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Clozapine, olanzapine and rhabdomyolysis

Introduction

Clozapine (Leponex®) is an atypical antipsychotic agent and a tricyclic dibenzodiazepine derivative. The SPC states that Clozapine use should be restricted to patients:
with schizofrenia who do not respond or are tolerant to treatment with antipsychotics, or with psychosis in Parkinson's disease when other treatmentstrategies have failed.
with an initial normal leucocyte distribution (white bloodcell count ≥ 3500 / mm3 (3.5*109 /l) and an absolute neutrophyls count (ANC) ≥ 2000/mm3 (2.0*109 /l) whose leucocyte count and ANC can be regularly checked as follows: weekly during the first 18 weeks of treatment, thereafter at least every 4 weeks during treatment. Tests should be continued during treatment and until 4 weeks after cessation of clozapine [1].
Clozapin has a weak dopamine-receptor-blocking effect on D1, D2, D3 and D5 receptors, but a strong effect on the D4 receptor. In addition, it has strong anti-alpha-adrenergic, anticholinergic, antihistaminergic and antiserotinergic effects. Common ADRs are somnolence, dizziness, headache, tachycardia, constipation and hypersalivation. Serious ADRs are agranulocytosis, myocarditis and neuroleptic malignant syndrome. Increased levels of serum creatine kinase (CK) had been observed in 1 in 1,000-10,000 patients [1].

Olanzapine (Zyprexa®) is an atypical antipsychotic agent (thienobenzodiazepine derivative) structurally similar to clozapine. It is indicated for treatment of schizophrenia. It is also used for treatment of moderate to severe manic episode, as well as for prevention of a relapse in patients with bipolar disorder [2]. Similar to clozapine, olanzapine is both a dopamine and serotonin (5-HT) antagonist. The drug binds more potently to the 5-HT2A receptor than the D2 receptor; greater activity at D4 compared to D2 receptors has also been reported.
Common ADRs are somnolence, dry mouth, dizziness, constipation and weight gain. Neuroleptic malignant syndrome have been reported in less than 0.01 % in postmarketing studies. In clinical studies high serum creatine kinase was observed in 1 in 100-1000 patients [2].

Reports

Up to August 30 2004, Lareb received 2 reports of rhabdomyolysis on clozapine and 1 on olanzapine (table 1).
One of the reports concerning clozapine (A) originated from the pharmaceutical company and included a second suspected drug, entacapone. CK level was above 1200 U/l (normal range globally < 150 U/l).
Patient B was admitted on the intensive care unit with a pneumonia and deteriorating level of consciousness. CK was 492,500 U/L, LDH 49,700 U/L, creatinine 717 µmol/L, urea 17.6 mmol/L indicating rhabdomyolysis and renal failure. Serum clozapine level was strongly elevated (1.10 mg/L). All medications were discontinued and patient received supportive treatment. After 2.5 weeks CK had decreased to 461 U/L.

Patient C had used olanzapine for 7 years. Ten days after discontinuation, he restarted olanzapine 10 mg, because of hallucinations. Within days, he experienced myalgia and dark urine. Urine analysis revealed myoglobinuria. On admission to the intensive care unit CK was 90,573 U/L, LDH 10,722 U/L, creatinine 270 µmol/L, urea 16.2 mmol/L. A positive culture for B-hemolytic streptococcus was found. Olanzapine was discontinued and patient received adequate hydration and sodiumbicarbonate. After 2.5 weeks patient was discharged in good condition.

Table 1. reports of rhabdomyolysis associated with the use of clozapine (A,B) or olanzapine (C).

Patient, Sex, age	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A M,87	clozapine 25 mg, not specified	entacapone *, levodopa/-carbidopa, rivastigmine, levothyroxine, paracetamol, hydrocobamine, mesalazine, budesonide caps, loperamide	rhabdomyolysis CPK increased	101 days, recovered
B M, 29	clozapine 150 mg, chronic psychosis	chlorprothixene, oxazepam, cefuroxim, erythromycine	rhabdomyolysis	unknown, recovered
C M, 28	olanzapine 10 mg, schizophrenia	none	rhabdomyolysis	days after restart, recovered

