ELSEVIER

Life Sciences 67 (2000) 2883–2887

Life Sciences

Pharmacology letters
Accelerated communication

Previous anesthesia can temporarily overshadow the expression of a withdrawal syndrome in opiate dependent rats

Emmanuel Streel[a,*], Philippe Bredas[a], Bernard Dan[b], Catherine Hanak[a], Isy Pelc[a], Paul Verbanck[a]

[a]*CHU Brugmann (Université Libre de Bruxelles), Institut de Psychiatrie, Clinique d'Alcoologie & Toxicomanies, Pl. Van Gehuchten 4, B-1020 Brussels, Belgium*
[b]*HUDERF (Université Libre de Bruxelles) Brussels, Belgium*

(Submitted December 21, 1999; accepted May 9, 2000;
received in final form May 31, 2000)

Abstract

We hypothesized that induction of opiate antagonist-precipitated withdrawal under anesthesia can decrease the expression of later withdrawal signs. Three groups of morphine-dependent rats were compared in different experimental conditions of withdrawal precipitation using naloxone. We showed that anesthesia can temporarily overshadow the expression of withdrawal signs, but that some signs can be delayed and increased in intensity. This can be explained by a parallel and temporary effect of anesthesia on arousal and pain threshold. This carries important implications on the use of anesthesia in detoxification procedures.

Keywords: UROD; Anesthesia; Opiate withdrawal

Introduction

In the past few years, a new approach has been developed for detoxifying opiate-addicted patients by using an infusion of opiate antagonist (see [11] for a review). In order to avoid the initial discomfort induced by this procedure, Loimer et al. [1–3] combined a continuous naloxone infusion with anesthesia. It was reported that this combination results in opiate detoxification within a few days with minimal withdrawal symptoms [3,4]. The procedure has therefore been called ultra-rapid opiate detoxification (UROD). Surprisingly, the clinical reports about UROD included a limited number of patients, did not specifically discuss pos-

* Corresponding author. Tel.: +3224772705; fax: +3224772162.
E-mail address: manu.streel@chu-brugmann.be (E. Streel)

0024-3205/00/$ – see front matter
PII: S0024-3205(00)00867-5

sible side-effects and risks [5], and did not address physiological mechanisms involved in this procedure. Moreover, pre-clinical support for clinical applications seems limited, as to our knowledge only one study addressed this topic [6]. The potential effect of chemical interaction between naloxone and anesthesia on the expression of delayed withdrawal signs may have been underestimated. The specific study of association of naloxone with anesthesia could bring further insights into withdrawal processes, and therefore assist clinicians in better helping addicted patients. We hypothesized that this association of anesthesia with naloxone could decrease the expression of withdrawal signs. The purpose of the present study is to evaluate the UROD procedure in an animal model of opiate dependence.

Material and methods

Experiment 1

Male Wistar rats weighing 250–300 g were individually housed in plastic cages with free access to food and water for one week before the experiment. Morphine dependence was induced by multiple injections of the drug following a schedule related to the incremental «staircase» dosage regimen [7–9]. The rats received increasing doses of morphine three time a day, at 9 am, 12 am and 5 pm. The doses were the following (in mg/kg): Day 1: 20, 20, 30; Day 2: 40, 40, 50 and Day 3: 50 and 100. The experiment was carried out at 5 pm on the third day of treatment. The saline controls received saline injection at the same time as the morphine-treated animals received morphine. On the third day at 5 pm morphine-treated rats were divided into two groups.

