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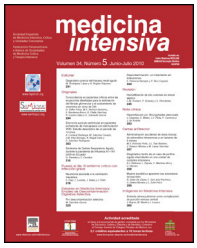

ORIGINAL

Withdrawal syndrome in the pediatric intensive care unit. Incidence and risk factors☆

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KEYWORDS
Iatrogenic withdrawal syndrome;
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Fentanyl;
Midazolam;
Intensive Care Units;
Pediatric

Abstract
Objective: To determine the incidence of withdrawal syndrome after prolonged infusion of fentanyl and midazolam in children, and the associated risk factors.
Design: Historic or retrospective cohort study.
Setting: Pediatric Intensive Care Unit in an academic center.
Patients: Forty-eight pediatric patients who received sedation and analgesia only with fentanyl and midazolam through continuous infusion for at least 48 h.
Interventions: None.
Main variables of interest: Collected data included demographic and clinical parameters, dose and duration of sedation received, and incidence, severity and treatment of withdrawal syndrome.
Results: Fifty percent of the patients developed withdrawal syndrome. There were significant differences between the patients who developed withdrawal syndrome and those who did not, in terms of the duration of infusion and the cumulative doses of both drugs. A cumulative fentanyl dose of 0.48 mg/kg, a cumulative midazolam dose of 40 mg/kg, and a duration of infusion of both drugs of 5.75 days were risk factors for the development of withdrawal syndrome. Most children developed mild or moderate disease, beginning about 12–36 h after weaning from infusion. Methadone was used in most cases for treating withdrawal.
Conclusions: There is a high incidence of withdrawal syndrome in children following the continuous infusion of midazolam and fentanyl. The duration of infusion of both drugs and higher cumulative doses are associated with the development of withdrawal syndrome.

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PALABRAS CLAVE
Síndrome de abstinencia iatrogénico;
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Fentanilo;
Midazolam;
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Pediátricos

Síndrome de abstinencia en Cuidados Intensivos Pediátricos. Incidencia y factores de riesgo

Resumen
Objetivo: Conocer la incidencia de síndrome de abstinencia tras perfusión prolongada de fentanilo y midazolam en niños, y los factores de riesgo asociados.
Diseño: Estudio de cohorte histórica o retrospectiva.
Ámbito: UCI pediátrica de seis camas de un hospital universitario.
Pacientes: Se incluyen 48 pacientes pediátricos que recibieron sedoanalgesia en perfusión continua con midazolam y fentanilo exclusivamente, durante al menos 48 horas.
Intervenciones: Ninguna.
Variables de interés principales: Se recogen datos clínicos y demográficos, dosis y duración de sedoanalgesia recibida, aparición de síndrome de abstinencia, gravedad y tratamiento del mismo.
Resultados: El 50% desarrolló síndrome de abstinencia. Hubo diferencias significativas entre los que lo desarrollaron y los que no en cuanto a duración del tratamiento previo y dosis acumulada de ambos fármacos. Una dosis acumulada de fentanilo de 0,48 mg/kg o de midazolam de 40 mg/kg, y una duración de la perfusión de ambos de 5,75 días fueron factores de riesgo para el desarrollo de abstinencia. La mayoría presentó un cuadro leve o moderado, que comenzó a las 12-36 horas de suspender la perfusión. El fármaco más utilizado en el tratamiento fue la metadona.
Conclusiones: La incidencia de síndrome de abstinencia en niños tras perfusión prolongada de midazolam y fentanilo es elevada. El desarrollo del síndrome se relaciona con tiempos de perfusión prolongados y con dosis acumuladas elevadas de ambos fármacos.

