

## INFECTION OR IDIOSYNCRATIC REACTION TO ANTIEPILEPTIC DRUGS?

Paola Presečki, Vlado Grošić, Ante Silić & Mate Mihanović

*Psychiatric Hospital Sveti Ivan, Jankomir 11, Zagreb, Croatia*

### SUMMARY

*Idiosyncratic reactions are serious, unpredicted adverse effects of antiepileptic drugs which are in use in psychiatry as mood stabilizers. Severe idiosyncratic reactions can manifest as systemic symptoms or Dress syndrome clinically manifested with increased body temperature, peripheral lymphadenopathy and potential one or multiple organ failure.*

*We present a 36 years old patient, who was hospitalized for the first time in our hospital after he attempted suicide by hanging. Patient was diagnosed as Bipolar affective disorder, current episode depressive with psychotic features and high suicidal risk. At the time of admission he was taking olanzapine and venlafaxine. Psychopharmacs were cross titrated to clozapine, valproic acid and lamotrigine. Two weeks later, patient's mood was stabilized but his somatic status worsened dramatically. He was forwarded to Clinic for Infective Diseases where he was diagnosed with severe sepsis. Dress syndrome, although initially suspected was not verified, but has to be taken into consideration in each patient prescribed with antiepileptic drugs.*

**Key words:** *antiepileptic drugs - dress syndrome - idiosyncratic reactions - infection*

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### INTRODUCTION

Antiepileptic drugs are in wide use in psychiatry as mood stabilizers (Bowden & Singh 2008). Idiosyncratic reactions are serious adverse effects of antiepileptic drugs and can not be foreseen before administration (Zaccara et al. 2007). Severe idiosyncratic reactions can manifest as skin changes, most commonly as rash with eosinophyllia and systemic symptoms – Dress syndrome typically presenting with high fever, peripheral lymphadenopathy and potential one or multiple organ failure (Amante et al. 2009).

Pathophysiology of idiosyncratic reactions is based on hypothesis of accumulation of toxic metabolites, production of antibodies and viral infections. Hypothesis based on accumulation of toxic metabolites is most commonly accepted, probably because it can be tested “in vitro” by the lymphocyte toxicity assay. On the other hand “in vivo” skin biopsy proves characteristic multiform erythema or typical leucocytoclastic angitis (Taillia et al. 2009). Most commonly such reactions develop 2 to 6 weeks after antiepileptic drug introduction (Veyrac et al. 2002) or according to other authors even up to 12 weeks after antiepileptic drug introduction (Taillia et al. 2009). Most commonly, mentioned reactions were observed as adverse effects of aromatic antiepileptics (carbamazepine, phenitoin and phenobarbital) (Galindo et al. 2002), but some authors suggest it can be observed with non-aromatic antiepileptic drugs such as lamotrigine (Amante et al. 2009, Taillia et al. 2009, Veyrac et al. 2002). The safest

antiepileptic in this regard seems to be valproic acid but what must be mentioned is that it is not well tolerated by patients with history of hypersensitivity to phenitoin and carbamazepine (Galindo et al. 2002).

Simultaneous administration of valproic acid and lamotrigine leads to increased plasma concentration of lamotrigine (Reimers et al. 2005) thus increasing the risk of development of rash within potentially fatal Stevens-Johnson syndrome (Perucca 2003, Hirsch et al. 2006). All antiepileptic drugs can potentially cause idiosyncratic reactions (Zaccara et al. 2007). Such reactions are generally considered to be the cause of up to 10% of all adverse reactions to drugs in general (Zaccara et al. 2007).

In this paper we present a patient with dramatic clinical deterioration while taking antiepileptics in combination therapy of his depressive episode within Bipolar affective disorder with psychotic symptoms and high suicidal risk. Dress syndrome, which was initially differential diagnostically suspected, was not diagnosed.

The aim of this paper is to point out that this potentially fatal side effect has to be considered in every patient with signs of clinical deterioration and is taking antiepileptic drugs.

