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SEVERE ACUTE PANCREATITIS, NEUROLEPTIC MALIGNANT SYNDROME AND GRAND MAL SEIZURES ASSOCIATED WITH ELEVATED AMISULPRIDE AND LOW CLOZAPINE SERUM LEVELS

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INTRODUCTION

Acute pancreatitis, neuroleptic malignant syndrome (NMS) and epileptic seizures are all known to be rare complications of clozapine-treatment (Steinert et al. 2011, Tenner 2014, Belvederi Murri et al. 2015). For amisulpride, only seven cases with NMS (Belvederi Murri et al. 2015) including one case with seizures (Musshoff et al. 2013) have been described yet. Recently, via a German pharmacovigilance project 4 schizophrenic adults being treated with amisulpride (600-1200 mg/d) and showing an elevation of their creatinine kinase (CK, ranging from 1500 U/l to 21000 U/l) were found, who suffered from myalgia without signs of NMS and whose myalgia and CK elevation were reversible after amisulpride discontinuation (Laoutidis et al. 2015). An amisulpride-related pancreatitis is not reported to the authors` best knowledge. Hereinafter, we report a patient treated with amisulpride and clozapine, who fell into a critical condition characterized by severe acute pancreatitis, NMS and seizures.

CASE REPORT

A 53-year-old male Caucasian (71 kg, 173 cm) with a 30 year history of paranoid schizophrenia was brought in by ambulance in critical condition. In the intensive care unit (ICU) a severe acute pancreatitis (C-reactive protein (CRP) 122 mg/dl (normal value <10mg/dl), lipase 4000 U/l (73-393), systemic inflammatory response syndrome/ sepsis (Vincent 2009), ketoacidosis and pleural effusion) (Tenner 2014) was found. This condition was complicated by generalized epileptic seizures and typical features of NMS (Belvederi Murri et al. 2015), such as muscular rigidity (moderately in all limbs), confusion, hyperreflexia, hyperthermia (39.2°C), dysautonomia (fluctuating blood pressure) and rhabdomyolysis (CK 4426 U/l (50-190 U/l) were identified. Transabdominal ultrasonography excluded cholelithiasis and revealed pancreatic enlargement and echotextural changes. Contrast-enhanced computed tomography (CT) showed no pancreatic pseudocysts or necrotizing. Brain-CT was normal and urinary drug screen was negative.

Prior to his critical condition the patient had been in a stable psychiatric condition (with modest executive dysfunctions) under the treatment of clozapine (150 mg b.i.d) and amisulpride (400 mg b.i.d.) for three years. At that time, amisulpride was added to an approximately 15-year-lasting clozapine monotherapy (200 to 600 mg/d) and improved sialorrhea, sedation as well as anxiety (Cook & Hoogenboom 2004, Chiu et al. 2011).

There were no further medications in the last weeks prior to the referral to the ICU by a caregiver. At admission, the serum levels of clozapine and amisulpride were significantly below and above its therapeutic ranges (clozapine 115 ng/ml (350-600), desmethyl-clozapine 100 ng/ml (100-300), amisulpride 450 ng/ml (100-320)) (Hiemke et al. 2011), respectively. However, both were in similar dimensions than the levels monitored the last time one year ago (clozapine 113 ng/ml, desmethyl-clozapine 70 ng/ml and amisulpride 401 ng/ml). Because regular outpatient medical routine visits (every 3 to 4 months) and psychiatric nurses providing home care did not notice adverse reactions or a clinical deterioration since then, further therapeutic drug monitoring (Hiemke et al. 2001) was not performed so that we could not exclude that the clozapine levels were consistently low in this patient in the past year. In addition, signs of a substance addiction or a metabolic syndrome, such as diabetes mellitus or hyperlipidemia were not apparent in the visits.

The NMS resolved within 72 hours after cessation of the antipsychotics and under dantrolene treatment (Perry & Wilborn 2012). Moreover, diazepam was transiently administered for seizure control, myorelaxation and to mitigate sensory overload. Simultaneously, the critical care management (including intravenous fluid hydration and standard infusion piperacillin-tazobactam (Layer et al. 2001)) quickly improved the pancreatitis within the next 10 days allowing the subsequent treatment in the psychiatric unit.

Although there is more evidence in literature for the symptom complex (pancreatitis-NMS-seizure) to occur under clozapine treatment than with amisulpride (Steinert et al. 2011, Musshoff et al. 2013, Tenner 2014, Belvederi Murri et al. 2015) we decided to reinstate clozapine for relapse-prevention because i) previously clozapine monotherapy had been well tolerated since long years in the management of this patient prior to amisulpride addition and ii) the symptoms appeared during significantly subnormal clozapine- but elevated amisulpride-serum levels (Hiemke et al. 2011). During the 8-month-follow-

up of the clozapine (200 mg b.i.d) re-challenge the patient remained in a stable physical and psychiatric condition. Executive dysfunctions slightly benefited from adding agomelatine 50 mg/d (Bruno et al. 2014). Routine lab including creatinine kinase, CRP and lipase, brain magnetic resonance imaging, electroencephalography (EEG), electrocardiogram, and serum clozapine-levels were unremarkable (low therapeutic range 352-384 ng/ml, desmethyl-clozapine 122-163 ng/ml).

