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Excessive daytime sleepiness in patients on intrathecal analgesia for chronic pain

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ABSTRACT. **Objectives:** ***Intrathecal (IT) drug administration is an advanced technique in pain treatment algorithm for patients poorly responsive to systemic pharmacological treatment or less invasive techniques. The aim is to improve analgesia lowering side effects; despite this premise, many side effects of long term IT therapy have been described, mainly related to opioid administration. We observed, in some of the patients regularly followed for pump refills in our Pain Unit, the appearance of excessive daytime sleepiness (EDS) interfering with daily life and work activity; this study aims to investigate the incidence of EDS in patients on IT analgesia with opioid or non-opioid drugs and its possible relationship with respiratory problems during sleep.***
Materials and Methods: ***21 patients on IT therapy for chronic pain answered the Epworth Sleepiness Scale (ESS). The incidence of EDS in patients receiving IT opioids was compared to a control group not receiving opioids. In 10 patients, who performed polysomnography (PSG) and maintenance of wakefulness test (MWT) for sleep complaints, we studied the relationship between PSG data and ESS scores and we verified the concordance of ESS and MWT results.***
Results: ***38% of the patients reported EDS, according to ESS data; all the patients with EDS were receiving an IT opioid. Even if some patients presented sleep apneas, we failed to correlate this data with daytime sleepiness. Subjective sleepiness is confirmed by the results of MWT.***
Conclusion: ***Our data demonstrate that EDS is a frequent and important side effect of IT analgesia and it seems related to opioids administration.***

Key words: *intrathecal therapy, chronic pain, opioids, excessive daytime sleepiness, polisomnography.*

RIASSUNTO. ***Obiettivo:*** **la somministrazione intratecale (IT) di farmaci è una tecnica avanzata nell'algoritmo terapeutico di pazienti con dolore cronico che non hanno trovato beneficio dalle terapie farmacologiche sistemiche o da tecniche antalgiche meno invasive. L'obiettivo è quello di migliorare l'analgesia riducendo gli effetti collaterali; nonostante questa premessa, sono stati descritti numerosi effetti collaterali dalla terapia IT, soprattutto dalla somministrazione di oppioidi. Nel corso degli anni, abbiamo osservato in alcuni pazienti seguiti regolarmente presso la nostra Unità di Terapia del Dolore per il rifornimento periodico della pompa la comparsa di eccessiva sonnolenza diurna (EDS) che interferiva con le attività della vita quotidiana e lavorative. Questo studio ha lo scopo di valutare l'incidenza di EDS in pazienti trattati con la somministrazione IT di analgesici oppioidi e non oppioidi e la sua possibile relazione con un'alterazione respiratoria durante il sonno.**
Materiale e metodo: **21 pazienti seguiti presso l'Unità di Terapia del Dolore con analgesia IT hanno compilato la Scala di Epworth sulla sonnolenza (ESS). L'incidenza di EDS nel gruppo**

Introduction

Intrathecal (IT) drugs administration, and in particular opioids administration, is an advanced technique in pain treatment algorithm for patients with chronic pain of different nature who have failed less invasive treatments and systemic drugs therapies. The IT route allows a better analgesia administering the drugs closer to their site of action (receptors or ionic channels) with lower dosages and less side effects related to systemic distribution (1). Nevertheless, a number of long term side effects have been described, particularly associated with chronic IT opioids administration: hormonal disfunctions for hypothalamic-pituitary suppression (in particular gonadic hormones), pedal edema due to increased release of Antidiuretic Hormone (ADH), constipation, nausea, hyperalgesia, neurologic impairment due to catheter tip granuloma formation, alteration of immune response and chronic respiratory depression (2).

In our Pain Centre we have been following chronic pain patients with spinal drugs administration through implantable pumps for 17 years.

Some years ago, some patients began to complain of excessive daytime sleepiness interfering with their daily activity.

Excessive daytime sleepiness associated with chronic systemic opioid therapy has been documented in patients with chronic non cancer pain (3, 4) and in patients on maintenance therapy due to an history of drug abuse (5, 6).