Introduction

Prolonged sedative and analgesic use in children gives rise to tolerance and withdrawal phenomena, which in turn have been related to a prolongation of mechanical ventilation and hospital stay.[1] The literature offers sedation and analgesia guidelines applicable to both pediatric[2] and adult Intensive Care,[3] though no specific protocols are available in reference to the management of withdrawal syndrome (WS) in children. Most of the existing information refers to the use of opiates (OP) and benzodiazepines (BZD), as these are the most widely used drugs in the Pediatric Intensive Care Unit (PICU),[4,5] and almost all the studies have been made in neonates or nursing infants—with very few studies in older children. Moreover, the published studies use different inclusion criteria and diagnostic methods, and the results are analyzed after applying different prevention or treatment protocols. As a result, very few data can be extrapolated to the general population. Based on the subjective impression that we had a high incidence of WS in our PICU, we decided to carry out a study with the primary objective of determining the true incidence of the problem in our Unit, and with the secondary objective of identifying risk factors for the development of WS in our patients.

Patients and methods

A retrospective or historical, single cohort study was made, including all patients admitted to our PICU between January 2004 and July 2007, requiring mechanical ventilation and who received sedoanalgesia in continuous perfusion exclusively with midazolam (MDZ) and fentanyl (FENT) for at least 48 h. Each patient was followed-up on throughout the duration of stay in the Unit. In these patients, on starting weaning from mechanical ventilation, the perfusion of FENT and MDZ was either abruptly suspended or decreased on a gradual basis. The appearance of WS was monitored based on clinical criteria, defining the syndrome as a clinical condition characterized by alterations of the central and/or autonomic nervous system, or gastrointestinal disorders[6] (fundamentally tremor, restlessness, insomnia, tachypnea, fever, arterial hypertension, vomiting or diarrhea), correlated in time to the suspension of sedoanalgesia. Furthermore, we used the Finnegan scale[7] as supporting diagnostic tool (Table 1) in all the patients, since it was the only such instrument available in pediatric practice during the period of the study. In this context, a score of 8 or more and of less than 12 was regarded as consistent with mild WS, while a score of 12–16 corresponded to moderate WS, and a score of over 16 indicated severe WS. The score obtained with this scale is always recorded in the case of patients in whom weaning from mechanical ventilation is started and prolonged perfusion of sedoanalgesia is suspended or reduced. In order to homogenize the results, we excluded all those patients administered some other sedative or analgesic in continuous perfusion additional to MDZ and FENT, as well as those administered replacement drug therapy for the prevention of WS. On the other hand, we also excluded patients who died or were moved to another PICU while receiving sedoanalgesia, along with those presenting disorders that could be confused with WS (since the diagnosis of WS was established on an exclusion basis): severe hemodynamic instability or respiratory failure, or serious neurological damage.

Table 1 The Finnegan scale.

Signs or symptoms	Score
1. Crying	
Acute	2
Continuous	3
2. Duration of sleep after feeding	
<1 h	3
<2 h	2
<3 h	1
3. Moro reflex	
Increased	2
Greatly increased	3
4. Tremor	
Mild with stimulation	1
Moderate with stimulation	2
Mild and spontaneous	3
Moderate and spontaneous	4
5. Hypertonia	2
6. Skin excoriations	1
7. Myoclonus	3
8. Seizures	5
9. Perspiration	1
10. Fever	
<38.4 °C	1
>38.4 °C	2
11. Yawning	1
12. Cutis marmorata (marble skin)	1
13. Nasal congestion	1
14. Sneezing	1
15. Nasal flutter	2
16. Respiratory frequency	
>60	1
>60 and retraction	2
17. Excessive suctioning	1
18. Inappetence	2
19. Regurgitation	2
20. Vomiting	3
21. Diarrhea	
Pasty	2
Watery	3

Clinical and demographic parameters were recorded such as age, gender, body weight, reason for admission and the Pediatric Risk of Mortality Score (PRISM), which expresses the probability of mortality as a percentage. We likewise registered the cumulative FENT and MDZ dose; maximum perfusion and the mean duration of continuous perfusion of both drugs up to the time of suspension or gradual reduction of perfusion; the joint administration or not of a muscle relaxant; the method of MDZ and FENT treatment withdrawal and the duration of the latter; the presence of WS and its severity as determined by the Finnegan scale[7]; and the treatment started and its duration. Since this was a historical cohort with no intervention of any kind, informed consent was not requested from the parents.