### CASE REPORT

Patient was born in 1974, married with one child, carpenter, self-employed. His first hospitalization in Psychiatry hospital “Sveti Ivan” was in June 2009 after he attempted suicide by

hanging. He reports first psychological symptoms in February 2009 when he was manic with psychotic symptoms. He was psychomotorily agitated, logorrheic, his mood was persistently elevated, expansive and irritable. He changed subjects rapidly, lost sleep and was overly involved in his work. Ideas of grandeur and influence, racing thoughts and distractibility were explored at the time. His spouse talked him into out-patient treatment where he was prescribed with olanzapine and his symptoms withdrew. At the beginning of May 2009, his child was hospitalized and in those circumstances he was left home alone for few days. His wife described him as depressed and with no energy, verbalizing suicidal thoughts without plans. At that point venlafaxine (225mg per day) was added to olanzapine in therapy. Eventually patient attempted suicide by hanging, the rope snapped and he was hospitalized in our hospital. At the time of admission, strangulation mark was visible at his neck. He was psychomotorily inhibited, depressive, anxious with low self esteem and feelings of worthlessness, diminished interest and pleasure in almost all activities, loss of energy, loss of appetite (in two weeks he lost 8 kilograms). He demonstrated delusional ideas of guilt and self accusation and he was suicidal. In family history, his father (who was diagnosed and treated for Major depression), committed suicide by hanging. Patient was diagnosed as depressive episode with psychotic features in Bipolar affective disorder with high suicidal risk. Clozapine, valproic acid and lamotrigine were introduced and venlafaxine tapered off. Two weeks later patients' psychological symptoms withdrew but his general condition worsened rapidly, initially with somnolence, febrility and diarrhea. Laboratory findings indicated inflammatory process. The patient was transferred to Clinic for infective diseases where he was diagnosed and successfully treated for severe sepsis complicated with acute pulmonary failure, subclinical pericarditis and paralytic ileus. The origin of infection was not localized and Dress syndrome was excluded.

## DISCUSSION

The patient (diagnosed as depressive episode with psychotic features in Bipolar affective disorder with high suicidal risk) was prescribed with combination of antiepileptic drugs and antipsychotic. Earlier, he was taking olanzapine and venlafaxine and psychopharmacs were cross

tapered to clozapine, valproic acid and lamotrigine according to Good clinical practice and current therapeutic algorithms. Clozapine (even though not first line treatment and as such reserved for therapy resistant Bipolar affective disorder) (Shiloh et al. 2000, Uzun et al. 2005) was introduced as first line because patient was psychotic and suicidal and clozapine is considered to be most effective antisuicidal drug for psychotic patients (Meltzer et al. 2003). Antisuicidal effect of lithium was also described (Goodwin et al. 2003), but clinical studies suggest that valproic acid and lamotrigine have less side effects than lithium (Smith et al. 2007). Among other factors contributing to high suicidal risk, patient also had positive family history for suicide (Meltzer 2002). Venlafaxine treatment of bipolar depression has somewhat higher risk of mania and/or hypomania induction compared to paroxetine (Vieta et al. 2002), while data from lamotrigine studies in bipolar depression suggest lamotrigine efficiency comparable to those of antidepressants (Calabrese et al. 1999).

Lamotrigine is recommended in combination with antimanic drugs for patients who recently experienced manic episode or have anamnestic data for manic episode. For all other patients lamotrigine can be considered as rational maintenance treatment (Suppes et al. 2005).

Worsening of somatic status and laboratory findings indicating inflammatory processes were suggesting infection which was eventually confirmed, but differential diagnostically it could have been the Dress syndrome because patient developed acute pulmonary failure, subclinical pericarditis and paralytic ileus, all treated in three week hospitalization in Clinic for Infective disorders. The origin of infection was not localized, but Dress syndrome, although initially suspected and described as possible antiepileptic drug side effect, was excluded. If a patient's general condition after introduction of antiepileptic drugs clinically deteriorates, idiosyncratic hypersensitivity reaction should be considered. Since clinical presentation of infectious disease can mask or mimic idiosyncratic reactions, later can be unrecognized. However, if a patient takes antiepileptic drug, such reaction should be considered and suspected drug excluded from therapy (Veyrac et al. 2002). Serious consequences of idiosyncratic reactions can be avoided or alleviated by careful and slow titration and by careful clinical monitoring of drug response as well (Zaccara et al. 2007).

