

Interference with withdrawal signs of naloxone-induced opiate withdrawal under anesthesia is anesthetic-specific in opiate-dependent rats

Emmanuel Streel^{a,*}, Bernard Dan^b, Philippe Bredas^c,
Béatrice Clement^c, Isy Pelc^a, Paul Verbanck^a

^aCHU Brugmann (Université Libre de Bruxelles), Institut de Psychiatrie,
Clinique d'Alcoologie & Toxicomanies, Pl. Van Gehuchten 4, B-1020 Brussels, Belgium
^bHUDERF (Université Libre de Bruxelles), Pl. Van Gehuchten 4, B-1020 Brussels, Belgium
^cCHU Brugmann (Université Libre de Bruxelles), Service d'Anesthesiologie,
Pl. Van Gehuchten 4, B-1020 Brussels, Belgium

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Abstract

We hypothesized that interference of opiate antagonist-precipitated withdrawal signs under anesthesia is anesthetic-specific. Three groups of morphine-dependent rats were compared in different experimental conditions using a protocol of rapid withdrawal induction by an antagonist under anesthesia. We observed that ketamine and midazolam have different effects on the expression of withdrawal. This brings specific insights into the pharmacological basis of therapy with induction of opiate antagonist. © 2001 Elsevier Science Inc. All rights reserved.

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Introduction

For more than 20 years, opiate-addicted patients have been detoxified by Rapid Induction of Antagonist (RIA) under anesthesia or various degrees of sedation. This type of treatment is widely used, often as part of state-funded programs. General anesthesia was first introduced by Loimer [1] in order to avoid the initial discomfort associated with RIA. Different anesthetic agents are now commonly used in RIA protocols (e.g. propofol, ketamine, isoflurane, thiopentone). As emphasized by Meurer et al [2], it is ethically justifiable to provide a high standard of anesthesia to any patient undergoing unpleasant and painful treatment. Furthermore anesthesia prevents patients from ceasing treatment, whereas patients treated with other

* Corresponding author. CHU Brugmann, Institute de Psychiatrie, Pl. Van Gehuchten 4, B-1020 Bruxelles, Belgium.

E-mail address: manu.streel@chu-brugmann.be (E. Streel)

detoxification regimens tend to abandon treatment before becoming opiate-free [3]. Parallel to the clinical studies, pre-clinical studies were performed. Spanagel et al [4] showed that naloxone-precipitated withdrawal under barbiturate anesthesia augments and prolongs the intensity of withdrawal signs in opiate-dependent rats. On the basis of this, these authors have questioned the possible pharmacological basis of RIA [5]. We qualified Spanagel's results by showing that naloxone-induced withdrawal under chloral hydrate can temporarily overshadow the expression of withdrawal signs, but potentiate some delayed signs [6]. This underlines the importance of the method of anesthesia in RIA procedures. In particular, the association between anesthesia and opiate antagonists in the management of opiate-addicted patients may have been underestimated in clinical practice, which perhaps accounts for heterogeneous results in RIA (see [7] for a review) and other contexts [8]. We hypothesized that different types of anesthetic interfere differently with the expression of withdrawal signs in a RIA protocol under anesthesia. As ketamine and midazolam are used in currently recommended RIA protocols, the aim of this study is to highlight the potential specificity of these two agents in the modulation of withdrawal signs in morphine-dependent rats.

Material and methods

Male Wistar rats weighing 200–300 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 specific schedule [6]. The rats received increasing doses of morphine (subcutaneously, in the scruff of the neck) three times a day, at 9 am, 12 am and 5 pm. The doses were the following (in mg/kg of body wt) : 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. After three days of morphine treatment, the experiment was carried out at 5 pm. The morphine-treated rats were divided in three groups. The first group (ketamine, K) (n = 10) was anesthetized with ketamine (10 mg /kg of body wt. Intramuscular, im). The second group (midazolam, M) (n = 10) was anesthetized with midazolam (1 mg/kg of body wt. im). The third group (No Anesthesia, C) (n = 10) received an injection of saline solution. Thereafter, the three groups followed the same experimental procedure. Ten minutes after the injections, the rats were injected with naloxone (1 mg/kg of body wt. Subcutaneously, sc). Two hours after the first naloxone induction the rats received a second injection of naloxone (1 mg/kg of body wt. sc). Two hours after the second induction of naloxone the rats received a third injection of naloxone (1 mg/kg of body wt. sc). Each of the three injections of naloxone is needed to induce an observable withdrawal. Fifteen minutes following each injection of naloxone the rats were placed in transparent cages and observed for withdrawal quantification. They were observed after the first naloxone injection (Time 1), after the second naloxone injection (Time 2) and after the third naloxone injection (Time 3). The following signs were observed and evaluated: 1) urine excretion by weighing the liquid content absorbed in the paper dishes after feces removal [8], 2) feces excretion by weighing stools on paper dishes, 3) Global Withdrawal Score (GWS) was calculated by attributing one point for each of the following signs : “wet dog shakes”, jumping, head lift, profuse salivation, escape attempts, vocalization when touched, abnormal posture, mastication, teeth chattering, cheek tremors, sniffing.

