Biperiden as a cause of a cognitive decline – case reports

Kognitivni upad zaradi biperidena – prikaz primerov

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Abstract

Introduction

Anticholinergic drug biperiden is used to treat and prevent the extrapyramidal side effects of antipsychotic therapy. With its anticholinergic properties it affects cognitive functions, especially while concomitant drugs with anticholinergic effects are used.

Methods

We present a severe cognitive decline in four patients treated with 2 to 6 mg of biperiden daily.

Results

A significant improvement of 3 to 8 points on Mini mental state exam was noticed immediately after discontinuation of biperiden in patients with psychosis and dementia.

Conclusions

Biperiden is frequently prescribed, in spite of known deterioration of cognitive functions following its administration. In elderly patients even a small dosage of biperiden can cause a significant cognitive decline which can manifest as dementia – like a syndrome or worsening of actual dementia.

Key words: cholinergic antagonists – cognition – psychotic disorders – dementia

Izvleček

Uvod

Antiholinergik biperiden se uporablja za zdravljenje in preprečevanje ekstrapiramidnih neželenih učinkov povzročenih z antipsihotiki. S svojim antiholinergičnim delovanjem vpliva na kognitivne funkcije, še posebej ob sočasni uporabi z drugimi zdravili z antiholinergičnim delovanjem.

Metode

V prispevku predstavljamo hud kognitivni upad pri štirih bolnikih, zdravljenih z 2 do 6 mg biperidena dnevno.

Rezultati

Pri bolnikih s psihozo in demenco je bilo po ukinitvi biperidena opazno bistveno izboljšanje rezultata Kratkega preizkusa spoznavnih sposobnosti za 3–8 točk.

Zaključki

Kljub znanemu poslabšanju kognitivnih funkcij po uporabi biperidena, se slednjega še vedno pogosto uporablja. Pri starejših bolnikih lahko že majhen odmerek biperidena povzroči pomemben kognitivni upad, ki se lahko kaže kot sindrom demence ali kot poslabšanje že prisotne demence.

Ključne besede: holinergični antagonist – spoznavne sposobnosti – psihotična motnja – demenca

Background

The anticholinergic medications are primarly used to treat medication–induced movement disorders, particularly neuroleptic–induced parkinsonism, acute dystonia and postural tremor (1). They block muscarinic receptors, which are distributed widely in the brain. The central side effects of anticholinergics are associated with decrease in cognitive functioning, including memory, learning, attention and executive function. The peripheral side effects can manifest as blurred vision, dry mouth, hyperthermia, constipation and urinary disturbances. The central and peripheral side effects can be more pronounced when concomitant medications with anticholinergic properties are used.

Insight into the major role of the central cholinergic system in memory arose from the finding that cognitive deficits are correlated with extensive cholinergic cell loss in the brain in Alzheimer's disease (2). Anticholinergic effects of the antiparkinsonics can cause cognitive impairment in non–psychiatrically ill subjects and in patients with schizophrenia (3) and represent widespread cause of delirium in elderly patients (4). Study of community– dwelling elderly people showed that the use of medications with anticholinergic properties was significantly associated with low cognitive performance (5). Another study showed that continuous anticholinergic use was a strong predictor of mild cognitive impairment, which was documented as poor performance on reaction time, attention, delayed non–verbal memory, narrative recall, visuospatial construction and language tasks (6). Positron emission tomography revealed that long–term anticholinergic therapy causes bilateral diffuse decrease of glucose metabolism in the cortex, basal ganglia, thalamus, hippocampus and cerebellum (7). Biperiden is often used as an anticholinergic to treat antipsychotic–induced side effects. Motor learning, visuospatial processes and episodic memory were shown to be impaired by biperiden (2). Biperiden had a marked dose dependent amnesic effect and induced amnesia in memory acquisition and retrieval phases (8).

Despite well known devastating effect of anticholinergics on cognitive functions, they are still often used. Cases of severe cognitive decline due to biperiden are presented to rise awareness of side–effects while prescribing anticholinergics.

Subjects

Clinical case 1

A 56–year–old retired factory worker with paranoid schizophrenia was admitted to our psychiatric clinic for the third time. In the past years he was suffering from psychotic episodes with delusions and was recently treated with olanzapine 10 mg, risperidone 1 mg and biperiden 2x2 mg.