The first group (Anesthesia, A2) ($n = 10$) was anesthetized with chloral hydrate (200 mg/kg intraperitoneally, ip). The second group (No Anesthesia, NA) ($n = 10$) received an injection of saline solution. Thereafter, both groups followed the same experimental procedure. Ten minutes after the injections, the rats were injected with naloxone (1 mg/kg sc) (Injection 1). Two hours after the first injection, the rats received a second injection of naloxone (1 mg/kg sc) (Injection 2). For the quantification of withdrawal signs rats were placed in transparent cages for 15 minutes following each injection of naloxone. The following signs were observed and evaluated as follows: 1) faeces excretion by weighing stools on paper dishes, 2) urine excretion by weighing the liquid content absorbed in the paper dishes after faeces removal [10], 3) global withdrawal score (GWS hereafter). The GWS was calculated by attributing one point when each of the following signs was present: “wet dog shakes,” salivation, jumping, head lift, mastication, profuse salivation, teeth chattering, abnormal posture, cheek tremors, sniffing, jumps, escape attempts, vocalization when touched.

Experiment 2

Our hypothesis posited that anesthesia could decrease the withdrawal signs in group A2 at Injection 2. As this decrease could be due to residual effect of chloral hydrate we performed another experiment with a third group of rats (Anesthesia, A4) ($n = 10$). This new group followed the same experimental procedure as Group A2, except for the second injection of naloxone and evaluation of withdrawal which were performed 4 hours (instead of 2 hours) after induction of anesthesia. In order to assess that the observed signs under anesthesia in experiment 1 were related to the injection of naloxone on opiate dependent rats, we used an

identical anesthesia procedure in a control group (n = 6) of saline pretreated rats. The protocol of this study was approved by the authorities of Hopital Universitaire Brugmann.

Results

Experiment 1

For statistical analysis we performed Repeated Measures ANOVAs separately for excretion of urine, excretion of faeces, and GWS. For urine excretion, we observed a group effect ($F(1,18) = 5.32$, $p \leq 0.03$), an injection effect ($F(1,18) = 168.98$, $p \leq 0.0001$) and an interaction ($F(1,18) = 5.27$, $p \leq 0.03$). For faeces excretion, we observed an injection effect ($F(1,18) = 39.68$, $p \leq 0.0001$). For GWS, we observed a group effect ($F(1,18) = 46.78$, $p \leq 0.0001$). Post-hoc comparisons between NA and A2 revealed that following Injection 1, urine excretion was greatest in group A2 ($F(1,18) = 6.83$, $p \leq 0.01$) and GWS was greatest in group NA ($F(1,18) = 45.40$, $p \leq 0.0001$). Following Injection 2, GWS remained greatest in group NA ($F(1,18) = 21.45$, $p \leq 0.0002$) (Table 1). In order to assess whether the signs recorded under anesthesia in experiment 1 were related to the injection of naloxone on opiate dependent rats, we used an identical anesthesia procedure in a control group (n = 6) of saline pretreated rats. No urine or faeces excretion and no withdrawal signs were observed in this control group. Therefore, the results in experiment 1 suggest that withdrawal induced by opiate antagonist injection under anesthesia could specifically augment (under anesthesia) the intensity of some signs (e.g. urine excretion at injection 1). They also decrease the later expression of withdrawal signs (e.g. GWS at injection 2). We also noticed that under anesthesia, naloxone provoked an important but short-lived motor activation in opiate dependent rats, sometimes accompanied by teeth chattering or cheek tremors.

Experiment 2

For statistical analysis we performed Repeated Measures ANOVAs separately for excretion of urine, excretion of faeces, and GWS. For urine excretion, we observed a group effect

Table 1
Urine and feces excretion and global withdrawal score in morphine dependent rats following naloxone injections

	Injection 1			Injection 2		
	Urine	Feces	GWS	Urine	Feces	GWS
Group NA	1.99 (SD 0.59)	1.66 (SD 0.58)	5.10 (SD 0.87)	0.29 (SD 0.29)	0.99 (SD 0.58)	4.70 (SD 1.15)
Group A2	2.64° (SD 0.51)	1.70 (SD 0.65)	2.50° (SD 0.84)	0.22 (SD 0.32)	0.62 (SD 0.35)	2.60° (SD 0.84)
Group A4	2.03 (SD 0.62)	1.55 (SD 0.57)	2.30* (SD 0.48)	1.38* (SD 0.58)	1.84* (SD 0.96)	4.20 (SD 0.63)

Groups A2 and A4 were pretreated with chloral hydrate. Group NA was pretreated with saline. Groups NA and A2 received injection 2 two hours after the injection 1. Group A4 received injection 2 four hours after injection 1. Mean of urine and feces excretion ± standard deviation (SD) and mean in number of withdrawal signs ± SD are given. * Indicates significant difference between group A4 and NA ($p \leq 0.05$). ° Indicates significant difference between group A2 and NA. ($p \leq 0.05$).