# THE EFFECTS OF CARDIAC SURGICAL PROCEDURES ON HEALTH – RELATED QUALITY OF LIFE, COGNITIVE PERFORMANCE, AND EMOTIONAL STATUS OUTCOMES: A PROSPECTIVE 6 – MONTH FOLLOW – UP STUDY

Hans-Bernd Rothenhäusler

Department of Psychiatry, University of Medicine of Graz, Auenbruggerplatz 31, A-8010 Graz, Graz, Austria

## SUMMARY

**Introduction:** The aim of this study was to assess the course of health – related quality of life, cognitive and emotional change during the six months after elective CABG, and to investigate how cognitive impairments, depression and posttraumatic stress symptoms were related to quality of life.

**Method:** In a prospective study, we followed up for 6 months 138 of the original 147 patients who had undergone elective CABG surgery.

**Conclusion:** Elective CABG is associated with significant improvements in HRQOL relative to the preoperative period, but impairments in HRQOL were found in a subgroup of post – CABG patients with evidence of PTSD, depression, or cognitive impairments at 6 – month follow – up.

**Key words:** coronary artery bypass graft surgery - cardiopulmonary bypass - cognitive impairments – depression - posttraumatic stress disorder - health – related quality of life - consultation – liaison psychiatry

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## INTRODUCTION

Owing to the continuous refinement of surgical techniques, the progress in cardiopulmonary bypass (CPB) technology and the significant advances in intensive care treatment, the survival rates after major cardiac surgery with CPB such as coronary artery bypass graft surgery (CABG) have considerably improved over the past 40 years. Hence, the success of routine CABG is now no longer judged solely by its effects on traditional end points (e.g. mortality rates) but by its influence on patients' psychosocial well – being (e.g. health – related quality of life), and by its neuropsychological and emotional sequelae. The aim of this study was to assess the course of health – related quality of life, cognitive and emotional change during the six months after elective CABG, and to investigate how cognitive impairments, depression and posttraumatic stress symptoms were related to quality of life.

## SUBJECTS AND METHODS

In a prospective study, we followed up for 6 months 138 of the original 147 patients who had undergone elective CABG surgery. Preoperatively, and at 6 months after surgery, a series of psychometric observer – rating and self – rating scales were administered to evaluate cognitive functioning (SKT), depressive symptoms (BDI),

posttraumatic stress symptoms (PTSS – 10), and health – related quality of life (SF – 36 Health Status Questionnaire).

## RESULTS

Preoperatively, 2.7% (4 out of 147 patients) valued SKT total scores indicating minimal cognitive impairments. At 6 months postsurgery, 17.4% (24 out of the 138 followed – up patients) demonstrated signs of a minimal (N=22), mild (N=1), or moderate (N=1) disturbance of cognitive functions. The obtained SKT total scores reflected significant increases in levels of cognitive impairments from preoperative to 6 – month follow – up evaluations (mean SKT total score before surgery =  $1.5 \pm 1.3$ ; mean SKT total score at 6 – month follow – up =  $2.5 \pm 2.3$ ;  $p < 0.001$ ). However, no extreme or severe cognitive deficits were recorded, and the vast majority of the cognitively impaired patients displayed only minimal cognitive deficits at 6 – month follow – up. Preoperatively, 17% (25 out of 147 patients) suffered from clinical depression: mild or moderate depression occurred in 21 patients, and severe depression in 4 patients, as measured on the BDI. At 6 months postsurgery, only 10.1% (14 out of the 138 followed – up patients) had the diagnostic status of clinical depression: mild or moderate depression in 10 patients, and severe depression in 4 patients. The ratings obtained from the BDI