Even if it has been stated that, in patients with chronic pain, daytime sleepiness seems to be mainly related to poor night sleep due to pain or depression (3), many papers demonstrate the interference of chronic opioid therapy with sleep architecture and sleep apnea (7, 8, 9, 10, 11, 12, 13, 14, 15,16) related to sleepiness.

To our knowledge, daytime sleepiness in patients receiving IT opioids for chronic pain has never been assessed. A literature search for the words IT opioids and daytime sleepiness or lethargy or hypersomnia or somnolence failed to find any specific paper on the topic. Only in a work of Kumar and coworkers of 2001 (17), lethargy was listed among the more common side effects of chronic IT opioid infusion.

The aim of this study was to evaluate the incidence of subjective daytime sleepiness, its relationship with the

di pazienti in terapia oppioide è stata confrontata con l'incidenza nei pazienti che non ricevevano un farmaco oppioide IT. In 10 pazienti che hanno eseguito una polisonnografia (PSG) e test multipli di vigilanza (MWT) per disturbi del sonno, abbiamo studiato la relazione tra i dati della PGS e il punteggio della ESS e verificato la concordanza tra ESS e i risultati dei MWT.
Risultati: **il 38% dei pazienti studiati risultava positivo per EDS, secondo i parametri della ESS; tutti i pazienti con EDS erano in terapia con un oppioide IT. Alcuni pazienti presentavano apnee notturne ma non vi era una correlazione evidente con la sonnolenza diurna. I risultati della ESS sono stati confermati dai MWT.**
Conclusioni: **i nostri dati dimostrano che l'EDS è un effetto collaterale frequente e importante dell'analgesia IT e sembra correlata alla somministrazione di oppiodi.**

Parole chiave: terapia intratecale, dolore cronico, oppioidi, sonnolenza diurna eccessiva, polisonnografia.

drugs used and with sleep disorders in patients receiving IT therapy for chronic non cancer pain of different origin not responsive to systemic or less invasive therapies.

Methods

A retrospective analysis of a cohort of patients treated with an intrathecal drug delivery system for chronic pain.

The study was approved by the Institutional Ethical Committee. Confidentiality was obtained through name and medical record number replacement.

Patient population and evaluation method

The study population included all the patients (n=21) who received spinal drugs for chronic non-malignant pain, regularly followed for refills at the Chronic Pain Unit of Maugeri Foundation, Pavia, in the period from May 2009 to September 2011.

All patients had an implantable pump, fix flow or programmable. The patients presenting with pain as the main symptom were tested with a spinal catheter connected through a port to an external pump. Morphine and, since 2007, ziconotide were the main tested drugs, administered alone or in combination in agreement with the guidelines of the Polyanalgesic Consensus Conference 2007 (2): morphine was tested first in patients with nociceptive or mixed pain, while ziconotide was tested first in patients with neuropathic pain. In case of patients experiencing side effects or failing to obtain sufficient analgesia with one drug, the other was consequently tested during the trial period. A pump was implanted only when the patient obtained adequate analgesia (usually more than 50% pain relief, even if priority was patient satisfaction). After the pump was implanted, either the analgesic IT drug could be replaced or other drugs could be added, to compensate loss of effectiveness or long-term side effects. Patients with pain and spasticity due to spinal lesions were tested with a baclofen bolus; if spasticity improved, a programmable pump was implanted and, once an adequate control of spasticity was reached with baclofen, an analgesic drug was added for pain relief.

To document the incidence of EDS in this patient population, we used the Epworth Sleepiness Scale (ESS) (18) Italian version (19), a simple, self-administered questionnaire for the measurement of daytime sleepiness. A score >10 indicates EDS. Even if some patients repeated the ESS for clinical monitoring, for the purpose of this study we considered the score of the first testing only; daily drug dosages, time of therapy, pain intensity were considered at that time. However, 22 ESS evaluations are reported, because one patient (Patient 3) repeated the evaluation after a complete withdrawal from IT opioids and a switch to ziconotide.

Pain intensity, measured with Numerical Rating Scale (where 0 is no pain and 10 worst possible pain) (20), was collected from patient files.