The SPSS version 19.0 statistical package was used for analysis of the results. The Student *t*-test, Mann–Whitney *U*-test and chi-squared test were applied to assess differences in the study variables between the two groups. Statistical significance was accepted for $p < 0.05$. Logistic regression analysis was used to analyze the variables that best explained the appearance of WS. To this effect a model was developed in which the dependent variable was withdrawal syndrome (yes/no), and the independent variables were those parameters yielding $p < 0.15$ in the univariate analysis and which did not constitute confounding factors. Logistic regression with the forward stepwise Wald method was carried out. Receiver operating characteristic (ROC) curves were plotted for this explanatory model to assess the predictive capacity of the variables referred to the development of the WS.

Results

During the 42 months of the study a total of 620 patients were admitted to our Unit and were subjected to follow-up for the full duration of admission; of these subjects, 73 required sedoanalgesia in continuous perfusion during more than 48 h. We excluded three patients transferred to another PICU, four who died while receiving sedoanalgesia, 7 administered other sedatives or analgesics in continuous perfusion (propofol, pentothal) in addition to MDZ and FENT, 6 in which replacement therapy was started with methadone and/or benzodiazepines, and 5 patients with severe neurological damage after weaning from ventilation. A total of 48 patients thus met all the inclusion criteria. The characteristics of these 48 patients are summarized in Table 2. The indications of sedoanalgesia were respiratory disease in 50% of the cases, traumatisms in 23%, septic shock in 10.4%, and others in 16.6%. Fifty percent developed WS, though this incidence increased to 80% on selecting the patients with perfusion for more than 5 days. There were no significant differences between the patients who developed withdrawal (WS group) and those who did not (non-WS

Table 2 Clinical and demographic data of the patients.

Total patients	48
Age (median and range)	3 years and 2 months (15 days, 13 years)
Males	60%
Weight (kg)	22.8 ± 16.8
Disease	
Bronchiolitis	18.7%
ARDS	18.7%
Respiratory failure	12.5%
Polytraumatism	12.5%
Severe TMI	10.4%
Septic shock	10.4%
Others	16.8%
PICU stay (median and range, in days)	12 days (5, 90)
Total WS	50%
WS if perfusion >5 days	80%

WS: withdrawal syndrome; ARDS: acute respiratory distress syndrome; TBI: traumatic brain injury.

Table 3 Comparison between patients with and without withdrawal syndrome.

Variables	WS group	Non-WS group	
Number of patients	24	24	
Mortality risk (PRISM)	38.8 ± 31.4%	29.3 ± 28.2%	ns
Duration FENT perf. (h)	320 ± 207.1	91 ± 30.4	$p < 0.001$
Duration MDZ perf. (h)	315.4 ± 207	87.3 ± 30	$p < 0.001$
Cumulative FENT dose (mg/kg)	0.98 ± 0.5	0.29 ± 0.1	$p < 0.001$
Cumulative MTZ dose (mg/kg)	70.5 ± 57.6	20.1 ± 9	$p < 0.001$
Maximum perf. FENT (μg/kg/h)	3.4 ± 1.4	3.1 ± 1.4	ns
Maximum perf. MDZ (mg/kg/h)	0.29 ± 0.1	0.29 ± 0.1	ns
Muscle relaxant	62.5%	25%	$p < 0.001$

FENT: fentanyl; MDZ: midazolam; perf: perfusion; ns: nonsignificant; PRISM: Pediatric Risk of Mortality; WS: withdrawal syndrome. Statistically significant, $p < 0.05$.

