Lithium Interaction with Flurbiprophen: A Case Report

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ÖZET:
Lityumun flurbiprofenle etkileşimi: Olgu sunumu

Lityum Bipolar Bozuklukta(BB) halen tedavi seçeneği olarak kabul edilmesine rağmen, duygudurum düzenleyici olarak klinik kullanımı dar terapötik aralıkta gerçekleşir. Serum düzeylerindeki küçük değişiklikler ciddi yan etkilere yol açarken terapötik aralıklardaki dozlar toksik reaksiyonlara neden olabilir. Bu nedenle lityumun diğer ilaçlarla güvenli kombinasyonu önemlidir. Nonsteroid anti-enflamatuvar ilaçların lityum seviyesini yükselttiği, renal atılımı azalttığı ve bu yolla lityum toksikasyonuna yol açabilirliği konusunda kesin kanıtlar mevcuttur. Bu olguda kas-iskelet ağrıları için başlanan flurbiprofen sonrasında lityum toksisitesi ile başvuran Bipolar II Bozukluk hastası sunulmaktadır.

Anahtar sözcükler: Lityum, flurbiprofen, ilaç etkileşimleri

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ABSTRACT:
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Although lithium continues to be regarded as the treatment of choice for bipolar disorder (BD), the clinical use of this mood stabilizer is associated with a narrow therapeutic range. Relatively minor increases in serum concentrations may induce serious adverse sequelae, and concentrations within therapeutic range may result in toxic reactions. The safety of combining lithium with other medications, therefore, is a major concern. There is conclusive evidence that nonsteroidal anti-inflammatory drugs can increase serum lithium levels, diminish renal lithium clearance, and possibly induce lithium toxicity. We described a patient taking lithium for BD II who presented with lithium toxicity after flurbiprophen was initiated for musculoskeletal complaints.

Key words: Lithium, flurbiprophen, drug interactions

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INTRODUCTION

Lithium is a drug used in prophylaxis of bipolar and unipolar affective disorder, mania, aggression, short term treatment of depression (1). Lithium is being used widespreadly around the world and still first choice in bipolar disorder (2). While absorption through gastrointestinal system is rapid and almost entirely complete, elimination is only through kidney via glomerular filtration. 70-80 % of lithium is absorbed through proximal tubules (3). Lithium has drug interaction with antipsychotics, antidepressants, other mood stabilizers, angiotensin converting enzyme (ACE) inhibitors, diuretics and calcium channel blockers (Table 1) (4).

Lithium has also interaction with nonsteroidal anti-inflammatory drugs (NSAIDs). Following lithium plus NSAIDs, lithium excretion is lowered leading increase in serum concentration of lithium. NSAIDs are oftenly prescribed in elder population. Interactions may also occur in patients with normal renal function. Phenylbutazone and oxyphenbutazone have high tendency to pharmacokinetic interaction. Indomethacin seems to have important interaction. There is no certain evidence about interaction of sulindac and aspirin effecting lithium serum concentration significantly. Ibuprophen and naproxen lead significant increase in serum concentration of lithium, but interpersonal variabilities are present (5). Ragheb and Powell, reported lithium intoxication following coadministration of lithium and naproxen in 64 years old man but symptoms subsided within five days after discontinuation of naproxen treatment (6). Ragheb, added ibuprophen to nine patients with lithium treatment and investigated

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Table 1: Drug Interactions of lithium

Drug Class	Reaction
Antipsychotics	Case reports of encephalopathy, worsening of extrapyramidal adverse effect, and neuroleptic malignant syndrome.
Antidepressants	Occasional reports of a serotonin-like syndrome with potent serotonin reuptake inhibitors.
Anticonvulsants	No significant pharmacokinetic interactions with carbamazepine or valproate. Reports of neurotoxicity with carbamazepine; combinations helpful for treatment resistance.
Nonsteroidal anti-inflammatory drugs	May reduce renal lithium clearance and increase serum concentration. Toxicity reported (exceptions are aspirin and sulindac)