Basic demographic data were collected as well as the pain type that motivated pump placement.

To evaluate the possible relationship of daytime sleepiness with IT opioid therapy we stratified the patients in two groups; the first group included all patients receiving an opioid (morphine, hydromorphone or fentanyl), while the second group included patients receiving no IT opioids; as other analgesic drugs like bupivacaine and clonidine were always associated to an opioid in our patient series, the sole IT analgesic used for this group was ziconotide. In the opioid group we evaluated the possible relationship between different variables and ESS.

Maintenance of wakefulness test and polisomnography

Ten patients on IT analgesic treatment referring sleep complaints performed, for clinical purposes, full standard polysomnography (PSG) aimed at investigating disorders of sleep architecture and of breathing during sleep that can interfere with daytime sleepiness (21) and maintenance of wakefulness test (MWT), a widely accepted objective measure of the individual's ability to remain awake (22). PSG and MWT were performed and analysed according to the American Academy Sleep Medicine (AASM) standards (23, 24).

Central Sleep Apnea (CSA) and Obstructive Sleep Apnea (OSA) were diagnosed according to international classification of sleep disorders (22). In brief, for CSA, the presence of a central apnoea-hypopnoea index (AHI_c) >5 events/hour of sleep and, for OSA, the presence of an obstructive apnea-hypopnea index (AHI_o) >15 independently of symptoms, or an AHI_o >5 in the presence of symptoms.

In this smaller group of patients we evaluated the concordance of MWT and the ESS and the possible interference of the IT therapy with sleep parameters.

Statistical analysis

Differences in terms of discrete variables between subgroups were tested with the Fisher Exact Test. Deviations from the normal distribution were tested by the Shapiro Test for normality. Differences in terms of quantitative variables distribution were tested by the Student's T-test (when the distribution was normal [Shapiro $p>0.05$]) or by the Wilcoxon Rank-Sum Test (when the distribution deviated from the normal distribution [Shapiro $p<0.05$]).

Sleep and MWT data analysis was performed by means of non-parametric test. Kruskal-Wallis Anova Test was used to assess differences between groups and Spearman Rank test was used to assess correlations between continuous variables.

