



## Lithium Intoxication Associated with Angiotensin II Type 1 Receptor Blockers in Women

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Lithium is like a two-edged sword; it is on the one hand a unique drug with psychoactive potential as a mood stabilizer and on the other hand a burdensome drug which can cause multisystem toxicity to alter basic cellular function. Many drugs interact with lithium, increasing its blood level. For example, elevated lithium concentrations after the initiation of angiotensin-converting enzyme (ACE) inhibitors have been well documented in literatures [1][2][3]. However interaction between angiotensin II type 1 receptor (AT1R) blockers and lithium is rarely documented. We present a case of lithium intoxication after administration of telmisartan, an AT1R blocker, and examined reported cases of lithium intoxication by AT1R blockers.

A 48-year old woman with a 30-year history of schizoaffective disorder was hospitalized for relapse due to poor compliance. After being given medications including lithium 1,200 mg/day, sodium valproate 400 mg/day, olanzapine 20 mg/day, levomepromazine 5 mg/day, and clonazepam 2mg/day, the patient's condition had been stable for a period of time. However the patient developed sustained hypertension (150-170/90-110 mmHg) about 2 months after the admission and was diagnosed with essential hypertension. Telmisartan 40 mg/day was prescribed to control blood pressure. At this time, routine examination revealed normal renal, liver and thyroid functions. The serum lithium concentration before the addition of telmisartan was 0.96-1.01 mEq/L for lithium 1,200 mg/day. Her blood pressure was gradually decreased to 120-130/ 70-90 mmHg by telmisartan. However

the patient suddenly experienced slurred speech, unsteady gait, and confusion 24 days after the initiation of telmisartan. Laboratory results at this time were as follows: lithium concentration, 3.06 mEq/L; valproate concentration, 38 µg/mL; clonazepam concentration, 12.4 ng/mL; blood urine nitrogen, 24.0 mg/dL; creatinine, 1.87 mg/dL; sodium, 139 mEq/L; potassium, 3.6 mEq/L; and chloride, 101 mEq/L. The patient was diagnosed as having lithium intoxication with acute renal failure. All drugs were discontinued and the patient was sent to the emergency department of a general hospital to receive intensive care.

The exact mechanism of lithium intoxication associated with AT1R blockers remains unclear, but it is supposed that natriuresis induced by AT1R blockers facilitate the retention of lithium from the kidney. Angiotensin II leads to stimulation of sodium reabsorption in the proximal tubules and secretion of aldosterone by the adrenal cortex. AT1R blockers might have resulted in decreasing sodium reabsorption in the proximal tubules and the decrease of aldosterone has a similar effect in distal tubules. Subsequently, the depletion of sodium might have in turn contributed to lithium reabsorption, eventually leading to lithium intoxication [1][2][3].

To our knowledge, there were seven case reports of lithium intoxication associated with AT1R blockers, including our case, and all of them were women shown in Table 1 [4][5][6][7][8][9]. Drug interaction between lithium and AT1R blockers might be more likely to occur in women. On the contrary, the sex differences are not recognized in ACE inhibitor-

induced lithium intoxication. For example, Lehmann et al. examined 10 cases of lithium intoxication associated with ACE inhibitors, and 6 cases were men [1]. What is the reason why sex differences are recognized in the development of lithium intoxication induced by AT1R blockers?

One possible reason is that telmisartan has agonistic activities on peroxisome proliferator activated receptor- $\gamma$  (PPAR $\gamma$ ) in which sex differences may exist [10]. Thiazolidinediones (TZDs) are agonists for PPAR $\gamma$  and the use of TZDs is associated with plasma volume expansion. TZDs rapidly stimulate sodium-coupled bicarbonate absorption from the renal proximal tubules, resulted in reduced excretion of lithium and free water without changing creatinine clearance or urinary sodium excretion [11]. Consistent with the stimulation of proximal tubules transport through the activation of PPAR $\gamma$ , a reduction in lithium clearance might have occurred in patients treated with telmisartan. Interestingly, TZD-induced volume expansion is high in incidence in women. Mechanism of sex differences in TZD-induced fluid retention is still unknown, but it is speculated that

estrogen and progesterone might have enhanced the PPAR $\gamma$ -dependent nongenomic stimulation of renal proximal transport by modulating Na/K ATPase in renal tissues [12].

Another reason is that there are sex differences in angiotensin II type 2 receptor (AT2R) expression. Selective intrarenal AT1R blockade induced a highly significant natriuresis that was abolished by intrarenal coadministration of AT2R specific antagonist, indicating that the natriuretic effect of AT1R blockers is mediated by AT2R activation [13]. AT2R elicits natriuretic effects and these effects are greater in female due to enhanced AT2R levels modulated by estrogen [14]. Subsequently, marked natriuresis due to AT1R blockade might have occurred in females, leading to more lithium reabsorption in women than in men.

Further studies are needed to determine whether AT1R blockers have more potential risk of lithium intoxication in women than in men. Anyway lithium's narrow therapeutic index requires frequent serum concentration monitoring and a reduction in the dose of lithium when combining AT1R blockers.

**Table 1. Reported Cases of Lithium Intoxication Associated with AT1R Blockers**

Age (y.o.)	Sex	Disease	AT1R Blocker	Lithium Dose (mg/day)	Lithium Level (mEq/L)	Reference
77	female	bipolar	losartan 50mg/day	625	2	4
51	female	bipolar	valsartan 80mg/day	750	1.4	5
58	female	bipolar	candesartan 16mg/day	900	3.25	6
74	female	bipolar	irbesartan 300mg/day	750	2.3	7
60	female	bipolar	valsartan 80mg/day	600	1.72	8
52	female	schizoaffective	termisartan 40mg/day	900	2.6	9
48	female	schizoaffective	termisartan 40mg/day	1200	3.06	this report

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