At admission the patient stated that he had experienced a tremor in his hands, speech difficulties and a left body tilt for two weeks. Otherwise he felt well, psychosis was in a stable remission. His ex–wife reported that his condition got worse in the last months so that he could not find things in his apartment and no longer knew how to use various items. Five days before admission he was examined by a neurologist, who wrote that the patient had tardive dyskinesia due to antipsychotic treatment. Two days before admission he was examined at an emergency department because of a high body temperature (38.6 ˚C), confusion, coughing and dyspnea. He was treated with antibiotics due to bacterial infection of unknown origin.

The patient was conscious, oriented in place, but not in time. The Mini Mental test score (MMSE) result was 17/30 and the Clock drawing test 0/4 points (Picture 1). There was an obvious dysfunction of short–term memory and concentration, his speech was incoherent. There were no florid psychotic symptoms, he was euthymic and without suicidal tendencies. He could not walk alone, had an unstable gait, body tilted to the left, a hand tremor and an increased muscle tone of the upper extremities. At admission the blood pressure was 205/125 mmHg, otherwise the physical examination showed no abnormalities.

On the first day of hospitalisation the antipsychotics were discontinued. There was a rapid improvement in his motor functions, but the cognitive decline had not changed. Biperiden was discontinued on the fifth day. A rapid improvement of the cognitive functions was immediately observed. On the eighth day of hospitalisation the MMSE result was 25/30 points, and the Clock drawing test 4/4 (Picture 1). He was oriented in time and place. Dystonia disappeared, leaving only a minor increase of the muscle tone of the left upper extremities. New antihypertensive therapy was prescribed. He was discharged with quetiapine 25 mg bid. Higher dosage of quetiapine was later prescribed.

The patient was admitted to hospital as rapid progressing dementia. While receiving olanzapine, risperidone and biperiden, he was also treated with an antibiotic, which can also influence pharmacokinetics of other medications. After discontinuation of both antipsychotics, the extrapyramidal side effects ceased, but his cognitive functions improved only after the discontinuation of biperiden.

Clinical case 2

A 59–year–old female patient was taking fluphenazine for two years because of paranoid delusions. At the age of 68 she became frightened due to exacerbation of persecutory delusions and was taking fluphenazine for the second time, for one year. The third outburst of psychotic symptoms began at the age of 73, when fluphenazine 2,5 mg tid, biperiden 2 mg tid, and citalopram 20 mg daily were prescribed. Following months the dosage of fluphenazine and biperiden was slowly reduced to 2,5 mg daily and 2 mg daily, respectively. Even though she remained free of psychotic symptoms, she complained about forgetfulness. Addenbrook's Cognitive Assesment confirmed cognitive decline (67/100) with the most prominent decline in memory subscale (16/26). MMSE score was 24/30. After discontinuation of biperiden, the patient reported improvement of memory, which was also confirmed with Addenbrook's Cognitive Assesment memory subscale (21/26) and MMSE (28/30).

Patient with delusional disorder was treated with fluphenazine and biperiden. After discontinuation of biperiden she noticed improvement of memory and no extrapyramidal side effects emerged. Dosage of antipsychotic remined unchanged. This case shows that even a low dosage of biperiden (2 mg daily) can affect cognitive functions.

Clinical case 3

A 89–year–old female patient with Alzheimer dementia was treated for a cognitive decline and occasional hallucinations and delusions in the outpatient unit of our psychiatric clinic. While living in a retirement home, she was treated with quetiapine 25 mg bid, olanzapine 5 mg and biperiden 2 mg tid.

During her first appointment at Psychogeriatric outpatient unit her son told that she had an intensive hand tremor for a month, which improved after she received higher biperiden doze (from 2 mg to 6 mg per day), but the cognitive decline got worse. She was frightened and had a feeling that someone is coming in her room at night.

The patient was conscious, oriented in place, but disoriented in time. There was a dysfunction of short–term memory and concentration, the MMSE was 17/30 points (a year and a half earlier the score was 22/30). She suffered from delusions and probably, hallucinations. She had a tremor of the right hand and the head and an increased muscle tone of the upper right extremity. Palmomental reflex was positive.

After consultation with a neurologist biperiden was discontinued and treatment with topiramat 25 mg bid was prescribed. One month later the tremor was alleviated and improvement of the cognitive function was noticed. The MMSE score was 20/30 points. The delusions and hallucinations yet remained, therefore olanzapine 5 mg was prescribed. We also started treatment with rivastigmine.

Patient with Alzheimer's disease benefited least of all after biperiden discontinuation. However, the three points improvement on MMSE presents approximately a progress of disease within one year. Acetylcholinesterase inhibitors, which are used for treatment of Alzheimer's disease only seldom improve cognitive functions in such an extent.

