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ORIGINAL ARTICLE

Delirium secondary to intrathecal baclofen

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Study design: Retrospective study based on a revision of the clinical histories of all patients carrying an intrathecal baclofen (ITB) infusion system between July 1988 and March 2007 in a neurorehabilitation hospital.
Objectives: To describe the psychiatric manifestations due to intoxication or withdrawal of ITB and to explore the possible risk factors for the presentation of delirium secondary to baclofen.
Setting: Spinal Cord Injury Unit in Barcelona, Spain.
Methods: We selected patients who presented delirium related to baclofen treatment. We filtered these cases by the search of key words. All the compatible episodes were then reviewed and positive cases were confirmed to perform a descriptive analysis of the different variables. Control subjects were randomly selected for a comparative analysis of the aspects of interest.
Results: A total of 12 of the 126 patients carrying the intrathecal system in our hospital presented delirium related to baclofen. Eight cases due to intoxication (66.6%) and four due to withdrawal (33.3%) were found. We provide a description of the psychiatric symptoms. There were no fatal cases due to delirium.
Conclusion: Delirium has a frequency of 9.5% in patients carrying the ITB infusion system, intoxication being more frequent than withdrawal.
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Keywords: spasticity; baclofen; withdrawal; intoxication; delirium

Introduction

Baclofen is a γ-aminobutyric acid analog that produces muscle relaxation by binding to presynaptic γ-aminobutyric $acid_B$ receptors in dorsal horns of the spinal cord. It inhibits both monosynaptic and polysynaptic stretch reflexes and diminishes the release of neurotransmitters by the presynaptic terminals.[1]

Oral baclofen is considered to be ineffective for treatment of spasticity in 25–35% of cases due to either a lack of response or the appearance of adverse intolerable effects during dosage increases.[2] To reduce the side effects and improve the antispastic action, baclofen administration through an intrathecal route began in 1984. This permitted higher concentrations in the central nervous system than the oral route.[3]

Baclofen was approved in June 1992 by the US Food and Drug Administration as an intrathecal treatment with a constant infusion device (baclofen pump). Medtronic's continuous infusion system (SynchroMed II Programmable Infusion System) has thus far been implanted in more than 65 000 people around the world. The system has proved to be effective and safe over the long term, and it is cost-effective in comparison with conventional medical treatments.[1,4]

Withdrawal is a risk situation associated with the use of baclofen. It exhibits a physical component characterized by pruritus without rash, tachycardia, hypotension, diaphoresis, diplopia, tremor, fever, spasticity, convulsions, hyperthermia and rhabdomyolysis,[5,6] and a psychiatric component with hallucinations, confusion, agitation and delusions.[7–9]

Symptoms begin 12–72 h after dose reduction or suppression and respond 24–72 h after the restoration of treatment and support measures. These manifestations are reminiscent of malignant neuroleptic syndrome secondary to antipsychotic and antidopaminergic drugs.[10]

In patients receiving intrathecal baclofen (ITB), some causes of withdrawal include obstruction or dislocation of the catheter, pump reservoir malfunction and low reservoir level; therefore, the evaluation of patients with symptoms of withdrawal must include a system review.[1] In case of pump malfunction, there is a rapid decrease in the cerebrospinal fluid concentration of baclofen and symptoms appear rapidly after 12–24 h.[11] Withdrawal to ITB seems to be a more serious problem than withdrawal to oral baclofen, and

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the systemic symptoms are usually more severe than the neurological and psychiatric ones.[12]

On the other hand, the baclofen intoxication syndrome causes neurological and cardiovascular manifestations secondary to the γ-aminobutyric acid and cholinergic effects. These manifestations consist of disorders of consciousness, drowsiness, ataxia, confusion, hypotonia, depression of the respiratory and cardiovascular centers, and convulsions.[13] Psychiatric symptoms, such as hallucinations and maniac episodes, have been reported in cases of chronic intoxication.[14]

Many patients with intoxication recover quickly as the average life of baclofen is 2–6 h; it is possible, however, to extend this lifetime up to 34.5 h.