group) for any of the demographic variables (age, gender, weight). The data relating to the treatment received and the development of WS are summarized in Table 3. The mean duration of treatment and the cumulative dose of both FENT and MDZ, together with muscle relaxant utilization, were significantly higher in the WS group than in the patients without WS. However, after stratifying the data, muscle relaxant use was identified as a confounding factor, since the patients receiving such medication had also received higher cumulative doses of FENT and MDZ. However, no differences were observed between the two groups in terms of the maximum perfusion dose of both drugs. Of all the variables showing significant differences between the two groups, logistic regression analysis with the forward stepwise Wald method showed the duration of MDZ perfusion to offer the best explanation of the development of WS, with an odds ratio (OR) of 1.061 (95%CI 1.021–1.103). Analysis of the ROC curves (Table 4) of the explanatory model identified the values offering the best sensitivity and specificity, and which most likely would be found in the case of a diagnosis of WS, namely: a cumulative FENT dose of 0.48 mg/kg, a duration of FENT or MDZ perfusion of 5.75 days, and a cumulative MDZ dose of 40 mg/kg. Brusque perfusion suspension was carried out in two patients with WS and in 7 without WS (no significant differences), while gradual suspension was carried out in 22 patients with WS and in 17 without WS. This gradual reduction in the non-WS group was always carried out simultaneously for the two drugs (mean duration of reduction 26.2 ± 11.7 h), while in the WS group the decrease in administration was carried out independently for the two drugs in most cases (decrease in MDZ: median 4 days, range 2–12; decrease in FENT: median 5 days, range 2–14). None of the patients showed discrepancies between the diagnosis based on clinical criteria and the diagnosis established on the basis of the Finnegan score. In this context, all the patients selected according to clinical criteria had a Finnegan score of 8 or higher. The majority developed mild (37.5%) or moderate WS (50%), and the syndrome proved severe in only 12.5%. Practically all of the patients developed clinical manifestations between 12 and 24 h after suspending sedoanalgesia. Treatment consisted of methadone in 87.5% of the cases (median 8 days, range 2–21), at a starting dose of 0.1 mg/kg every 6 h, though in some patients we had to increase the dose to 0.2–0.3 mg/kg. Other drugs used were diazepam in 58.3% of the cases (median 7 days, range 2–14), dipotassium clorazepate in 25%, and clonidine in 16.6%.

Discussion

The present study confirms the high incidence of WS in children following the prolonged use of MDZ and FENT in continuous perfusion. The analysis was limited to patients receiving only MDZ and FENT in continuous perfusion, and who had not received previous preventive or replacement therapy for withdrawal syndrome (WS); accordingly, the only intervention in the study was the gradual reduction of perfusion. We consider this to be the best approach for determining the true incidence of WS with hardly no intervention, since it would not be ethical to brusquely suspend perfusion in all the cases, knowing that the use of OP and BZD in prolonged perfusion produces secondary WS beyond certain cumulative doses or perfusion times.[1] In any case, the incidence found in our patients is high, but consistent with the limited data published to date. Bicudo et al.[8] collected information on 36 children under two years of age administered MDZ and FENT for more than 24 h, with a WS incidence of 50%, coinciding with our own data. Furthermore, in the same way as in our study, on selecting the

Table 4 Analysis of the receiver operating characteristic curves.

Variables	Risk value	Sens	Spec	AUC	95%CI	*p*
Time MDZ (h)	5.75 days	83.3%	91.7%	0.96	0.92–1	<0.001
Time FENT (h)	5.75 days	83.3%	87.5%	0.96	0.91–1	<0.001
Total FENT dose (mg/kg)	0.48	83.3%	87.5%	0.92	0.84–0.99	<0.001
Total MDZ dose (mg/kg)	40	79.2%	95.8%	0.92	0.84–1	<0.001

AUC: area under the curve; Spec: specificity; FENT: fentanyl; 95%CI: 95% confidence interval; MDZ: midazolam; Sens: sensitivity. Statistically significant, $p < 0.05$.

patients subjected to perfusion for more than 5 days, the incidence approached 100%, in concordance with the 86% incidence reported by Franck et al.[9] in another study involving 15 children under 28 months of age receiving OP and BZD perfusion for over 5 days. In the other published study offering data in this respect,[10] a global incidence of 34% was reported–this percentage reaching 49% in the subgroup administered the highest drug doses. A point to be taken into account in the aforementioned studies is the fact that the age of the patients did not exceed two years in most cases, while in our series 24 children were under 22 months of age and the remaining 24 were between 3 and 13 years of age. This implies that our series is one of the few to contribute data on the incidence of WS due to MDZ and FENT in the PICU in pediatric patients not limited to neonates or nursing infants.