($F(2,27) = 7.27$, $p \leq 0.003$), an injection effect ($F(1,27) = 127.66$, $p \leq 0.0001$) and an interaction ($F(2,27) = 13.55$, $p \leq 0.0001$). For faeces excretion, we observed a tendency for group effect ($F(2,27)$ 2.93, $p \leq 0.07$), an injection effect ($F(1,27) = 11.45$, $p \leq 0.002$) and an interaction ($F(2,27) = 7.84$, $p \leq 0.002$). For GWS, we observed a group effect ($F(2,27) = 30.83$, $p \leq 0.0001$), an injection effect ($F(1,27) = 9.52$, $p \leq 0.004$), and an interaction ($F(2,27) = 16.33$, $p \leq 0.0001$). Post-hoc comparisons between NA and A4 revealed that following Injection 1, the GWS was greatest in group NA ($F(1,18) = 78.4$, $p \leq 0.0001$). Following Injection 2, urine excretion was greatest in group A4 ($F(1,18) = 27.4$, $p \leq 0.0001$), and faeces excretion was greatest in group A4 ($F(1,18) = 5.74$, $p \leq 0.02$). Post-hoc comparisons between A2 an A4 revealed that following Injection 1, urine excretion was greatest in group A2 ($F(1,18) = 5.75$, $p \leq 0.02$). Following Injection 2, urine excretion was greatest in group A4 ($F(1,18) = 30.36$, $p \leq 0.0001$), faeces excretion was greatest in group A4 ($F(1,18) = 14.10$, $p \leq 0.001$) and GWS was greatest in group A2 ($F(1,18) = 23.04$, $p \leq 0.0001$) (Table 1).

The resumption in group A4 of GWS similar to group NA following Injection 2 suggests that the decrease in GWS two hours after the induction of anesthesia is due to a residual effect of anesthesia or to a more complex mechanism related to interaction between naloxone and the anesthetic agent. Furthermore in Group A4 we also observed a larger urine and feces excretion following Injection 2. This suggests that injection of opiate antagonist under anesthesia does not decrease withdrawal signs but can temporarily overshadow some of them (GWS) and aggravate some others (urine, faeces). We did not observe significant increase in urine excretion following Injection 1 in group A4. Which does not provide strong evidence that naloxone- precipitated withdrawal increases withdrawal signs under anesthesia. Further studies need to be done to clarify, under anesthesia, the specific effects of opiate antagonist induction in an opiate dependent organism.

Discussion

Our results show that injection of opiate antagonist in opiate dependent rats under Chloral hydrate anesthesia can interfere with the expression of a subsequent forced withdrawal 2 hours after anesthesia. If the second forced withdrawal occurs 4 hours after anesthesia, withdrawal signs reappear, some of them being potentiated. These results show that previous anesthesia does not decrease the expression of withdrawal signs but overshadows them temporarily. Our results are in accordance with the recent clinical reports on the topic [11,12], which have questioned the initial enthusiastic reports [2,4] that claimed that UROD can suppress withdrawal syndrome almost completely in opiate addicts. The interference with withdrawal signs we observed when the second injection of naloxone was made 2 hours after anesthesia could be due to a residual effect of the anesthetic agent. Alternatively, it could be due to a more complex mechanism involving the interaction between naloxone and the anesthetic agent. The modification of withdrawal signs could be mediated by both temporary decrease in arousal and elevation in the pain threshold. The differences we observed in the reappearance of different categories of withdrawal signs (GWS vs. urine and faeces) 4 hours after anesthesia reflect the multilevel effects of UROD on central nervous system and peripheral system, shedding some new light on the withdrawal processes. The potentiation of some withdrawal signs we observed 4 hours after anesthesia is in accordance with the only previous animal