occuring drug interactions. Ragheb, reported increase in lithium concentration and decrease in excretion of lithium (7). Serum lithium increase is also confirmed in case reports concerning healthy volunteers following lithium and ibuprophen combination (8). Interactions with diclophenac, ketoprophen, mephenamic acid, niflumic acid and piroxicam are reported (5). Shelley, reported a case of BD taking lithium therapy developing lithium intoxication after addition of mephenamic acid (9). Gay et al, presented two cases of lithium intoxication after combination of acetazolamide and niflumic acid (10). Herschberg et al, reported a bipolar patient taking lithium therapy developing delirium after adding indomethacin for arthritis (11). Reimann et al, studied pharmacokinetics of drug interactions between lithium and nonsteroidal anti-inflammatory drugs on ten female volunteers. Indomethacin is found to decrease excretion and increase serum concentration of lithium. No difference of serum lithium concentration after adding 4gr/day of aspirin in five female volunteers as well (12). Rabelink et al, discovered that indomethacin increased re-uptake of lithium in healthy volunteers (13).

CASE PRESENTATION

A 45 years old, married, housewife who had diagnosis of bipolar affective disorder (BAD) admitted to emergency room. During the previous 5 years she had been treated with lithium carbonate 600 mg in the morning, 600 mg at night. Regular monitoring of the serum lithium carbonate concentrations during this time showed concentrations in the 0.5-0.9 mmol\L range. Before four days of admission to hospital, she was commenced on 200 mg/day flurbiprophen for musculoskeletal complaints. After combining flurbiprophen with lithium therapy, she gradually became sleepy, had feeling of malaise followed by nausea and vomiting. On the day of complaints, she refered to emergency room of the hospital. On admission she had hypotension, tremor in the hands. Biochemical findings were within normal limits. Lithium carbonate concentration was 1.3 mmol\L. Following psychiatry consultation, the patient was mentally assessed. In mental status examination, her appearance was in accord with her socioeconomic status, the patient had eye contact, affect was anxious, speech was slurred, she was sleepy, cooperative and oriented, judgement and reality testing was normal. All drugs were stopped on admission. Sleepiness, tremor, poor concentration, slurred speech, vomiting gradually decreased, subsided completely in five days. Serum concentration of lithium carbonate was 0.8 mmol/L at third days of intoxication, 0.5 mmol/L at seventh days and she was discharged from hospital with lithium carbonate 1200 mg\day treatment.

DISCUSSION

Lithium has central importance in psychiatric diseases. It is considered as primary long term preventive treatment of bipolar affective disorders (1). It is removed from body almost entirely by kidneys. It was demonstrates that long-term lithium treatment may cause an impairment in renal concentrating ability some of which may originate from the effects of lithium on hypothalamic level, and a decrease in glomerular filtration rate (14).

Adding drugs effecting glomerular filtration and electrolyte exchange in nephron may influence pharmacokinetic disposition of lithium. Minor increase in serum concentration of lithium may induce serious adverse effects due to narrow therapeutic range of

lithium . As a result, safety of lithium coadministration with other medications is a major concern (15).

Nonsteroidal anti-inflammatory drugs decrease glomerular filtration rate by inhibiting prostaglandin synthesis, thus lead electrolyte imbalance rarely result renal failure, nephrotic syndrome or papillary necrosis. Experimental and clinical observations support similar adverse effects of selective cyclooxygenase inhibitors (COX) 2. Slordal et al, detected somnolence, abdominal pain, nausea, bradycardia, hypotension in a bipolar patient following combination of lithium and selective COX 2 (celecoxib). After celecoxib treatment, renal function impaired and lithium intoxication occured thus it is warned to be attentive about intoxication during coadministration of selective cyclooxygenase inhibitors (16).

Flurbiprophen which is a nonsteroidal anti-inflammatory drug having analgesic and antipyretic effect being used oftenly in rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis (17). Hughes et al., studied effect of flurbiprophen on lithium pharmacokinetics in placebo controlled, single blind study. Flurbiprophen is given to eleven bipolar female patients taking lithium within normal therapeutic range and it is stated that patients with clinically normal renal function may experience an increase lithium levels with the initiation of flurbiprophen therapy (18). If we look through the lithium toxic effects and association with plasma concentration; lithium serum concentration about 1-1.5 mmol/L leads poor concentration, lethargy, irritability, weakening of muscle, tremor, slurred speech and nausea (mild intoxication). In medium level of intoxication with serum lithium concentration of 1.6-2.5 mmol/L leads confusion, restlessness, numbness, unsteady gait, coarse tremor, dysartria, twitching and nausea. Higher than 2.5mmol/L serum concentration leads clouding of conciousness, delirium, ataxia, generalized twitching, extrapyramidal symptoms, convulsions, dysfunction of renal excretion (3).