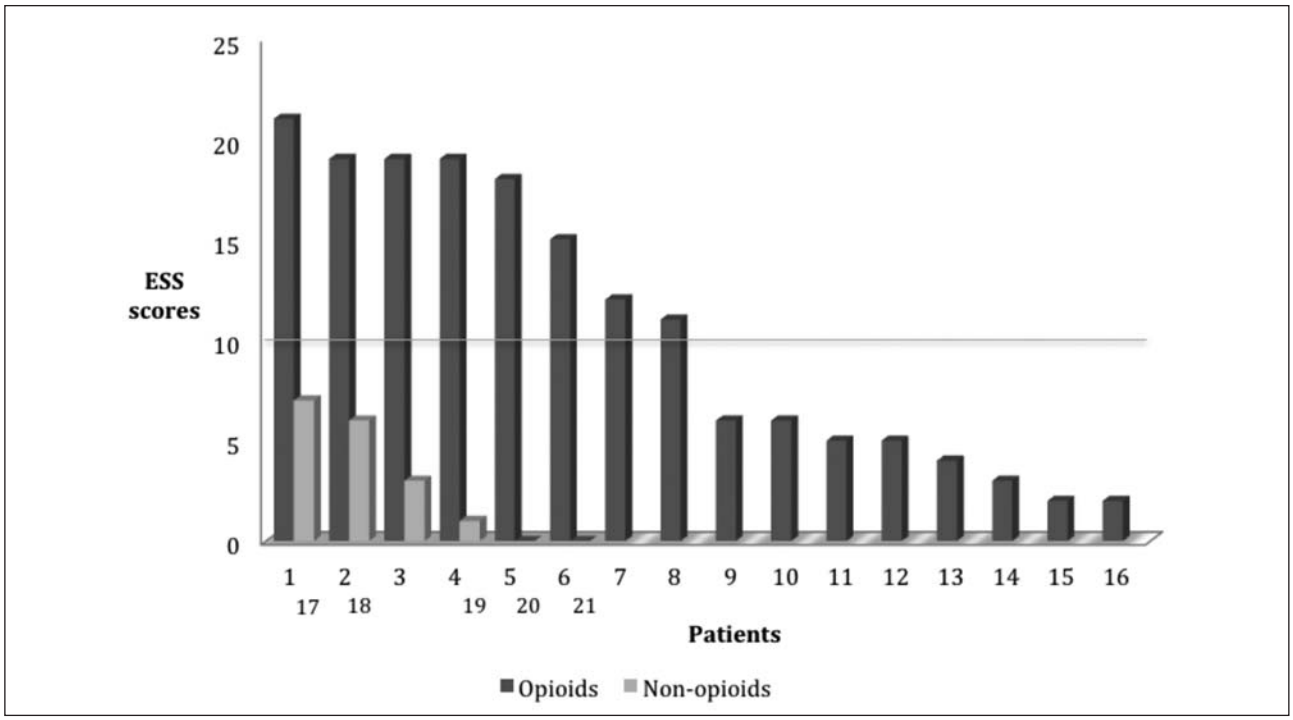

Figure 1. *ESS scores for each patient. For patient 3, two scores are represented, during opioid and non-opioid IT therapy*

The threshold for identifying statistically significant associations has been set to p-value <0.05. All statistical procedures were performed by the R statistical Software (www.r-project.org/).

Results

ESS evaluation

EDS was present in 8 of the 21 patients at their first evaluation (38%); all the patients with ESS score > 10 were in treatment with an IT opioid (Figure 1). In the IT opioid patients group, 50% of subjects were positive for EDS. The expected incidence of EDS in European general population is 8.7% (25).

Demographic data, different IT therapies, as well as pain type and intensity and treatment duration are listed in Table I. The majority of patients were also on a systemic drug therapy for pain management but only 4 used systemic opioids (Table II). Although the same drugs classes are present in both groups, in the non-opioid group a higher percentage of patients takes medications possibly interfering with sleep: opioids, antiepileptic drugs, antianxiety drugs, muscle relaxants or antidepressants. The use of these classes of drugs is related to the prevalence of neuropathic pain.

The two groups were comparable in terms of age and body mass index (BMI) (a parameter related to sleep apnea and daytime sleepiness), while differences in duration of IT therapy were present (the treatment durations with opioid and ziconotide were considered separately for the patient that changed therapy): the treatment was longer in patients in the opioid group because ziconotide (the only analgesic drug administered in the non-opioid group) became commercially available in Italy only since 2007. Average pain intensity was similar in the two groups, while the predominant pain type was neuropathic in the non-opioid group and mixed in the opioid group (Table III).

In the opioid patients group we investigated the possible relationship between daytime sleepiness (by considering ESS as dependent variable) and different variables, like spinal opioid daily dosage (expressed in morphine equivalent), time of spinal opioid therapy (months since beginning), age, pain intensity, BMI.

The statistical analysis, comparing the association of different variables with the ESS, considered as dependent variable revealed no relationship between positivity to ESS and any of the variables tested (Table IV).

Sleep and opioids in patients performing PSG and MWT

Demographic, anthropometric and sleep data of the ten patients who performed PSG and MWT are reported in Table V. No differences were found for age, BMI, MED and sleep data between patients with normal or elevated ESS score. Patients with ESS >10 presented a mean sleep latency lower than in patients with ESS < 10 during MWT (12.7±14 min versus 39.2±1.5 min; Mann-Whitney test Z 2.5, p=0.003).