Results

The results shows interference with withdrawal signs (urine, feces and GWS) of naloxone-induced opiate withdrawal under anesthesia according to the type of anesthetic used (Figure 1, sections A-B-C). For statistical analysis we performed Repeated Measures ANOVA's separately for excretion of urine, excretion of feces, and for GWS. For urine excretion we observed a group effect ($F(2,27) = 14.936$, $p = 0.0001$), a time effect ($F(2,54) = 72.005$, $p = 0.0001$) and a group \times time interaction ($F(4,54) = 4.998$, $p = 0.027$). For feces excretion we observed a group \times time interaction ($F(4,54) = 4.998$, $p = 0.0017$). For GWS we observed a group effect ($F(2,27) = 22.765$, $p = 0.0001$), a time effect ($F(2,54) = 20.363$, $p = 0.0001$) and a group \times time interaction ($F(4,54) = 29.316$, $p = 0.0001$). Post Hoc comparisons revealed the following results.

Concerning urine excretion

At Time 1, K group is lower than both M and C groups ($F(2,27) = 10.145$, $p = 0.0005$). At Time 2 there is no significant difference between the three groups. In Time 3 K group was lower than both M and C groups ($F(2,27) = 3.794$, $p = 0.035$).

Concerning feces excretion

At Time 1, M group was greater than both C and K groups ($F(2,27) = 7.944$, $p = 0.0019$). At Time 2 there was no significant differences between the three groups. In Time 3, K group is greater than both M and C groups ($F(2,27) = 4.111$, $p = 0.027$).

Concerning GWS

At Time 1, M group was lower than both C and K groups ($F(2,27) = 16.805$, $p = 0.0001$). At Time 2, M group is greater than C group who is greater than K group ($F(2,27) = 19.938$, $p = 0.0001$). At Time 3 C group is greater than M group who is greater than K group ($F(2,27) = 50.912$, $p = 0.0001$). The results (Table 1) show that naloxone-precipitated withdrawal under anesthesia can interfere with the later expression of withdrawal signs, this interference is anesthetic-specific.

Discussion

Our results show that anesthesia with ketamine or midazolam interfere differently with withdrawal signs in naloxone-induced opiate withdrawal under anaesthesia in opiate dependent rats. During the first induction of the antagonist (under anesthesia) ketamine decreased the intensity of urine excretion whereas midazolam increased the intensity of feces excretion and decreased the GWS. During the second injection of antagonist (on woken up animals), midazolam increased the GWS. During the third injection of antagonist, ketamine increased the intensity of feces excretion and decreased the intensity of urine excretion of. The two anesthetics also had some common effects such as decreasing the GWS after the third injection of antagonist. This implies that the type of anaesthetic used in opiate-antagonist precipitated withdrawal under anesthesia is a major element in the specific expression of withdrawal signs in opiate dependent rats. This specific role of the anesthetic support the existence of a

