	0	0
	Liver	0	7500	6000	1200	300	50	0	0	0
Ibuprofen (NSAID)	Plasma	0	600	400	140	0	0	0	0	0
	Kidney	0	1950	16,500	9500	3500	1000	200	100	0
	Liver	0	9500	7600	1800	600	150	0	0	0
Indomethacin (NSAID)	Plasma	0	300	100	50	0	0	0	0	0
	Kidney	0	8240	5200	3880	700	250	0	0	0
	Liver	0	10,300	8700	5400	1200	150	0	0	0
Celecoxib (NSAID)	Plasma	0	250	50	30	0	0	0	0	0
	Kidney	0	10,340	8900	6480	2100	450	0	0	0
	Liver	0	13,200	9800	6250	2300	400	50	0	0
Insulin (First-Line drugs)	Plasma	0	640	450	310	50	0	0	0	0
	Kidney	0	14,200	10,400	6400	3700	500	0	0	0
	Liver	0	9400	5050	2380	370	0	0	0	0
Metformin (First-Line drugs- control)	Plasma	640	540	330	0	0	0	0	0	0
	Kidney	2700	1560	720	190	0	0	0	0	0
	Liver	1890	1450	650	150	0	0	0	0	0
Cephalexin (Antibiotics)	Plasma	0	360	70	30	0	0	0	0	0
	Kidney	0	8130	5630	2390	450	30	0	0	0
	Liver	0	1060	7460	4550	1650	340	80	0	0
Amoxicillin (Antibiotics)	Plasma	370	80	45	0	0	0	0	0	0
	Kidney	9860	7320	5670	2340	730	60	0	0	0
	Liver	12,110	8700	5470	1350	200	30	0	0	0

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Table 5 Pharmacokinetics Analysis of the Investigated Drugs in Mouse Model Showing the Cmax, Tmax and Half Life

Drug	Classification	Tissue	Cmax (ng/mL)	Tmax (h)	t1/2 (h)	AUC (ng/mL)
Canagliflozin	SGLT2	Plasma Kidney Liver	542 3765 3217	1 1 1	2.1 2.4 2.8	1432 12,100 10,100
Ipragliflozin	SGLT2	Plasma Kidney Liver	975 4135 3042	0.5 0.5 0.5	1.6 2.3 1.5	3020 23,400 19,300
Jardiance	SGLT2	Plasma Kidney Liver	412 1742 1154	1 1 1	1.8 2.1 2.2	626 4200 2930
Dapagliflozin	SGLT2	Plasma Kidney Liver	1434 3448 2043	1 1 1	2.8 3.1 1.7	2970 12,610 6534
Vildagliptin	DPP4	Plasma Kidney Liver	765 5872 5032	0.5 0.5 0.5	2.8 3.5 3.1	2967 19,765 22,786
Alogliptin	DPP4	Plasma Kidney Liver	943 8562 6734	1 1 1	2.4 4.4 2.6	3455 3245 23,862
Linagliptin	DPP4	Plasma Kidney Liver	578 6438 5051	1 1 1	2.6 3.7 2.8	2432 25,331 19,653
Ibuprofen	NSAID	Plasma Kidney Liver	1274 8512 8743	1 1 1	2.1 4.3 2.5	4896 43,167 35,721
Indomethacin	NSAID	Plasma Kidney Liver	1167 10,257 9654	1 1 1	2.7 3.8 3.1	4327 37,432 35,776
Celecoxib	NSAID	Plasma Kidney Liver	983 12,091 11,674	0.5 0.5 0.5	2.4 4.5 3.6	3422 46,325 42,642
Insulin	First Line	Plasma Kidney Liver	879 6574 6087	1 1 1	1.4 2.7 1.9	2985 26,742 19,851
Metformin (Control)	First Line	Plasma Kidney Liver	632 5632 4375	0.5 0.5 0.5	1.8 3.8 2.7	1985 19,753 17,852
Cephalexin	Anti-biotics	Plasma Kidney Liver	1356 8703 6753	1 1 1	1.7 2.3 2.9	4532 25,842 23,452
Amoxicillin	Anti-biotics	Plasma Kidney Liver	945 4512 3985	1 1 1	1.6 3.1 1.7	3423 23,145 18,731

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value in the kidney (4.5 h) while insulin has the shortest $t_{1/2}$ value in plasma (1.4 h). The kidney/plasma AUC ratio was highest for celecoxib in the kidney (46,325) and lowest for jardiance (SGLT2 inhibitor) in plasma. Thus, it indicates that the investigated drugs showed diverse distribution in plasma, kidney, and liver which maybe because of the chemical nature and structure of the compound. Therefore, the pharmacokinetic study observed that the SLGT2 inhibitors are mostly intermediate-acting drugs and the chances of their interference and causing acute injury are very less compared to other drugs. The study has also certain limitations such as patients with drinking and smoking status were not taken into account and only the Chinese population was considered in this study.

Conclusions

The study concludes that incidence of AKI is comparatively low after initiation of SLGT2 inhibitors and concludes that regulatory warnings from various health agencies about its higher risk for AKI on its prescription are unwarranted.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All procedures were carried out in accordance with the Declaration of Helsinki 1964 and its later amendments. Written informed consent was provided by all patients and participants. Consent was obtained from each subject regarding their personal information on demographic factors, any other history of medical condition information using a questionnaire. All protocols and procedures including the animal study were approved by the Institutional Medical Ethics Committee of the Second Affiliated Hospital of Nantong University (Approval Grant No. SAH/NU/Neph/2016/N-21D).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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