Secondary psychiatric manifestations to baclofen withdrawal or intoxication fit with the diagnosis of delirium or confusional state by medications, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV-TR).[15] Symptoms include decreased consciousness, inversion of the sleep–wake cycle, cognitive disorders, delusions and hallucinations, and all of these have a fluctuating presentation pattern throughout the day.

We have a population of patients with neurological diseases in our center (Institut Guttmann, Neurorehabilitation Hospital), and most of these are spinal cord injury patients carrying a continuous infusion system. We intend to describe our experience about delirium in patients with severe spasticity receiving ITB.

Objectives

- To describe delirium due to intoxication or withdrawal of ITB in patients with a constant flow infusion system.
- To determine the frequency of this alteration in the implanted patients.
- To explore possible risk factors for the presentation of delirium secondary to ITB.

Methodology

We performed a retrospective cohort study based on a review of the clinical histories of all the patients carrying an ITB infusion system for spasticity treatment of spinal or cerebral origin.

The infusion pump system implanted in our hospital is Medtronic SynchroMed EL models 8626, 8627 and SynchroMed II model 8637. The follow-up period was from July 1988 to February 2006. Patients were observed between 1 and 14 years.

From 126 patients carrying the intrathecal system, we selected those who presented confusional state related to baclofen infusion. The cases were filtered by the following search of key words: intoxication, withdrawal, psychiatric evaluation, delirium, confusion, drowsiness, insomnia, delusions, hallucinations, disorientation and agitation.

All the compatible episodes were then reviewed and positive cases were confirmed to perform a descriptive analysis of the different variables.

A total of 12 of the 126 patients carrying the intrathecal system in our hospital presented delirium related to baclofen. To study differences between the patients who presented confusional state and those who did not, we randomly selected 12 control patients from the total ITB population studied without a history of delirium, intoxication or withdrawal from baclofen. These patients were homogeneous for age, sex, injury level, time of implantation of the pump and baclofen dose.

The complete group was comprised of 24 patients (83.3% men, mean age 44.7 years). All patients had spinal cord injury, 66.7% due to traumatic etiology and 33.3% non-traumatic etiology.

We collected the following data from all the subjects included in the study:

- Demographic and clinical characteristics: age, sex, level of injury, time from the implantation of the system, baclofen dose and mortality outcome.
- Episode characteristics: age, presence of fever, presence of cognitive impairment, presence of depression, number of drugs (overmedication >9 drugs), psychoactive medication use, etiology of the episode (withdrawal or intoxication) and neuropsychiatric symptoms (confusion, drowsiness, insomnia, delusions, hallucinations, disorientation and agitation).

We calculated frequencies and percentages for categorical demographic and clinical variables and means and standard deviations for continuous variables.

Group comparisons were performed by the χ^2-test, Fisher's exact test or Mann–Whitney non-parametric test, as appropriate, at the 95% confidence level. We performed statistical analysis using SPSS for Windows, version 14.0.

The collected data were treated in accordance with confidentiality procedures in our hospital, and we obtained prior approval of the study from the research and ethical committee.

Results

The frequency of delirium secondary to ITB in our sample was 9.5% in the 14 years of follow-up. Eight cases of intoxication (66.6%) and four cases of withdrawal (33.3%) were present. We did not have fatal cases during the episode of baclofen delirium.

The average dose of ITB on those subjects with delirium was 266 mg day^{-1}. We did not observe any statistically significant difference between the doses received by cases and controls, and there was no difference in the average dose for patients with intoxication versus withdrawal.

Only 1 out of the 24 patients studied was overmedicated (more than nine drugs), and 41.7% of patients were taking psychoactive medication.

A total of 3 (25%) of 12 patients with delirium had a fever at the time of the onset of the psychiatric symptoms, and 4 (33.3%) presented baseline cognitive impairment.