The symptoms of our patients were similar to those described in the literature, and although quantification was not possible due to the retrospective cohort design of the study, most of the patients suffered tremor, arterial hypertension, tachypnea, fever, perspiration, vomiting, diarrhea and mydriasis. In the study published by Bicudo et al.,[8] 100% of the subjects presented insomnia, tremor and tachypnea; 83% suffered fever; and a lesser percentage presented symptoms more characteristic of small children, such as excessive suctioning, nasal flutter or an exaggerated Moro reflex. All this coincides with the literature analysis published by Birchley,[6] who concluded that the most frequent symptoms of WS due to OP and BZD in children are tremor, restlessness, irritability, insomnia, tachypnea, hypertension, fever, vomiting and diarrhea.

The mean cumulative FENT dose in the WS group was 0.98 mg/kg, which is similar to that reported by other authors,[8] while the cumulative MDZ dose was 70.57 mg/kg in the WS group–this being higher than the dosage generally described in the few studies that have examined WS due to BZD on an isolated basis.[11–13] There were no differences between the two groups in terms of the maximum perfusion of one drug or the other; this parameter therefore did not constitute a risk factor, in coincidence with the findings of most other investigators. The mean duration of perfusion was 13 days in the WS group, versus 3–4 days in the non-WS group. This likewise coincides with the data found in the literature. Only one patient who developed WS received perfusion for less than 5 days, while 7 of the 24 patients who did not develop WS received perfusion for more than 5 days. This observation is useful for establishing the ideal time for monitoring or preventing WS: if a preventive protocol is adopted for patients with more than 5 days of perfusion, few will develop the syndrome without first having started replacement therapy–though this implies starting such therapy in some individuals who would not develop WS. On the other hand, if the appearance of WS is monitored in children with more than three days of perfusion, even when replacement therapy is not introduced from the start, we will be able to identify those patients who would develop WS despite having received perfusion for less than 5 days–thereby allowing us to start symptomatic treatment as soon as possible. In fact, this is consistent with the data obtained from the analysis of the ROC curves, whereby a perfusion time of over 5.75 days for both drugs significantly increases the risk of developing WS. To date, other authors have found that both the cumulative dose and the duration of perfusion of OP constitute risk factors for the development of WS. Specifically, in studies involving neonates,[14–17] cumulative FENT doses of between 0.4 and 1.6 mg/kg have been identified as risk factors. In older children, only one study[18] has analyzed the possible risk factors, though it was limited to patients under two years of age. This study found a total FENT dose of 1.5 mg/kg or a duration of perfusion in excess of 5 days to imply a risk for the development of WS. Regarding BZD, there is only one previous study involving few patients,[19] which has found a cumulative MDZ dose of 60 mg/kg to constitute a risk factor, while in our series the MDZ dose correlated to increased risk was 40 mg/kg. Of all the variables, logistic regression analysis found the MDZ perfusion time to be the parameter that best predicts the appearance of WS. In the analysis of the ROC curves, this variable yielded the largest area under the curve (AUC) and the best sensitivity and specificity performance. However, this result is not evaluable, due to the colinearity of the independent variables analyzed in the explanatory model. Accordingly, on considering the WS predictors separately, they lose predictive capacity in the multivariate model. Although there were differences between the WS group and the non-WS group in terms of the concomitant perfusion of a muscle relaxant, there were also significant differences in terms of the cumulative dosage of FENT and MDZ between those who had received muscle relaxant treatment and those who did not. This was also observed in a study of adult patients[20] and in another study involving children,[4] where for the same reason as mentioned above the authors were unable to establish risk for the development of WS.