Following four days of adding flurbiprophen; sleepiness, tremor, poor concentration, slurred speech, nausea and vomiting were observed in our case. These findings were in accord with mild intoxication signs and lithium carbonate concentration at admission was 1.3 mmol\L which was within mild toxic serum lithium concentrations. Sleepiness, tremor, poor concentration, slurred speech, vomiting gradually decreased and subsided completely within five days. Serum concentration of lithium carbonate was 0.8 mmol/L at third days of intoxication, 0.5 mmol/L at seventh days.

This case report presents a lithium intoxication following combination with flurbiprophen, a phenylpropionic acid derivative. Nonsteroidal anti-inflammatory drugs decrease renal blood flow and glomerular filtration rate by inhibiting prostaglandin synthesis which are important in maintenance of renal perfusion and tubular function. Also lithium which has a narrow therapeutic range is excreted almost completely through kidneys. In our case; lithium excretion which was decreased by this mechanism and led to symptoms due to increased serum levels of lithium.

Best way of preventing lithium intoxication is training patients about conditions leading intoxication and early signs of intoxication. An effective educational programme may greatly reduce the hazards of lithium treatment.

References:

1. Peet M, Pratt P. Lithium, current status in psychiatric disorders. Drugs 1993;46:7-17
2. Şengül C, Şengül CB, Okay T, Dilbaz N. Ellibeşinci Yılında Lityumun Öyküsü. Klinik Psikofarmakoloji Bülteni 2004; 14:50-56
3. Kayaalp O. Antidepresan ve antimanik ilaçlar. Ankara: Hacettepe Taş,1998: 465-470
4. Kaplan HI, Sadock BJ, Sadock VA. Comprehensive Textboook of Psychiatry. In: Jeffersın J.R, Kammen DP, editors. Drug interactions with lithium., 7nd ed. Philadelphia: Lippincott Williams& Wilkins, 2000:2388-2390
5. Ragheb M. The clinical significance of lithium-nonsteroidal anti-inflammatory drug interactions. J Clin Psychopharmacol 1990;10:350-354
6. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. J Clin Psychopharmacol 1986;6:150-154
7. Ragheb M. Ibuprophen can increase serum lithium level in lithium treated patients. J Clin Psychiatry 1987;48:161-163
8. Kristoff CA, Hayes PE, Barr WH, Small RE, Townsend RJ, Ettigi PG. Effect of ibuprophen on lithium plasma and red blood cell concentrations. Clin Pharm 1986;5:51-55

9. Shelley RK. Lithium toxicity and mephenamic acid. A possible interaction and the role of prostaglandin inhibition. Br J Psychiatry 1987;151:847-848

10. Gay C, Plas J, Granger B, Olie JP, Loo H. Lithium poisoning 2 unpublished interactions: Acetazolamide and niflumic acid. Encephale 1985;11:261-262

11. Herschberg SN, Sierles FS. Indomethacin-induced lithium toxicity. Am Fam Physician 1983;28:155-157

12. Reimann IW, Diener U, Frolich JC. Indomethacin but not aspirin increases plasma lithium ion levels. Arch Gen Psychiatry 1983;40:283-286

13. Rabelink AJ, Koomans HA, Boer WH, Dorhout Mees EJ, Van Rijn HJM. Indomethacin increases renal lithium reabsorption in man. Nephrol Dial Transplant 1989;4:427-431

14. MT Turan, E Eşel, B Tokgöz, SS Aslan, S Sofuoğlu, C Utaş. Effects of long-and short-Term lithium treatment on kidney functioning in patients with bipolar mood disorder. Klinik Psikofarmakoloji Bülteni 2001;11:149-154

15. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. Clin Pharmacokinet 1995;29:172-191

16. Slordal L, Samstad S, Bathen J, Spigset O. A life-threatening interaction between lithium and celecoxib. Br J Clin Pharmacol 2003;55:413-414

17. Brogden RN, Heel RC, Speight TM, Avery GS. Flurbiprophen: A rewiev of its pharmacological properties and therapeutic use in rheumatic diseases. Drugs 1979;18:417-438

18. Hughes BM, Small RE, Brink D, Mckenzie ND. The effect of flurbiprophen on steady-state plasma lithium levels. Pharmacotherapy 1997;17:113-120