We did not observe differences in sex, age at the time of implantation of the system, injury level, baclofen dose, use

Table 1 Characteristics of patients

	Patients with delirium (n = *12*)	*Patients without delirium* (n = *12*)
Mean age	51 years (s.d. 14.1)	38.5 years (s.d. 15.9) ($P=0.8$)
Male sex	83.3%	83.3%
Etiology	83.3% traumatic	50% traumatic ($P=0.1$)
Level of injury/AIS		
	C3 AIS C ($n=2$)	C4 AIS C ($n=1$)
	C4 AIS C ($n=1$)	C6 AIS C ($n=1$)
	C5 AIS C ($n=1$)	C6 AIS B ($n=1$)
	C6 AIS B ($n=1$)	C7 AIS C ($n=1$)
	C6 AIS C ($n=2$)	C8 AIS A ($n=1$)
	C7 AIS B ($n=1$)	T4 AIS B ($n=1$)
	T6 AIS C ($n=1$)	T4 AIS A ($n=2$)
	T7 AIS A ($n=1$)	T4 AIS C ($n=1$)
	T11 AIS A ($n=1$)	T5 AIS A ($n=1$)
	T11 AIS D ($n=1$)	T6 AIS C ($n=1$)
		T7 AIS B ($n=1$)
Depression	58.3%	33.3% ($P=0.2$)
Overmedication >9 drugs	0	8.3% ($P=0.5$)
Psychoactive medication	41.7%	41.7% ($P=0.6$)
Cognitive impairment	33.3%	8.3% ($P=0.15$)
Baclofen dose	266 μg day^{-1} (s.d. 187.8)	222 μg day^{-1} (s.d. 171.1) ($P=0.4$)

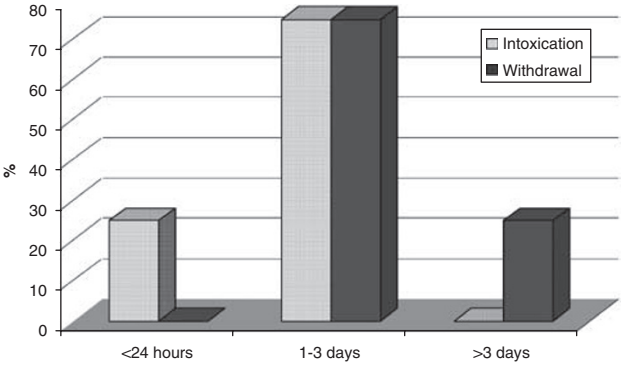

Figure 1 Duration of delirium.

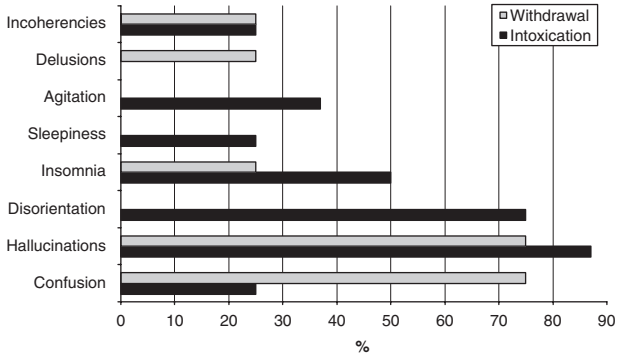

Figure 2 Neuropsychiatric symptoms of delirium.

of psychoactive medication, presence of fever, cognitive impairment, depression and long-term mortality.

Table 1 shows the clinical characteristics of all patients studied.

Intoxication symptoms coincided with the first filling of the pump in four patients, after pump refill in two patients and after a dose increase during a refill in two patients. The average time from the pump implantation to the presentation of the intoxication symptoms was 8 months (from day 1 to 4.5 years).

Withdrawal causes were due to empty pump reservoir in two cases and end of battery life in two cases. The average time from the pump implantation to the presentation of withdrawal symptoms was 7.4 years (from 4.9 to 9.9 years).

Likewise, we found statistically significant differences in the time from the implantation of the pump to the presentation of the confusional state between groups; this time was greater in cases of withdrawal than in cases of intoxication ($P=0.016$).

