Case Report

A Case Report on The Probable Herb-Drug Interaction between Stevia Products and Etoricoxib Relating to Declined Kidney Function

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Stevia rebaudiana or its metabolites, steviol glycosides, has been used as a sweetener and has shown diuretic effects with excretion of sodium in long-term use. There is no report on nephropathy related to Stevia. The aim of the present study is to report a probable herb-drug interaction between Stevia and etoricoxib that may lead to acute kidney injury (AKI). A 47-year-old Thai woman reported that she took Stevia daily with etoricoxib 90 mg, 2 to 3 times a week for 6 months, and subsequently developed AKI. Her serum creatinine showed a significant increase. She had euthyroid and did not take any medications during that period. After the patient discontinued Stevia and etoricoxib, her serum creatinine returned to normal. A probable herb-drug interaction between Stevia products and etoricoxib was likely to be associated with prerenal AKI.

The authors postulated an interaction with each other's hemodynamic effects. A causal relationship between AKI and Stevia was assessed by the modified Naranjo algorithm. This algorithm indicated a probable relationship (5 scores) for Stevia. In summary, this is the first case report for humans relating to a probable herb-drug interaction between Stevia and etoricoxib associated with AKI. To prevent AKI, people who would like to use Stevia should be advised to drink large amounts of water and avoid using Stevia with NSAIDs or COX-2 inhibitors.

Keywords: Stevia, Herb-drug interaction, Acute kidney injury

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Asian people tend to use herbal medicines due to the fact that it is embedded in their culture as self-care management[1]. They believe that herbal medicine is natural and safe. Leaves of *Stevia rebaudiana* or its active compound, steviol glycosides, are commonly used as a sweetener for diabetic patients and people who would like to control their body weight, globally[2]. The European Food Safety Agency (EFSA) has recommended that steviol equivalents at 4 mg/kg/day was the acceptable daily intake (ADI)[3]. Regarding to other pharmacological effects of Stevia, a meta-analysis of randomized controlled trials (RCTs) found that Stevia for long-term use might reduce diastolic blood pressure and fasting blood glucose (FBG) despite a high heterogeneity[4]. Aqueous extract of Stevia for long-term use had a diuretic effect and natriuresis[5]. People should be concerned about Stevia allergy when using it as a crude preparation[1]. Other adverse events of Stevia were gastrointestinal discomfort (e.g. nausea, abdominal pain and fullness) and dizziness[4]. However, numerous case reports indicated that herbal medicines can cause acute kidney injury (AKI) or worsening kidney function[6]. Toxic mechanisms of herbal medicines related to AKI were similar to conventional medicines, e.g. cyclooxygenase-2 (COX-2) inhibitors. These mechanisms were acute tubular necrosis, acute interstitial nephritis and renal calculi[6,7]. Moreover, some herbal medicines had laxative effects and could cause dehydration that led to developing AKI[8]. Theoretically, herbal diuretics might induce dehydration, might reduce renal blood flow, and then developed AKI. Recently, there were no human case reports on Stevia relating to kidney damage. The study was aimed to report on the probable herb-drug interaction between *Stevia rebaudiana* and etoricoxib that was likely to be associated with AKI.

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Case Report

A 47-year-old Thai woman was diagnosed with thyrotoxicosis with diffuse goiter in 2016. She has been treated with standard medical therapy and developed euthyroid in July, 2017. She took a maintenance dose (5 mg once daily) of methimazol and intermittently took etoricoxib. In April 2017, she was concerned about an upper borderline limit for her fasting blood glucose level (FBG) of 110 mg/dL that drove her to seek information on the recommended daily dosages of both, a Stevia extract and Stevia tea from the labels, after taking both for 6 months (Figure 1). A Stevia extract is a

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registered food product. The patient took Stevia daily and when a Stevia extract ran out, she took Stevia tea. Simultaneously, she took etoricoxib (90 mg), one tablet every 2 to 3 days. She bought etoricoxib by herself without medical prescription from the pharmacy. Six months later, her serum creatinine was increased from 0.8 to 1.3 mg/dL in September 2017 (Table 1). She felt dizzy and fatigue. Physical examination revealed dry lips and oral mucosa. Her serum sodium and potassium levels in October, 2017 were not normal and she had shown mild hyponatremia and hyperkalemia which were associated with renal tubular dysfunction and could recover later than glomerular filtration. Her blood sugar levels seem to be reduced after she took Stevia. Therefore, a doctor advised her to stop taking both Stevia products and etoricoxib. Consequently, her serum creatinine and electrolytes returned to normal.