Mean sleep latency during MWT was reduced (<30 minutes) in five patients, all of them with ESS >10. Sleepier patients were found to have higher percentage of light sleep and more frequent episodes of central apnea or central hypopnea (Table VI). The morphine equivalent dose was higher in patients with reduced mean sleep latency in comparison with those with normal sleep latency at MWT, even if this difference was only a trend to statistical significance (p<0.07) (Table VI). According to Spearman Rank test, mean sleep latency at MWT was significantly correlated to percentage of N_2 sleep (-0.73, p<0.05) and to index of central apnea-hypopnea (-0.79, p<0.01). Finally, the mean equivalent dose of morphine

Table I. ***Patient population demographic data, time of therapy, pain type and intensity (NRS), intrathecal therapy and ESS.*** In the lighter lines are listed the patient on IT opioids; in the darker lines the non-opioid patients. Patient 3 is present in both groups

Pt	Sex	Age	BMI	Months of Therapy	Pain Type	Spinal Therapy (mg or ug/day)	Morphine Equivalents	NRS	ESS
1	F	50	20,72	122	Mixed	Morphine 6	6	7	21
2	F	46	20,4	50	Nociceptive	Morphine 10	10	6	19
3	F	30	22,14	34	Mixed	Morphine 5 Clonidine 100	5	8	19
4	F	52	27,34	11	Neuropathic	Hydromorphone 0,6	3	7	19
5	F	52	16	14	Nociceptive	Morphine 3	3	6	18
6	F	69	27,34	163	Mixed	Morphine 0,75 Hydromorphone 0,45	3	9	15
7	M	47	33,2	10	Neuropathic	Morphine 0,15 Baclofen 240	0,15	7	12
8	M	60	35,86	93	Nociceptive	Hydromorphone 1,75	8,75	7	11
9	F	73	28,9	140	Mixed	Morphine 7	7	3	6
10	F	38	25,4	4	Neuropathic	Morphine 1,5 Hydromorphone 0,125 Clonidine 37,5	2,125	0	6
11	F	63	24,22	125	Mixed	Morphine 2,7 Bupivacaine 0,7	2,7	10	5
12	F	61	26,48	37	Nociceptive	Morphine 4 Clonidine 40	4	7	5
13	F	55	27,86	83	Mixed	Morphine 0,75	0,75	5	4
14	F	57	31,25	148	Mixed	Morphine 2,5 Hydromorphone 0,85	6,75	8	3
15	F	50	30	83	Nociceptive	Morphine 1,15 Fentanyl 1,4	2	7	2
16	M	47	28,33	28	Neuropathic	Morphine 4 Ziconotide 3	4	8	2
17	M	63	29,41	11	Neuropathic	Ziconotide 6	//	8	7
18	M	31	24,7	20	Neuropathic	Ziconotide 3 Baclofen 50	//	3	6
3	F	32	19,37	24	Mixed	Ziconotide 5,7	//	8	3
19	F	70	24,16	10	Neuropathic	Ziconotide 6	//	5	1
20	F	65	25,66	8	Neuropathic	Ziconotide 4,7 Baclofen 160	//	3	0
21	F	57	33	18	Mixed	Ziconotide 2,5	//	8	0

was statistically significantly correlated to the central apnea-hypopnea index (Spearman Rank 0.6, $p<0.05$).

Four patients showed recurrent central apnea or hypopnea events (>5 events/hour of sleep). Subjects with central sleep apnea presented higher equivalent morphine dose (7.7±4.0 versus 2.7±1.9 mg, p=0.04) than patients not experiencing apnea. Similarly, the mean sleep latency during MWT was lower in central sleep apnea patients than in those with no apnea (13.3±9.6 min versus 27.7±17.9 min), but these differences did not reach the statistical threshold.

Nonetheless, a significant association was found between development of CSA and reduced ability to maintain wakefulness during daytime (χ^2 4.44, p=0.03).

Five patients were found experiencing OSA. These subjects were older than patients without OSA (61.8±7.0 yrs versus 49.5±2.5 yrs, respectively; p=0.01). No differences were found between patients with or without OSA for MED, BMI, ESS or PSG indexes.

Discussion

The main finding of our study is that, among patients with chronic severe pain on IT therapy, EDS is a very common side effect. To the best of our knowledge, this is the first study designed to assess the prevalence of subjective (by ESS) and objective (by MWT) EDS and to describe sleep quality in patients with IT therapy.