study on this topic, which showed a more pronounced and long-lasting withdrawal syndrome under barbiturate anesthesia [6]. With another anesthetic agent (chloral hydrate) we succeeded in replicating recent clinical data [12,13] in laboratory animals. This could underline the importance of the choice of the method of anesthesia in UROD procedure. We also observed that, under anesthesia, the withdrawal signs emerge sharply and rapidly after the injection of naloxone in the form of major motor activation, cheek tremors and/or teeth chattering. As these signs did not appear in rats previously treated with saline solution, we consider that these signs are related to a withdrawal of opiate substances. Among opiate dependent rats, we did not quantify precisely the duration of the signs observed under anesthesia. However, it seems important to note that these signs were expressed in an extremely short time, suggesting a possible effect on the temporal expression of the first withdrawal signs. To our knowledge, this study provides the first pre-clinical explanation about the effect of UROD under anesthesia on the expression of withdrawal signs. Further studies are needed to better clarify the neurobiological mechanisms of this phenomenon and to approach more closely the clinical situation.

References

1. Loimer N, Schmid RW, Presslich O, and Lenz K. Continuous naloxone administration suppresses opiate withdrawal symptoms in human opiate addicts during detoxification treatment. Journal of Psychiatry Research 1989; 23(1):81–6.
2. Loimer N, Schmid RW, Lenz K, Presslich O and Grunberger J. Acute blocking of naloxone-precipitated opiate withdrawal symptoms by methohexitone. British Journal of Psychiatry 1990; 157:748–52.
3. Loimer N, Hofmann P, and Chaudhry H. Ultrashort noninvasive opiate detoxification. American Journal of Psychiatry 1993; 150(5):839.
4. Legarda JJ and. Gossop M. A 24-h inpatient detoxification treatment for heroin addicts: preliminary investigation. Drug and Alcohol Dependence 1994; 35(2):91–3.
5. Gossop M and Strang J. Rapid anaesthetics-antagonist detoxification of heroin addicts: what origins, evidence base and clinical justification? British journal of intensive care 1997; 3:66–9.
6. Spanagel R, Kirschke C, Tretter F and Holsboer F. Forced opiate withdrawal under anaesthesia augments and prolongs the occurrence of withdrawal signs in rats. Drug and Alcohol Dependence 1998; 52(3):251–6.
7. Dafny N. Neurophysiological evidence for tolerance and dependence on opiates: simultaneous multiunit recordings from septum, thalamus and caudate nucleus. Journal of Neuroscience Research 1980; 5(4):339–49.
8. Dougherty PM, Drath DB and Dafny N. Evidence of an immune system to brain communication axis that affects central opioid functions: muramyl peptides attenuate opiate withdrawal. European Journal of Pharmacology 1987; 141(2):253–60.
9. Dougherty PM and Dafny N. Trans-cranial electrical stimulation attenuates the severity of naloxone-precipitated morphine withdrawal in rats. Life Sciences 1989; 44(26):2051–6.
10. Pinelli A, Trivulzio S and Tomasoni L. Effects of ondansetron administration on opioid withdrawal syndrome observed in rats. European Journal of Pharmacology 1997; 340(2–3):111–9.
11. Simon DL. Rapid opioid detoxification using opioid antagonists: history and the state of the art. Journal of addictive disease 1997; 16(1):103–22.
12. Tretter F, Burkhardt D, Bussello-Spieth B, Reiss J, Walcher S and Buchele W. Clinical experience with antagonist-induced opiate withdrawal under anaesthesia. Addiction 1998; 93(2):269–75.
13. Cucchia A, Monnat M, Spagnoli J, Ferrero F and Bertschy G. Ultra-rapid opiate detoxification using deep sedation with oral midazolam:short and long-term results. Drug and Alcohol Dependence 1998; 52(3):243–50.