Figure 1. Stevia products used by the patient.

This case was reported following the process of ethical standards and in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Discussion

The patient had stage 1 AKI due to a 1.6 times serum creatinine increase, based on the definition of the Acute Kidney Injury Network (AKIN) working group[9]. Stevia products and etoricoxib were suspected as the primary cause

Table 1. Laboratory tests

Test/date	Dec 2016	April 2017	July 2017	Sep 2017	Oct 2017
Timeline of Stevia and etoricoxib use	Occasional use of etoricoxib	Using both Stevia and etoricoxib			Stopped both
FBG (mg/dL)	102	110	84	91	90
HbA1C (<7%)	5.5	4.9	5.8	4.2	
BUN (mg/dL)	10	9	13	15	11
SCr (mg/d/L)	0.7	0.8	0.8	1.3	0.8
Uric acid (mg/d/L)	3.9	4.8	5.1	6.5	4.7
Na (mEq/L)	142				133
K (mEq/L)	4.4				5.4
Cl (mEq/L)	102				94
Bicarbonate (mEq/L)	23				29
Albumin (mg/dL)		4.2	4.5	4.0	
Globulin (g/dL)			3.0	3.0	
AST (U/L)		19	32	23	
ALT (U/L)		21	29	20	
ALP (U/L)			70	60	
Cholesterol (mg/dL)	180	204	208	209	191
Triglyceride (mg/dL)	70	89	70	69	60
HDL (mg/dL)	59	59	57	57	56
LDL (mg/dL)	107	127	137	138	123
TSH (□IU/L)	0.26	0.28	2.93		4.46
FT_3 (pg/ml)	7.6	2.67	2.54		2.56
FT_4 (ng/dL)	1.79	1.25	1.09		1.08
Urinalysis					
Sp. Gr.				1.005	
Color/Transp				Yellow/Clear	
Ketone				Neg	
Protein				Neg	
Blood				Neg	

of AKI. The quality of Stevia products taken by the patient seemed to be acceptable as she took a registered Stevia extract and Stevia tea was less likely to be adulterated with conventional medicines, such as corticosteroids, or contaminated with microorganism, yeast and molds. The prevalence of herbal products contaminated with microorganism, yeast and molds in Thailand indicated that herbal tea was less likely to be contaminated with them[10]. Therefore, the quality of Stevia products was less likely to link to a kidney problem. Stevia for long-term use was more likely to produce the excretion of urine and sodium[4]. As a result, it might lead to dehydration in the patient if she did not consume enough water. This hemodynamic effect could reduce blood flow to the kidneys. Concurrently, the patient took etoricoxib, which is a COX-2 inhibitor and known as a nephrotoxic agent, for 6 months. It could reduce blood flow to the kidneys via an afferent arteriole vasoconstriction and the onset of AKI related to etoricoxib was approximately 3-6 months after initiation[11,12]. The greater the dose or duration of etoricoxib consumption increased the risk of kidney damage[12]. Although this patient took a low dose of etoricoxib, she used it for an extensive period. In this case, the patient occasionally took etoricoxib and did not develop AKI prior to using Stevia.

The patient took Stevia products and etoricoxib together for a long period prior to developing AKI. The authors proposed that the onset of prerenal AKI in this patient was associated with the hemodynamic effect from the combination of Stevia and etoricoxib. When the patient discontinued them, her serum creatinine returned to normal. Theoretically, etoricoxib was more likely to be a major factor related to AKI and Stevia products appeared to synergize the hemodynamic effect of etoricoxib. This interaction was possible to gradually decrease blood flow to kidneys and then induced AKI. To our knowledge, the present study was the first report in human identifying a probable herb-drug interaction between a Stevia product and etoricoxib related to AKI via a hemodynamic effect. However, further studies need to confirm this finding whether a Stevia product alone could cause AKI.

To determine a causal relationship between Stevia products and an adverse event, we used the modified Naranjo algorithm (Table 2)[13]. This algorithm has been recommended as an optimal tool to evaluate herbal adverse events by using information from a leaflet of herbal products and any objective data that confirms an adverse event. On the other hand, the original Naranjo algorithm assesses a causal relationship using evidence from any scientific publication and the blood level of a drug of an exposure that is minimally possible to gain such information from herbal products[14]. Therefore, the origin Naranjo algorithm is appropriate for evaluating adverse drug reactions of conventional medicines. By using the modified Naranjo algorithm[13], a finding indicated that the casual relationship between Stevia and AKI in this patient was probable (5 scores).