* is also suspected drug

Other sources of information

Literature

For olanzapine and clozapine several publications describe a marked elevation of CK (MM type), without criteria for neuroleptic malignant syndrome (NMS) [3-7]. The increases were much larger than usually found in acutely psychotic patients or patients with NMS (range 500-3,000 U/L):4,000-15,000 for olanzapine and 11,000-27,000 for clozapine, predominantly without clinical symptoms.
Olanzapine-induced rhabdomyolysis has been published several times and is mentioned in the Summary of product characteristics[8-10]. Myalgia and increasing weakness were present in a 13 year old patient, starting 6 days after initiation with olanzapine 2.5 mg. CK levels on day 28 were 11,300 U/L, 100 % MM subfraction. Urine dipstick revealed the presence of erythrocytes without gross hematuria [9].
The FDA Medwatch program obtains another 12 cases of rhabdomyolysis associated with olanzapine, without NMS. Symptoms developed 1-12 months after initiation of therapy, with CK ranges of 6,000-100,000 U/L [9]. Two chronic schizophrenic patients on olanzapine experienced rhabdomyolysis associated with pneumonia; NMS was excluded [8].
Rhabdomyolysis in a 21-year-old man was reported after 19 weeks treatment with clozapine for schizophrenia [11]. In this patient the calcium-dependant potassium permeability of cell membranes was decreased. After overdosage of clozapine 3-4 gram, a 40- year-old schizophrenic man was found unconsciousness, with

twitching of the limbs, constricted pupils, sinus tachycardia and mild rhabdomyolysis [12].
Also on other antipsychotics like risperidone, haloperidol, quetiapine and aripiprazol, rhabdomyolysis has been reported rarely.
Databases
On August 24 2004 the database of the Uppsala Monitoring Centre of the WHO contained 102 associations of olanzapine and rhabdomyolysis, which is disproportional (ROR 3.42; CI-95% 2.81-4.17). For clozapine 56 reports of rhabdomyolysis were observed (ROR < 1). CK increase on the other hand, was associated with clozapine use (ROR 4.08, CI-95% 3.73-4.47).

Mechanism
The underlying mechanism seems to involve the calcium-dependant potassium efflux, which is normally responsible for membrane hyperpolarisation and muscle refractoriness [11]. Patients with defects in calcium-activated potassium channels have more calcium influx during longer depolarizations in skeletal muscle and therefore may be more prone to increased cell membrane permeability which in turn is involved in rhabdomyolysis. Infections, leading to a decreased metabolism of clozapine and olanzapine and therefore resulting in higher serum levels [13], may contribute to rhabdomyolysis.

Another postulation concerns the role of serotonin, which accumulates in skeletal muscle by passive diffusion [4]. Serotonin (5-HT) can be toxic to skeletal muscle, leading to necrosis and massive increases in CK activity in rodents. Tricyclic antipsychotics, including clozapine and olanzapine, might interact with endogenous 5-HT to cause some skeletal muscle injury.

Prescription data

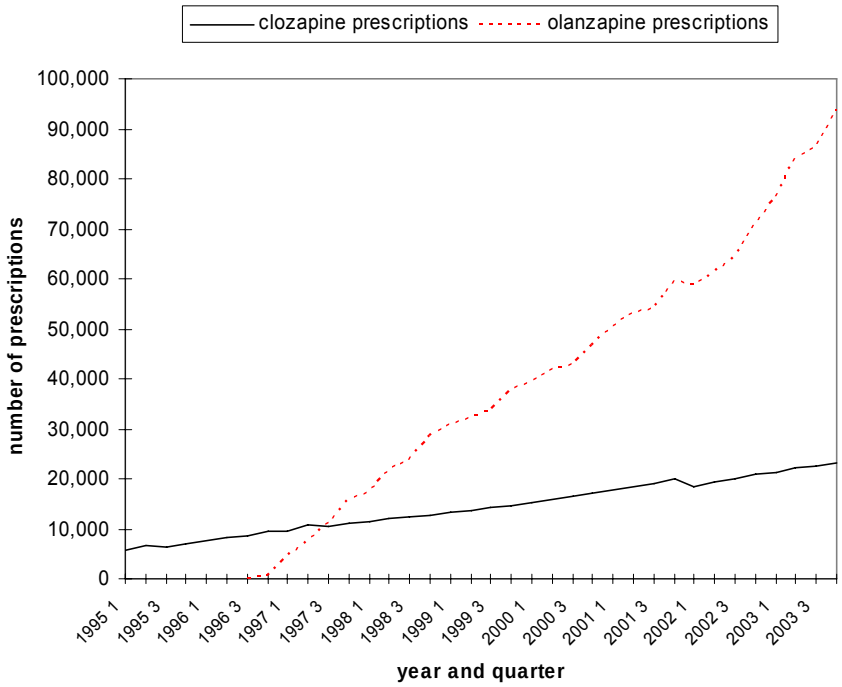

Figure 1. Total number of clozapine and olanzapine prescriptions per quarter since 1995 (Source: GIP College voor Zorgverzekeringen, Diemen).

Conclusion

Lareb received 3 reports of rhabdomyolysis associated with use of the atypical antipsychotics clozapine and olanzapine without criteria for NMS. Case reports in the literature and a plausible mechanism support this association. For olanzapine, this association is supported by the WHO data. CK increase was disproportionally present for both olanzapine and clozapine in the WHO database. CK increase is mentioned in the SPC of both clozapine and olanzapine, whereas the life-threatening reaction of rhabdomyolysis is not.

References

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