Despite the study outcome could be limited by the presence of risk factors and bias in the control group, - zi-

Table II. ***Pain related systemic therapy and daily dosage***

Pt	Opioids	NSAIDs acetaminophene	Antiepileptics Antianxiety Agents Muscle Relaxants	Antidepressants
1	//	//	Delorazepam 0,5 mg OD	//
2	//	Acetaminophene 1000 mg OD	//	//
3	//	//	Clonazepam 1,8 mg	//
4	Tramadol 100 mg x2 Morphine 10 mg x 3	//	Clonazepam 1,8 mg	Duloxetine 60 mg
5	//	//	//	//
6	//	Diclofenac 50 mg OD	//	//
7	//	//	Eperisone 100 mg x 2	//
8	//	//	//	//
9	//	//	//	//
10	Oxycodone 10 mg OD Tramadol 50 mg OD	+Acetaminophene 330 mg OD	//	//
11	//	//	Clonazepam 0,4 mg	//
12	//	Diclofenac 100 mg x 2	//	//
13	//	//	Clonazepam 1,8 mg	Nortriptiline 10 mg + Fluphenazine 0,5 mg x2
14	//	//	Lorazepam 1,8 mg	//
15	//	//	//	//
16	//	//	Clonazepam 2 mg	//
17	Morphine 10 mg x 3	Acetaminophene 1000 mg OD	Clonazepam 1,8 mg	//
18	Buprenorphine 52 ug/h	//	Gabapentin 400 mg x 4	Nortriptiline 10 mg + Fluphenazine 0,5 mg x2
3	//	//	Clonazepam 1,8 mg	//
19	//	//	Clonazepam 2 mg	Nortriptiline 10 mg + Fluphenazine 0,5 mg
20	//	//	Clonazepam 0,7 mg	Duloxetine 60 g
21	//	Acetaminophene 500 mg OD	//	//

Table III. ***Distribution of clinical variables in patients treated with opioids (n = 16) and non-opioid IT drugs (n = 6)***

Variable	Opioids	Non opioid	p-value
Therapy (months)*$	66.5 (24.50-122.75)	14.5 (10-19.50)	0.020
Gender – Females – Males	 13 (81%) 3 (19%)	 4 (67%) 2 (33%)	0.585
Age (years)	53.12 ± 10.9	53 ± 17.17	0.987
NRS$	7 (6-8)	6.50 (3.50-8)	0.734
ESS – ≥ 10 – < 10	 8 (50%) 8 (50%)	 0 (0%) 6 (100%)	0.051
Pain Type – Mixed – Neuropathic – Nociceptive	 7 (44%) 4 (25%) 5 (31%)	 2 (33%) 4 (67%) 0 (0%)	0.156
BMI	26.59 ± 5.07	26.05 ± 4.69	0.817

Variable, analyzed variable; Opioids/Non opioid, for discrete variables: counts (frequency, %) of observations within patients treated with opioids and non-opioid IT drugs, for quantitative variables mean ± standard deviation (SD) or median (interquartile range [IQR]) when deviating from normality ($); p, p-value
* denotes statistically significant difference ($p < 0.05$)

Table IV. ***Distribution of clinical variables in patients treated with opioids characterized by ESS < 10 and ESS ≥ 10 respectively***

Variable	ESS < 10 (n = 8)	ESS ≥ 10 (n = 8)	p
Age(years)	55.50 ± 10.72	50.75 ± 11.27	0.402
Gender – Females – Males	 7 (88%) 1 (12%)	 6 (75%) 2 (25%)	 1
Months of therapy	81 ± 54.23	62.12 ± 57.69	0.511
NRS$	7 (4.50-8)	7 (6.75-7.25)	0.787
Dosage	3.67 ± 2.25	4.86 ± 3.28	0.411
BMI	27.8 ± 2.35	25.38 ± 6.8	0.367

Variable, analyzed variable; Opioids/Non opioid, for discrete variables: counts (frequency, %) of observations within patients treated with opioids and non-opioid IT drugs, for quantitative variables mean ± standard deviation (SD) or median (interquartile range [IQR]) when deviating from normality ($); p, p-value
* denotes statistically significant difference ($p < 0.05$)