There were no other risk factors related to AKI in this patient as the patient took only methimazol, which has no nephrotoxic effects. Hypothyroidism might reduce kidney function but the patient had euthyroid during the occurrence of AKI[15].

Several animal and human studies tried to prove that long-term use of Stevia extracts were able to prevent diabetic nephropathy[16-18]. Findings from animal studies appeared to convince that Stevia might decrease kidney damage[16,18]. There was a study reported that Stevia did not affect glomerular filtration rate (GFR)[5]. However, a study in patients with chronic kidney disease showed inconsistent findings of albuminuria and eGRF[17]. The study reported that Stevia extracts decreased microalbuminuria, but did not change albumin to creatinine ratio. In addition, Stevia extracts significantly increased serum creatinine and did not affect eGFR levels[17]. Therefore, further studies would be needed to confirm whether Stevia protects or causes kidney damage.

Long-term use of Stevia extracts was more likely

Table 2. The modified Naranjo algorithm

Question	Yes	No	Do not know
1) Is there any notification about the adverse event on the label or package insert of HDS?	+1	0	0
2) Did the adverse event appear after the suspected HDS intake?	+2	-1	0
3) Did the adverse event improve when the suspected HDS was discontinued?	+2	0	0
4) Did the adverse event reappear when the HDS was retaken?	+3	-1	0
5) Are there any alternative causes (other than the suspected HDS) that could on their own have caused the event?	-1	+2	0
6) Was the event more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
7) Did the consumer have a similar event to the same or a similar HDS in any previous exposure?	+1	0	0
8) Was the adverse event confirmed by any objective evidence?	+2	0	0

The total score >9 = highly probable; 5 to 8 scores = probable; 3 to 4 scores = highly possible; 1 to 2 score(s) = possible; <0 = unlikely
HDS = Herbal and dietary supplement
The present case study had 5 scores from No. 2 (+2), No. 3 (+2), No. 5 (-1), and No. 8 (+2)

to decrease serum blood sugar and blood pressure[5,17,18]. Our case report suggested that Stevia might decrease serum blood sugar in the patient who did not have diabetes.

Not only the interaction between Stevia and etoricoxib were linked to AKI, but this interaction could also lead to electrolyte imbalances. The patient developed mild hyperkalemia and hyponatremia after taking Stevia and etoricoxib for a long period. Stevia might induce hyponatremia while etoricixib was related to hyperkalemia[5,12].

To prevent AKI from Stevia products, health care providers suggest that if the patients would like to use a Stevia product as a sweetener, they should drink large amounts of water in order to prevent dehydration. This suggestion is implemented from the mechanism of long-term use of Stevia[4]. They also should not take Stevia products together with COX-2 inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs). Acetaminophen (paracetamol), a capsaicin gel, and topical NSAIDs are suggested for pain relief, when patients, e.g. diabetes, would prefer to use Stevia as a sweetener. When the patients become ill with poor consumption of food and liquid, they should stop using Stevia products altogether.

Conclusion

The probable herb-drug interaction between Stevia and a COX-2 inhibitor might induce prerenal AKI in people with normal kidney function. This should be of concern when taken in combination. It should be noted that herbal medicines associated with AKI might interfere with electrolyte levels. Health care providers should be more cautious about the use of herbal medicines by their patients. General population should be concerned about herb-drug interactions as well. The belief of the people that the natural herbal medicines are safe should be reconsidered by evidence of previous case reports of those who had complications from these products. Further studies need to be done to confirm these findings.

What is already known on this topic?

Some herbal medicines could cause acute tubular necrosis, acute interstitial nephritis and renal calculi which lead to AKI or worsening kidney function. In addition, some herbal medicines have laxative effects and could cause dehydration that leads to developing AKI. Stevia has a diuretic effect and natriuresis especially in the long-term usage. As a result, patients who take stevia with drinking less water are prone to develop dehydration.

What this study adds?

This is the first report of the probable herb-drug interaction between Stevia and a COX-2 inhibitor which might induce prerenal AKI in a Thai female with normal kidney function. The mechanism of prerenal AKI in this patient was associated with the hemodynamic effect from the combination of Stevia and etoricoxib. To prevent AKI from Stevia products, health care providers should suggest that patients should not take Stevia products together with COX-2 inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs). When the patients are aware of illness with poor consumption of food and liquid, they should stop using Stevia products altogether.

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Potential conflicts of interest

The authors declared no conflicts of interests.

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