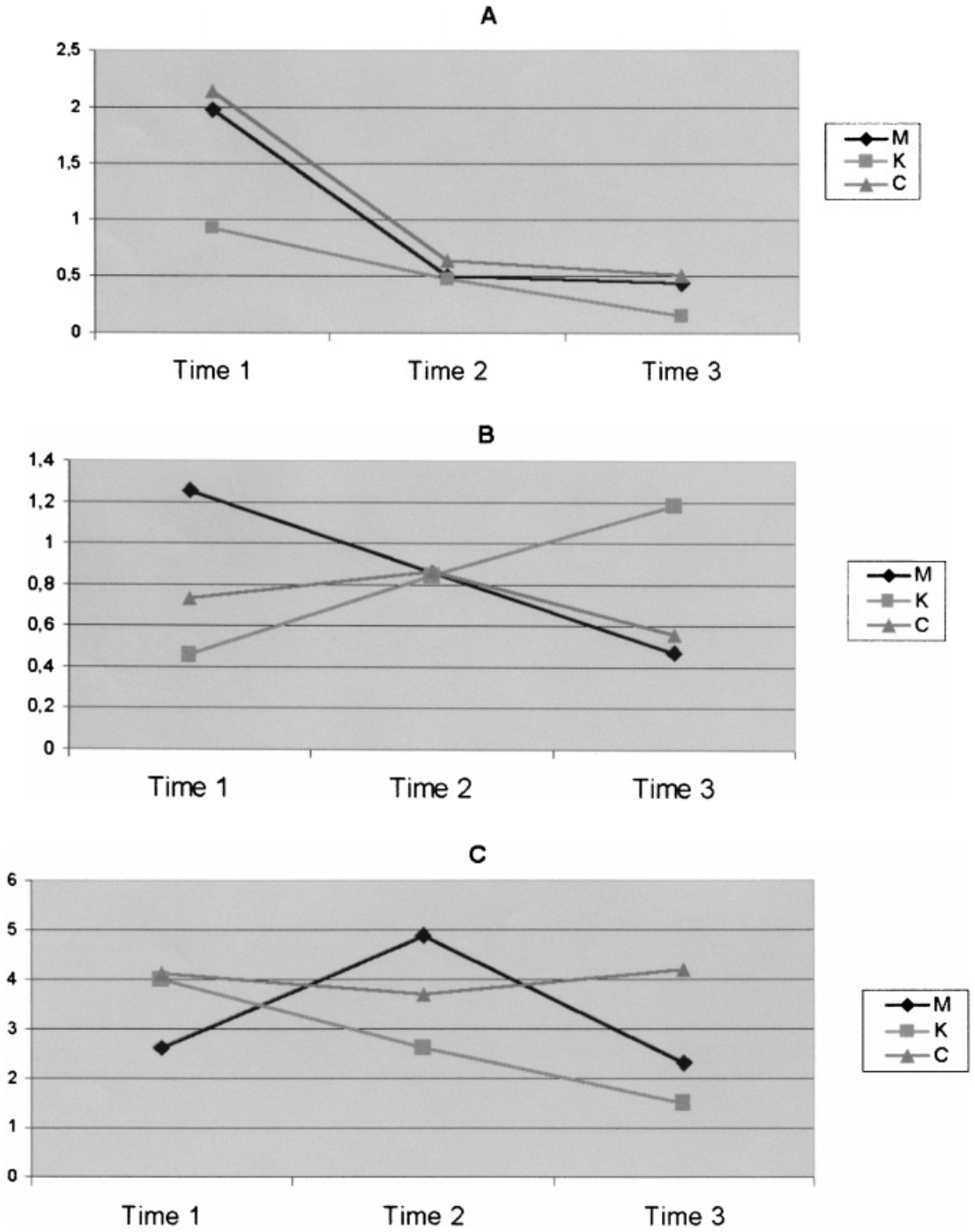


Fig. 1. Interference with naloxone-induced opiate withdrawal signs in opiate-dependent rats after the first (Time 1), second (Time2) and third (Time3) naloxone injections; C = control group, M = midazolam group, K = ketamine group. Section A: Changes in urine excretion (expressed in g.). Section B: Changes in feces excretion (expressed in g.). Section C: Changes in GWS (expressed in number of withdrawal signs).

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

	Time 1			Time 2			Time 3		
	Urine	Feces	GWS	Urine	Feces	GWS	Urine	Feces	GWS
Group K	0.934 (SD 0.49)	0.49 (SD 0.39)	4 (SD 0.47)	0.475 (SD 0.24)	0.84 (SD 0.43)	2.6 (SD 0.69)	0.16 (SD 0.15)	1.18 (SD 0.78)	1.5 (SD 0.70)
Group M	1.98 (SD 0.70)	1.25 (SD 0.51)	2.6 (SD 0.51)	0.49 (SD 0.35)	0.85 (SD 0.48)	4.9 (SD 0.99)	0.43 (SD 0.37)	0.47 (SD 0.37)	2.3 (SD 0.48)
Group C	2.13 (SD 0.72)	0.73 (SD 0.39)	4.1 (SD 0.87)	0.64 (SD 0.32)	0.86 (SD 0.79)	3.7 (SD 0.82)	0.50 (SD 0.32)	0.55 (SD 0.58)	4.2 (SD 0.63)

Group K was pretreated with ketamine. Group M was pretreated with midazolam. Group C was pretreated with saline. The three groups received the first naloxone injection (Time 1) two hours after the pretreatment. The three groups received the second naloxone injection (Time 2) two hours after the first naloxone induction. The three groups received a third naloxone injection (Time 3) two hours after the second naloxone induction. Mean of urine and feces excretion \pm standard deviation (SD) and mean in number of withdrawal signs \pm SD are given.

pharmacological basis in the mode of action of RIA under anesthesia. The specific effect of each anesthetic shown in this research also raises the problem of the choice of anesthetic in antagonist-precipitated opiate withdrawal under anesthesia, which may vary according to the clinical situation. There still are no standardized RIA protocols, nevertheless different clinical teams (e.g. [10]) tried to identify an anesthesia protocol which would suppress withdrawal symptoms. Although, the pharmacological basis of RIA remains to be clarified [5], this study provides insights into it as well as a potentially useful paradigm for further research in this field. The understanding of the pharmacological basis of RIA under anesthesia should lead to a better understanding of the phenomenon associated with opiate withdrawal and consequently help clinicians to intervene in a more efficient way in the treatment of patients suffering from opiate-dependence. Now, it will be necessary to specify the pharmacological mechanisms by which anesthesia can modulate naloxone-induced opiate withdrawal. This experimental framework can also be extended to address other questions pertaining to longer term effects of RIA, in relation with relapse, abstinence and other clinically relevant outcome parameters. It may thereby lead to a better understanding of opiate withdrawal and eventually to improved therapy for opiate dependence.

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