Table V. ***Demographic, anthropometric, sleep and MWT data***

	Mean (SD)	Minimum	Maximum
Age (yrs)	56.9 (8.3)	46	70
NC (cm)	36.9 (5.1)	30	47
BMI (kg/m2)	25.6 (5.9)	20.3	38.1
MED (mg)	4.52 (3.2)	2	10
ESS	10 (1)	1	18
TST (min)	339.2 (78.3)	180	411
SE (%)	80.7 (18.7)	42.9	98
N_1 (%)	6 (4.35)	1.3	13.1
N_2 (%)	42.5 (18.2)	18.1	67.1
N_3(%)	20.4 (17.5)	0.2	53.8
REM (%)	14.6 (7.3)	4.6	25.7
AHI (ev*hr^{-1})	29 (29.2)	3.3	83.3
OAHI (ev*hr^{-1})	24.6 (25.7)	0	70.8
CAHI (ev*hr^{-1})	4.6 (6.6)	0	20
ODI (ev*hr^{-1})	23.9 (31.7)	1.7	87.9
T_{90} (%)	3.8 (6.6)	0	18.6
MSL (min)	23.3 (17.2)	3	40

Legend
NC = neck circumference. MED = morphine equivalent dose. BMI: body mass index. ESS = Epworth sleepiness score. TST = total sleep time. SE = sleep efficiency. AHI = apnoea-hypopnoea index. OAHI = obstructive apnoea-hypopnoea index. CAHI = central apnoea-hypopnoea index. ODI = oxygen desaturation index. T90 = % of total sleep time spent with SpO2<90%. MSL = mean sleep latency during MWT.

Table VI. ***Demographic, anthropometric and polysomnographic indexes in patients with normal or reduced mean sleep latency (MSL) at MWT.***
Differences were analyzed by Kruskal-Wallis H test

	MSL>30min	MSL<30 min	H (p)
AGE (yrs)	58.4 ± 8.2	55.4±9.2	n.s.
MED (mg)	2.9±2.4	6.1±3.2	3.23 (0.07)
BMI (kg/m2)	25.7 ±5.2	25.5±7.2	n.s.
ESS	5.6±7	14.4±3	n.s.
TST (min)	305±101	373±22.9	n.s.
SE (%)	72.6±24.3	88.8±5.5	n.s.
N1 (%)	7±4.3	5±4.7	n.s.
N2 (%)	29±10.7	55.9±13.3	4.8 (0.02)
N3 (%)	26.9±19.9	13.9±13.6	n.s.
REM (%)	17.7±7.7	11.5±6.1	n.s.
AHI (ev*hr^{-1})	20.3±14.8	37.8±38.8	n.s.
OAHI (ev*hr^{-1})	19.8±15	29.4±34.6	n.s.
CAHI (ev*hr^{-1})	0.5±0.4	8.7±7.5	6.9 (0.008)
ODI (ev*hr^{-1})	10.2±9.2	37.5±41.4	n.s.
T_{90} (%)	1.1±1.8	6.6±8.7	n.s.

Legend
MED = morphine equivalent dose. BMI: body mass index. ESS = Epworth sleepiness score. TST = total sleep time. SE = sleep efficiency. AHI = apnoea-hypopnoea index. OAHI = obstructive apnoea-hypopnoea index. CAHI = central apnoea-hypopnoea index. ODI = oxygen desaturation index. T90 = % of total sleep time spent with SpO2<90%.

conotide (26) and systemic drugs have a potential for somnolence - it seems that EDS is mainly related to IT opioids, as it has already been documented with their systemic use.

One of our younger patients, during treatment with morphine, complained of severe daytime sleepiness that completely resolved when morphine was discontinued because of amenorrhea and substituted with ziconotide at a dosage up to 6.5 ug/day; clonidine associated with morphine and, initially, to ziconotide did not modify this outcome.

In a long-term follow up study of 16 patients on chronic IT therapy, Kumar and coworkers reported that lethargy was among the more common (75% of patients) and lasting side effects of morphine therapy. In the majority of patients this side effect persisted albeit decreasing in severity over time (17). Sleepiness is a known side effect of acute opioid administration or occurring at the beginning of chronic therapy, however tolerance occurs quite rapidly as these analgesics are used for a long time.