Clinical case 4

75–year–old female patient with dementia of mixed ethiology was admitted to our psychiatric clinic for the third time. She suffered from an acute cognitive decline, tardive dyskinesia and dystonia. In the past she was hospitalised due to depression with psychotic symptoms. Her medication was unchanged for the last ten years (amitriptyline 25 mg tid, clozapin 25 mg – 50 mg – 25 mg, biperiden 2 mg tid, lorazepam 1,25 mg + 2,5 mg). Memantine 20 mg was added after cognitive decline was noticed. High blood pressure was treated with enalapril 20 mg bid.

At admission she complained about sleeplessness and fatigue. She first noticed mild oral tardive dyskinesic movements 15 years ago. Afterwards the movements became more intense and spreaded to the legs and arms. In the last 6 months she noticed difficulties in walking and a right body tilt. Neurologist excluded parkinsonism.

The patient was conscious, oriented in time, but not in place. She was able to answer the questions only after long breaks, there was an obvious lack of concentration and cognitive dysfunction; the MMSE score was 12/30 points. There was also an obvious dysfunction of speech fluency, short–term memory and language. However no florid psychotic symptoms were observed, she was euthymic and without suicidal tendencies. She had orofacial and hand dyskinesia, and a right body tilt.

During hospitalisation we discontinued treatment with biperiden, memantine and lorazepam. There was a rapid improvement of the cognitive functions (the MMSE scored 18/30 points), especially the fluency of speech. Increased anxiety was alleviated with propranolol (40 mg three times daily) and consequently reduction of enalapril followed. Later, there was a subtle improvement of tardive dyskinesia during slow reduction of dosage of clozapin, which was ultimately discontinued. Amitriptyline was replaced with mirtazapine 30 mg daily and venlafaxine 75 mg daily, her final MMSE score was 21/30.

Patient with dementia of mixed etiology, depressive symptoms and tardive dyskinesia was treated with three drugs known for their anticholinergic properties: amitriptyline, biperiden and clozapin. Discontinuation of biperiden resulted in cognitive improvement. However, observed improvement could be also due to simultaneous discontinuation of benzodiazepines. She additionally improved after cessation of amitriptyline and clozapine.

Results

In all cases improvement of cognitive functions was noticed after discontinuation of biperiden. The effect on MMSE is presented in table 1. In addition, in case 1 significant improvement in Clock drawing test was described, in case 2 a significant improvement in Addenbrook's Cognitive Assesment, especially on memory subscale, was noticed, and in case 4 more fluent speech was also observed.

Discussion

As Nerat & Kos presented, 22.4 to 35.9 per cent of the elderly patients in Slovenia were prescribed at least one inappropriate medication (9). In addition, side–effects are more frequent in elderly patients. It is therefore necessary to pay special attention when prescribing medications to elderly patients.

It is well documented that cholinergic activity is reduced in patients with Alzheimer's disease. Furthermore, acetylcholinesterase inhibitors can also be effective in dementia with Lewy bodies and vascular dementia. Therefore, a significant cognitive improvement after discontinuation of biperiden, which occured in our patients with dementia, was expected. Surprisingly, patients with psychosis benefited even more from discontinuation of biperiden compared to patients with dementia. We presented cases of severe cognitive decline due to anticholinergic activity, which is equal to cognitive decline during up to three years of progression of Alzheimer's disease.

Biperiden has an important influence on patient's cognitive functioning. Many psychiatrists are prescribing it for prevention or treatment of extrapyramidal side effects of antipsychotic therapy. The medication is often prescribed for long periods of time. Discontinuation of long–term biperiden use in patients with schizophrenia treated with second generation antipsychotics may improve cognitive function, subjective quality of life and psychiatric symptoms with no significant adverse effects (10). Cognitive symptoms are relatively reversible after the discontinuation of biperiden.

Anticholinergic medications may also reduce the effectiveness of antipsychotic medications (11) or even induce psychotic symptoms in schizophrenia by weakening the brain's ability to inhibit repetitive and irrelevant incoming sensory stimuli (3). Anticholinergics can also commonly cause drug induced delirium (12). Several medications are known for their anticholinergic activity: sedating antihistamines, antispasmodics, oxybutynin, ipratropium bromide, muscle relaxants, iphenoxylate/atropine and antiarhythmics. The most important medications with anticholinergic activity in psychiatry are some antipsychotics, antidepressants and anticholinergic antiparkinsonian agents like biperiden. Atypical antipsychotics differ in their affinity for binding to muscarinic receptors, olanzapine and clozapine have the highest (13). Thioridazine and tricyclic antidepressants are also known for a significant anticholinergic activity.

