

## Case Report

SUPERIOR SAFETY OF REBOXETINE OVER AMITRYPTILINE  
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**Abstract:** Under antidepressive treatment with amitriptyline (100 mg/d) a 71-year old woman developed delirious symptoms, hyponatremia and a grand mal seizure followed by cardiovascular arrest. A few month later she ingested 48 mg reboxetine with suicidal intent. Overdosing of reboxetine, a selective noradrenaline re-uptake inhibitor, proceeded without complications.

**Key words:** Reboxetine; Amitriptyline; Elderly

## INTRODUCTION

Depressive disorders are one of the most frequent diseases in patients of old age. Most of these patients are treated by primary care practitioners and other non-psychiatric health care providers. In this light progressive knowledge of antidepressive pharmacotherapy is an important issue not only for psychiatrists. Recently an excellent review on novel antidepressants concluded that these drugs are superior to classical tricyclics (TCAs) regarding drug safety indices, especially in cases of overdose [6]. Here we report on a patient in whom fatal, life-threatening complications arose with amitriptyline treatment, when a later intoxication with reboxetine, a selective noradrenaline re-uptake inhibitor, proceeded without complications.

## CASE REPORT

During amitriptyline (75-100 mg/d) treatment, a 71-year old woman, healthy apart from suffering major depression, reported mouth dryness and urinary retention. About six days after raising amitriptyline to 100 mg/d, she was admitted to the hospital because of agitation, severe confusion, and scenic optical hallucinations. Clinical examinations showed no pathological findings excepting a raised blood pressure (190/100 mmHg). ECG showed a sinus tachycardia (103/min); PQ-conduction time 108 ms, QRS 84 ms, frequency corrected QT time (QTc) 426 ms. Cranial computer tomography (CCT), EEG and lumbar puncture revealed normal findings. Laboratory testing revealed serum hyponatremia (121 mval/l; normal

range 134-145 mval/l); urinary osmolality and amitriptyline plasma concentration were not determined. Six hours after hospitalisation the patient suffered a grand mal seizure and then cardiovascular arrest. After successful resuscitation she was supervised for 48 hours at the intensive care unit. The patient recovered completely; sodium concentration was normal four days after amitriptyline discontinuation (138 mval/l).

A few months later the patient was hospitalised again after ingestion of 48 mg reboxetine with suicidal intent. Subjectively, the patient was without complaints. The ECG showed a sinus rhythm (79/min); PQ-conduction time 120 ms, QRS 74 ms, QTc time 413 ms. Blood pressure was 130/80 mmHg. Plasma noradrenaline was raised at 1007 ng/l (normal range: 130-475 ng/l), while the remaining laboratory parameters showed no significant pathology. Plasma reboxetine was 1281 ng/ml (therapeutic range: 10-100 ng/ml). During 12 hours of intensive care supervision there was always a sinus rhythm with frequencies between 80-96/min; the systolic (diastolic) blood pressure ranged from 120-160 (60-90) mmHg. The patient recovered completely.

## DISCUSSION

Mild anticholinergic side effects including mouth dryness and reversible bladder dysfunction have been reported during treatment with TCAs as well as reboxetine. In the case presented here unwanted central nervous system (CNS) effects, in particular, a grand mal seizure and an anticholinergic delirium, complicated amitriptyline treatment. A seizure incidence of 0.1-2.2% has been reported for a wide range of TCAs, whereby older patients and patients with pre-existing cerebral damage are affected more often [3, 5]. The risk for a TCA induced delirium is about 6%; risk factors include high patient age, female gender and high TCA plasma levels [8]. An important differential diagnosis is hyponatremia, which clinically can mimic delirious, psychotic and depressive symptoms and also can provoke seizures [10]. Hyponatremia has frequently been reported during antidepressive therapy with TCAs or serotonin

reuptake inhibitors (SSRIs), especially in patients over 65 years of age [2, 10]. Recently a single case of hyponatremia under reboxetine was published [9]. In our patient hyponatremia might also result from the syndrome of an inappropriate secretion of antidiuretic hormone (SIADH) under amitriptyline, however, we failed to determine plasma and urinary osmolality to exclude this diagnosis.

Our knowledge regarding complications to be expected following reboxetine overdosing is very sparse [6]; no published case report on reboxetine overdose was found in the "Medline" database up to May 2002. Since the market introduction of reboxetine in 1997 at least three other cases of overdosing were reported to the manufacturer; the highest doses taken (208-416 mg/d) were survived without residual effects, and the only abnormality reported was tachycardia [7]. The favourable outcome in these patients corresponds well to the lack of effects of reboxetine on ECG time relations (PQ conduction and repolarization time) [1, 4]. Since reboxetine acts as a selective noradrenaline reuptake inhibitor, it has no significant anticholinergic and antihistaminergic properties. Therefore the risk of unwanted CNS complications seems to be lower compared to TCAs. As illustrated in the case presented here, this aspect is important for avoiding unnecessary suffering by depressive senior patients, who are at risk for such CNS complications, and for preventing unnecessary treatment costs.

## REFERENCES

1. Agelink MW, Ullrich H, Baumann B, Strum S, Majewski T (2002) Effects of reboxetine, a selective norepinephrine reuptake inhibitor, on sympathetic and parasympathetic outflow to the heart. *Psychopharmacology (Berl)* 163: 151-156
2. Chan TY (1997) Drug-induced syndrome of inappropriate antidiuretic hormone secretion. Causes, diagnosis and management. *Drugs Aging* 11: 27-44
3. Edwards JG, Long SK, Sedgwick EM, Wheal HV (1986) Antidepressants and convulsive seizures: clinical, electroencephalographic, and pharmacological aspects. *Clin Neuropharmacol* 9: 329-360
4. Fleishaker JC, Francom SF, Herman BD, Knuth DW, Azie NE (2001) Lack of effect of reboxetine on cardiac repolarization. *Clin Pharmacol Ther* 70: 261-269
5. Jabbari B, Bryan GE, Marsh EE, Gunderson CH. (1985) Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 42: 480-481
6. Kent JM (2000) SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 355: 911-918
7. Leroux M, Schüler P (2000) Noradrenergic reuptake inhibition and suicidal behaviour. *Nervenarzt* 71 (suppl.1): S134
8. Preskorn SH, Jerkovich GS (1990) Central nervous system toxicity of tricyclic anti-depressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. *J Clin Psychopharmacol* 10: 88-95
9. Ranieri P, Franzoni S, Trabucchi M (2000) Reboxetine and hyponatremia. *N Engl J Med* 342: 215-216
10. Sharma H, Pompei P (1996) Antidepressant-induced hyponatremia in the aged. Avoidance and management strategies. *Drugs Aging* 8: 430-435

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