A gradual decrease in perfusion was carried out in a larger number of patients who developed WS than in patients who did not develop the syndrome. Moreover, while in the non-WS group we always lowered MDZ and FENT at the same rate, in the WS group the decrease in each drug was carried out on an independent basis–thereby precluding statistical comparisons. Dose reduction was rapid in most cases: within 24–36 h among the patients who did not develop WS, and in 4–5 days in those who presented the syndrome. This protocol has also been used in most other studies.[14,17,18,21] Although this practice is widely used for the prevention of WS,[22] there is still no universally accepted protocol for the reduction of sedoanalgesia in children. In fact, no major differences have been found between the results of studies in which rapid dose reduction was carried out and those in which a slower regimen of up to 5–10 days was preferred.[9] Likewise, no gradual dose reduction protocol has been able to fully eradicate the development of WS.

The Finnegan scale[7] was used to support the clinical diagnosis and to monitor WS, since it was the only instrument available during the period of the study. Most cases were mild or moderate. Although the scale was originally developed for application to the newborn offspring of women addicted to opiates, and has not been validated in older children, most authors have used the Finnegan scale for diagnostic and follow-up purposes. In recent years other tests specifically designed for older children have been proposed[9,23,24]–some of them still pending validation[25]–and have been adapted to the clinical characteristics of WS in non-neonate children. Such instruments therefore should be used for diagnosing and monitoring WS in

Table 5 WAT-1 (Withdrawal Assessment Tool-1).

Signs or symptoms. Score 0 = no, 1 = yes
Information previous 12 h
1. Diarrhea (0.1)
2. Vomiting (0.1)
3. $T > 37.8\,^{\circ}C$ (0.1)
Observation 2 min before stimulation
4. Calm 0, irritable 1
5. Tremor (0.1)
6. Perspiration (0.1)
7. Abnormal or repetitive movements (0.1)
8. Yawning or sneezing (0.1)
Stimulation 1 min (call by name, gently touch, pain stimulus if unresponsive to previous stimuli)
9. Startled in response to touch (0.1)
10. Increased muscle tone (0.1)
Recovery following stimulus
11. Time to calmness
<2 min (0)
2–5 min (1)
>5 min (2)

A score of ≥3 indicates WS.
WAT-1: Withdrawal Assessment Tool-1 (Pediatr Crit Care Med 2008;9:573–80).

children (Table 5), reserving the Finnegan scale[7] for neonates and small nursing infants.

The treatment of the patients in our series was not preventive but symptomatic, once the syndrome had already developed. Methadone was used in most cases, with a median duration of 8 days. In this context, the literature describes protocols lasting between 5 and 10 days[26–28] and several weeks.[1] Most patients also received BZD via the oral route as symptomatic treatment. Although in recent years most protocols include clonidine for treatment in the context of WS, this drug was little used in our series–being reserved particularly for children with associated arterial hypertension. Recently, some studies have analyzed the role of clonidine in the management of WS, with good results.[29–31]

Our study has a number of limitations. On the one hand, the limited sample size can condition the validity of the results obtained. Moreover, the results can only be extrapolated to those patients who have exclusively received MDZ and FENT in continuous perfusion. In part because of this, and in view of the colinearity of the analyzed independent variables, the results obtained were invalidated following the logistic regression analysis. Thus, we were unable to analyze the effect of each drug separately upon the development of WS. Retrospective cohort studies allow us to control many of the limitations of case–control series (pure retrospective studies), since the information is obtained on a prospective basis, even though the posterior analysis has effect–cause directionality. Furthermore, another limitation of the study is the fact that several observers diagnosed and assessed the severity of WS–though it is true that use was made of the Finnegan scale,[7] which shows agreement of up to 82% between different evaluators.[32] Another limitation precisely corresponds to the fact of having used the Finnegan scale in support of the diagnosis, since this instrument has not been validated in children over 2–3 months

Table 6 Protocol for the prevention and treatment of withdrawal syndrome due to opiates and benzodiazepines in critically ill children.