Schizophrenia is a chronic disease with cognitive symptoms present in many patients even without anticholinergic treatment. On the other hand, patients with dementia can have psychotic and depressive symptoms which need to be treated. While taking medicines with an anticholinergic activity, cognitive functions may be significantly affected. In elderly patients even small dosage of biperiden can cause significant cognitive decline which can manifest as a dementia–like syndrome or worsening of actual dementia (14). The choice of appropriate antipsychotic and antidepressive therapy is therefore necessary to avoid additional cognitive decline.

Conclusion

Our cases present influence of biperiden on cognitive functions in patients with dementia and psychosis. Recognition of cognitive decline and correct identification of its cause is crucial for appropriate treatment and better prognosis. Mild memory problems caused by anticholinergic effects might well be overlooked in patients who were already cognitively impaired or sedated (15), despite the availability of the quick screening tests for cognitive functions. Failure to identify anticholinergic side–effects may lead physicians to use other drugs to treat symptoms, rather than to quit the responsible ones (16). Discontinuation of all medications with possible anticholinergic effect has to be considered before cognitive modulators are prescribed.

Conflict of Interest.

None to declare.

References

1. Sadock BJ & Sadock VA: Kaplan and Sadock's Synopsis of psychiatry, 1004–6. Philadelphia: Lippincott Williams and Wilkins, 2007.
2. Wezenberg E, Verkes RJ, Sabbe BGC, Ruigt GSF, Hulstijn W. Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects. Psychopharmacol 2005; 181: 582–94.
3. Adler LE, Olincy A, Waldo M, Harris JG, Griffith J, Stevens K, et al. Schizophrenia, sensory gating and nicotinic receptors. Schizophr Bull 1998; 24: 189–202.
4. Tune LE. Anticholinergic delirium: assessing the role of anticholinergic burden in the elderly. Current Psychosis & Therapeutics Reports 2004; 2: 33–6.
5. Lechevallier–Michel N, Molimard M, Dartigues JF, Fabrigoule C, Fourrier–Reglat A. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. Br J Clin Pharmacol 2005; 59: 143–151.
6. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 2006; 332: 455–592.
7. Nishiyama K, Momose T, Sugishita M, Sakuta M. Positron emission tomography of reversible intellectual impairment induced by long–term anticholinergic therapy. J Neurol Sci 1995; 132: 89–92.
8. Kimura Y, Ohue M, Kitaura T, Kihira K. Amnesic effects of the anticholinergic drugs, trihexyphenidyl and biperiden: differences in binding properties to the brain muscarinic receptor. Brain Res 1999; 834: 6–12.
9. Nerat T, Kos M. Analysis of inappropriate medication prescribing in Slovenian elderly patients based on the Beers and Laroche criteria. Zdrav Var 2011; 50: 34–44.
10. Ogino S, Miyamoto S, Tenjin T, Kitajima R, Ojima K, et al. Effects of discontinuation of long–term biperiden use on cognitive function and quality of life in schizophrenia. Prog Neuropsychopharmacol Biol Psych 2011; 35(1): 78–83.
11. Johnstone EC, Crow TJ, Ferrier IN, Frith CD, Owens DG, Bourne RC, et al. Adverse effects of anticholinergic medication on positive schizophrenic symptoms. Psychol Med 1983; 13: 513–27.
12. Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. Postgrad Med J 2004; 80(945): 388–93.
13. Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Kirshner MA, et al. A model of anticholinergic activity of atypical antipsychotic medications. Schizophr Res 2006; 88: 63–72.
14. Pirtošek Z. 'Bad guys' among the antiparkinsonian drugs. Psychiatr Danub 2009; 21(1): 114–18.
15. Schatzberg AF, Cole JO, DeBattista (eds): Manual of Clinical Psychopharmacology, 222–6. Arlington: American Psychiatric publishing, 2007.
16. Cancelli I, Beltrame M, Gigli GL, Valente M. Drugs with anticholinergic properties: cognitive and neuropsychiatric side–effects in elderly patients. Neurol Sci 2009; 30: 87–92.

Diagnosis	Gender	Age (years)	Daily biperiden dosage (mg)	Improvement of MMSE
Schizophrenia	M	56	4	+8
Delusional disorder	F	74	2	+4
Alzheimer's dementia	F	89	6	+3
Dementia of mixed etiology, depression	F	75	6	+6

Table 1. *Improvement of MMSE and dosage of biperiden.*

MMSE – Mini Mental test score