On the contrary, our experience indicates that patients who begin IT opioid therapy switching from systemic therapy refer less confusion and sleepiness. However, sleepiness tends to reappear over time and its interference with daily living and work can become a disabling condition. Four patients in our group referred that daytime sleepiness interfered with their daily activity, in particular with driving ability, and that this side effect began or worsened years after the beginning of IT therapy, even if we could not document a relation of this symptom with the duration of therapy.

According to the Polyanalgesic Consensus Conference 2012 on morbidity and mortality related to IT therapy, somnolence is considered one of the symptoms of respiratory depression (27). However, none of the patients enrolled in the present study showed clinical or PSG signs of respiratory depression.

Development of central events during sleep has been reported in patients receiving opioids therapy as well as in subjects receiving stable methadone maintenance treatment (5-14). Webster and coworkers found a direct relationship between the central apnea index and the daily dosage of methadone or benzodiazepines in a group of patients receiving oral opioid therapy for chronic pain (9). Unfortunately, no data are reported about the prevalence of EDS.

In a retrospective study, Walker and collaborators found a higher prevalence of central apneas in patients with chronic opioid use for chronic pain compared with patients not taking opioids (8). In contrast with our data, this group found a dose-response relationship between morphine dose equivalent and both obstructive and central apnea indexes. However, no differences were found for ESS between patients with or without opioid therapy (8).

We failed to demonstrate a relationship between sleepiness and opioid dosage in the general group of opioid patients and this can be attributed to the small number of patients observed in this study. Notably, there is no relationship between IT opioid daily dosage and the probability of EDS.

We showed that opioid dosage correlates with sleepiness and central apnea or hypopnea in the smaller group of patients performing PSG and MWT, even if these patients had the bias of presenting sleep complaints. The small size of the sample precludes a conclusive explanation of this finding.

MWT is a test that objectively measures the sleep propensity in a standard situation avoiding any possible bias related to subjective sensation. In our study we found a correlation between subjective and objective sleepiness: 5 patients of the 6 with ESS > 10 presented reduced mean sleep latency during MWT and none of the patients with ESS < 10. However, because of the small number of patients, there was no significant correlation between the mean values of ESS in patients with sleep latency > or <30 minutes.

Even if long-term effectiveness of IT therapy was not among the objectives of this study, it can be noted that the mean NRS values are in the range of moderate to severe pain (7 and 6,5 in the two groups); if it is true that effectiveness of IT analgesia reduces over time, the majority of our patients reports from "minimally to greatly improved" at the Patient Global Impression of Change Scale. Only 2 patients referred a complete loss of effectiveness over time.

The majority of our patients is not on a stable IT regimen; trying to reach a better analgesia, therapies vary over time and this can be argued from the number of patients receiving a drug mix; in some patients two opioids are associated due to a progressive switch from a drug to another. Many of our patients tried ziconotide, bupivacaine or clonidine associated to morphine or hydromorphone. Baclofen was associated to analgesic therapy only in patients with spasticity (3) mainly present in the non-opioid group.

Conclusions

Despite the limits of this study - the small number of patients observed and the lack of objective sleep measures (PSG and MWT) in all patient population - we want to signal another possible side effect of long term IT therapy for pain management. Excessive daytime sleepiness is a symptom interfering with patient's quality of life, one of the goals of our treatment. It is persistent over time and especially disabling in younger patients who are still working and with a more active life. We hope that further studies will better understand its relationship to IT analgesics.

Opioids are the only analgesic agents that can be administered systemically and intrathecally; the IT administration of opioids is expected to increase efficacy and reduce central side effects due to lower dosages. This is true for short term side effects but many long term side effects have been reported (17) and their incidence does not seem to differ between systemic and intrathecal route of administration.

Chronic opioid therapy, whichever route of administration is used, should be considered only in patients that do not have other therapeutic options and for whom continuous monitoring is guaranteed. ESS could be a valuable instrument to assess the presence of subjective daytime sleepiness.

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