In the case of OP and BZD perfusion >5 days, or if the cumulative dose of fentanyl >0.5 mg/kg or midazolam >40 mg/kg:
1. Administer methadone via the oral route: 0.2 mg/kg every 6 h, and at the same time.
2. Administer BZD via the oral route, alternating the dose with methadone:
- diazepam 0.1 mg/kg every 6 h, or
- dipotassium clorazepate (pediatric Tranxilium®, sachets 2.5 mg): 0.2 mg/kg/day, every 12 h.
3. After the second dose of methadone, start decrease in perfusion of sedoanalgesia: 20% of the starting dose every 12 h until suspension in 3 days, if prior perfusion duration between 5 and 8 days; or 10% every 12 h until suspension in 5 days, if prior perfusion duration ≥9 days.
4. Monitorization of WS using some of the available scales validated for children: WAT-1 or Finnegan scale in <3 months.
5. If WS symptoms appear, gradually increase replacement therapy dose, assessing response: methadone up to 0.3–0.4 mg/kg every 6 h; diazepam up to 0.2–0.3 mg/kg every 6 h; and/or dipotassium clorazepate up to 0.3–0.4 mg/kg/day every 12 h. In addition, evaluate point 6.
6. In case of moderate-severe WS, especially in case of arterial hypertension or tachycardia: clonidine 1 μg/kg every 8 h via the oral route, which can be gradually increased to 4–5 μg/kg every 8 h, depending on the course.
7. In the event of no response or worsening of the condition despite elevation of the above replacement therapy doses, reduce perfusion more slowly: 10% every 12 h if perfusion for 5–8 days; 5% every 12 h if perfusion for ≥9 days.
8. In the event of severe clinical manifestations interfering with patient course, evaluate perfusion of ketamine 0.2–1 mg/kg/h.
9. In case of important restlessness or hallucinations, haloperidol via the oral route, 0.01–0.05 mg/kg/day, every 12 h.
10. If WS has not developed during the reduction process, 24–48 h after suspension of infusion start the decrease in methadone and BZD, 20–30% a day until suspension. If WS has developed, start decrease in methadone and BZD, 10% a day, when WS is controlled and the patient has been symptoms free for 24–48 h.
11. If compatible manifestations reappear during the decrease in methadone and BZD, increase the dose again to the level in which the patient was asymptomatic, and continues decrease on a slower basis.

BZD: benzodiazepines; OP: opiates; WAT-1: Withdrawal Assessment Tool-1 (Pediatr Crit Care Med 2008;9:573–80).

of age, even though the diagnosis was fundamentally established on a clinical basis. The score obtained was always recorded in the clinical history of those patients in which the prolonged sedoanalgesia regimen was gradually withdrawn or suspended–a fact that eliminates possible selection bias referred to patients in the WS group or non-WS group. The variability in the decrease in perfusion may have influenced the number of patients who did or did not develop WS, or at least may have influenced the severity of the syndrome, though it must be emphasized that this was the only interventional measure adopted in the study. On the other hand, the fact that the diagnosis of WS was established on an exclusion basis may imply that the true incidence of the syndrome is higher or lower than the reported incidence. In this sense, we always considered the clinical manifestations in relation to reduction of the medication.

After analyzing the results and reviewing the literature, our Unit adopted a protocol for the prevention and treatment of WS following the perfusion of OP and BZD (Table 6). This protocol was subsequently modified and adopted by the Spanish Society of Pediatric Intensive Care (SECIP), and we hope to evaluate its usefulness in future studies.

In conclusion, it can be affirmed that the prolonged administration of OP and BZD is associated with the development of withdrawal syndrome. The appearance of this syndrome is related to high cumulative doses of both drugs, and to prolonged administration times. In patients who meet these criteria, monitoring is required in order to detect the syndrome, using an appropriate clinical scale and adopting preventive measures to avoid development of the syndrome or at least lessen its severity.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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