DISCUSSION AND CONCLUSION

We suggest that the patient`s critical condition was more likely secondary to amisulpride than to clozapine treatment. NMS/seizures and pancreatitis were estimated to be probable (5 points) and possible (4 points) adverse effects of amisulpride according to the Naranjo-score (Naranjo et al. 1981), respectively. Clozapine attained only 3 points for each symptom in this score (Naranjo et al. 1981). Our assumption, which was based on i) the temporal relationship between start of treatment and onset of the symptoms and ii) the results of the therapeutic drug monitoring, is supported by missing signs of NMS, pancreatitis or seizures as well as by the absence of EEG-abnormalities during the current antipsychotic monotherapy with clozapine so far. In literature, one male adult with acute paranoid schizophrenia was reported who developed myalgia and CK-elevation (21 000 U/l) under combined treatment with amisulpride (800 mg/d) and clozapine (700 mg/d) and whose symptoms vanished after cessation of both drugs (Laoutidis et al. 2015). In similar to the presented case the adverse effects did not recur after re-challenge with clozapine (625 mg/d) alone (Laoutidis et al. 2015).

Alternatively, an initial idiopathic pancreatitis (Tenner 2014) might have facilitated the transfer of the neuroleptics through the blood-brain-barrier by inflammation/ sepsis, thereby precipitating NMS and lowering the seizurogenic threshold (Adam et al. 2013). In comparison with clozapine the blood-brain-barrier penetration of amisulpride is considerably poorer under normal conditions (Härtter et al. 2003, Natesan et al. 2008).

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References

1. *Adam N, Kandelman S, Mantz J, Chrétien F & Sharshar T: Sepsis-induced brain dysfunction. Expert Review of Anti-Infective Therapy 2013; 11:211-21.*
2. *Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G et al.: Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. Drugs in R&D 2015; 15:45-62.*
3. *Bruno A, Zoccali RA, Abenavoli E, Pandolfo G, Scimeca G, Spina E et al.: Augmentation of clozapine with agomelatine in partial-responder schizophrenia: a 16-week, open-label, uncontrolled pilot study. J Clin Psychopharmacol 2014; 34:491-4.*
4. *Chiu HW, Ku YC, Li TC & Huang HT: Amisulpride augmentation of clozapine in refractory schizophrenia. J Neuropsychiatry Clin Neurosci 2011; 23:E15.*
5. *Cook B & Hoogenboom G: Combined use of amisulpride and clozapine for patients with treatment-resistant schizophrenia. Australas Psychiatry 2004; 12:74-6.*
6. *Härtter S, Hüwel S, Lohmann T, Abou El Ela A, Langguth P, Hiemke C et al.: How does the benzamide antipsychotic amisulpride get into the brain? An in vitro approach comparing amisulpride with clozapine. Neuropsychopharmacology 2003; 28:1916-22.*
7. *Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K et al.: AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 2011; 44:195-235.*
8. *Laoutidis ZG, Konstantinidis A, Grohmann R, Luckhaus C, Mobascher J & Cordes J: Reversible Amisulpride-induced Elevation of Creatine Kinase (CK): A Case Series from the German AMSP Pharmacovigilance Project. Pharmacopsychiatry 2015; 48:178-81.*
9. *Layer P, Rünzi M, Goebell H, Büchler MW, Ell C, Fölsch U et al.: Therapy of Acute Pancreatitis. Dt Ärztebl 2001; 98:A3139–3141[Heft 47].*
10. *Musshoff F, Doberentz E & Madea B: Lethal neuroleptic malignant syndrome due to amisulpride. Forensic Science Medicine Pathology 2013; 9:218-20.*
11. *Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al.: A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics 1981; 30:239-45.*
12. *Natesan S, Reckless GE, Barlow KB, Nobrega JN & Kapur S: Amisulpride the 'atypical' atypical antipsychotic--comparison to haloperidol, risperidone and clozapine. Schizophr Res 2008; 105:224-35.*
13. *Perry PJ, Wilborn CA: Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. Ann Clin Psychiatry 2012; 24:155-62.*
14. *Steinert T, Baier H, Fröscher W & Jandl M: Epileptic seizures during treatment with antidepressants and neuroleptics. Fortschritte Neurologie Psychiatrie 2011; 79:138-43.*
15. *Tenner S: Drug induced acute pancreatitis: does it exist? World Journal of Gastroenterology 2014; 20:16529-34.*
16. *Vincent JL: Definition of Sepsis and Non-infectious SIRS. In Cavaillon JM & Adrie C (eds): Sepsis and Non-infectious Systemic Inflammation, 3-12. Wiley-VCH Verlag GmbH & Co. KG, 2009.*

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