Psychiatric manifestations were present for 1–3 days in 75% of the patients with delirium. In the intoxication group, symptoms did not persist beyond the third day and roughly 25% of these patients had symptoms for less than 24 h. These findings are opposite of those in patients with withdrawal. In this group, no patients had symptoms for less than 24 h and 25% of patients presented symptoms for more than 3 days. Figure 1 shows the duration of delirium symptoms.

Intoxication was characterized by visual hallucinations with disorientation and insomnia. In the clinical pattern of withdrawal, confusion with hallucinations and delusions was more prominent. These patients, unlike the cases of intoxication, did not present agitation, drowsiness or disorientation. Figure 2 presents the clinical symptoms of delirium.

Table 2 Treatment of delirium secondary to intrathecal baclofen

Therapeutic measures	*Intoxication cases* (n = *8*)	*Withdrawal cases* (n = *4*)
Modifications of the intrathecal baclofen dose	3	2
Pump stop	2	0
Pump refill	0	1
Supportive measures	2	1
Neuroleptics	2	0
Benzodiazepines	1	1
Total	10	5

The therapeutic interventions used consisted mainly of modifications of the ITB dose and supportive measures. Neuroleptics were not prescribed in withdrawal cases. All the patients received at least one therapeutic intervention, with some of them receiving more than one. Table 2 shows the therapeutic measures.

Discussion

According to the findings of our study, delirium has a frequency of 9.5% in patients carrying the ITB infusion

system. This result is similar to reports of delirium in patients hospitalized for different pathologies ranging from 5 to 20%.[16,17]

In our group of patients, intoxication (6.3%) was more frequent than withdrawal (3.2%). In both cases, the psychiatric symptoms are consistent with the diagnosis of delirium or confusional state according to the DSM-IV-TR.[15]

We provide a description of the psychiatric symptoms in cases of ITB acute intoxication. To date, the cases reported have included only chronic intoxication. In these patients, we found symptoms, such as agitation and drowsiness, that were not observed in our cases of withdrawal.

According to our results, the clinical syndrome of delirium by ITB withdrawal was similar to the description of Leo and Baer.[18] They found auditory hallucinations that were not present in our patients, as are more typical of functional psychosis than organic psychosis.

Delirium associated with baclofen withdrawal occurs in patients who carried a pump for 5–10 years. Intoxication is not related to the duration of the treatment, as we found two cases of intoxication during the first month after implantation of the system.

It was not possible to determine the presence of risk factors described for delirium, such as masculine sex, advanced age, cognitive impairment and depression, in our study. Other risk factors, such as functional dependence, immobility, neurogenic bladder and severe physical disease, are present in all of our cases.[17]

The duration of the clinical episode of delirium was similar to that described in other studies, and the time to complete resolution of the symptoms was 4–72 h (average 42.9 h). It is remarkable that 2 out of 12 patients had symptoms that subsided during several days but then reappeared later for a few hours. Our results suggest that the symptoms seem to extend for a greater amount of time in cases of baclofen withdrawal.

The therapeutic measures established in our hospital are typical and consist of dose modifications and the administration of benzodiazepines and neuroleptics for symptomatic control particularly in cases of agitation.[6]

We did not have fatal cases during the episode of baclofen delirium, and the mortality outcome was not different in patients with delirium or without it. This, in spite of studies in different medical contexts, associates delirium with a high mortality.[19]

Conclusion

Owing to the high frequency of delirium caused by intoxication or withdrawal of ITB, this drug must be used with caution in patients with risk factors for confusional state such as increasing age, cognitive impairment, use of multiple medication specially with anticholinergic properties and benzodiazepines. Patients with severe spasticity often present predisposing factors like immobility, high functional dependence and bladder catheterization.

Although delirium is by definition transient and does not leave sequelae from the psychiatric standpoint, it is essential to make appropriate diagnoses and interventions to reduce the morbidity and long-term mortality associated with this condition.

Finally, it is important to educate rehabilitation physicians and emergency unit doctors regarding the clinical pattern of delirium associated with ITB. We must also inform patients of the symptoms of intoxication or withdrawal and the importance of early consultation.

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