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Tolerance to the mydriatic effect of buprenorphine, butorphanol, nalbuphine, and cyclorphan, and cross-tolerance to morphine in mice

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Abstract: An increase in the use of opioid derivatives in the treatment of pain syndrome in clinical practice, and especially in the treatment of cancer, has added impetus to the search for an agent which does not induce tolerance and cross-tolerance to other opioids. The mydriatic effect of opioids in mice, the correlation between analgesia and mydriasis, and tolerance to the analgesic effect of morphine in mice were evaluated previously. In the present work, tolerance to the mydriatic effect of four agonist-antagonists and cross-tolerance to morphine were examined. Measurement of the pupillary diameter was performed using a binocular operating microscope. Tolerance and cross-tolerance to morphine were developed following a chronic use of buprenorphine, nalbuphine, and cyclorphan. After chronic injection of butorphanol, no tolerance or cross-tolerance to morphine was observed.

Key words: Morphine, Buprenorphine, Butorphanol, Nalbuphine, Cyclorphan, Tolerance, Cross tolerance, Opioids, Pupil, Mydriasis

Introduction

Pure opioids and opioid agonist-antagonists produce pupillary mydriasis in mice [1–3]. There is a strong correlation between mydriatic and analgesic effects of pure opioids [1] and of agonist-antagonist [3] opioid derivatives in mice. Tolerance to the mydriatic effect of morphine in mice was evaluated previously [4]. The use of opioid derivatives for chronic treatment of pain syndrome, especially with oncologic patients, demands a considerable increase in the dose of opioid up to very high doses [5]. One of the causes of this phenomenon is the development of tolerance to the opioid derivatives. It is necessary to identify an agent with appropriate analgesic properties, but which does not induce tolerance and cross-tolerance to other opioids. In this experimental work, we evaluated tolerance to the mydriatic effect of four agonist-antagonist drugs and the possibility of cross-tolerance to morphine of each of these agents (buprenorphine, butorphanol, nalbuphine, and cyclorphan).

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Materials and methods

Male albino ICR mice (Sackler School of Medicine) weighing 20–25 g were used in all experiments. Measurement of the pupillary diameter, using a binocular operating microscope, employed methods similar to those described in the work of Korczyn et al. [2] The drugs investigated were buprenorphine, butorphanol, nalbuphine, and cyclorphan. Morphine was used to evaluate cross-tolerance with the four investigated drugs on the mydriatic effect in mice. In all the animals, each injection of the examined drugs, morphine, or normal saline was performed intraperitoneally in a volume of 0.2 ml. Each experiment (during 16 days) in each group of animals was performed once.

Three groups of mice (10 mice in each group) were used for the examination of each agonist-antagonist agent. For examination of each agent, 3 groups of mice were included in experiment. Group A was the group used for evaluation of the development of tolerance. The evaluated agent was injected at a dose of 30 mg·kg^{-1} twice daily for 14 days. Group B was the group used for evaluation of cross-tolerance to morphine. Morphine at a dose of 200 mg·kg^{-1} was injected twice daily for 14 days. Group C was the control group injected with normal saline 0.2 ml intraperitoneally twice daily. Pupil diameter after injection of 3 mg·kg^{-1} of investigated agent was measured on the first and 16th days of the experiment. After examination of the

mydriatic diameter (baseline), the animals in all three groups were treated with the investigated agent at a dose of 3 mg·kg^{-1}. Thirty minutes thereafter, the mydriatic effect was measured by repeated examination of the pupil. The dose of 3 mg·kg^{-1} was selected on the basis of information from our previous work [3]. There we showed which does of the examined agonist-antagoists produces a distinct, but not a maximal mydriatic effect in mice. Twelve hours thereafter, one of the agonist-antagonists was injected in the mice of group A at a dose of 30 mg·kg^{-1} This is the maximal nontoxic dose of buprenorphine [3]. Animals in group B were treated with a nontoxic dose of morphine [2,4] (200 mg·kg^{-1}). The animals in control group C were treated with 0.2 ml of normal saline. These injections were performed twice daily for 14 days. Sixteen hours after the last injection, the diameter of the pupils was measure in the animals of all three groups, and immediately after that, the dose of the examined which dose of the examined agonist-antagonists produces a distin Twelve hours thereafter, one of the agonist-antagonists was injected at a dose of 3 mg·kg^{-1}. The effect was measured after 30 min.

Three groups (A, B, and C) were compared statistically according to each examined agent. Statistical analysis was performed using analysis of variance (single factor) for identification of the difference of mean values, followed by paired *t*-test for comparison. A level of probability less than or equal to 0.05 was considered to be significant.

Results

All four examined agents at a dose of 3 mg·kg^{-1} produced mydriasis in each group on the first day of the experiments (Table 1, Fig. 1). The development of tolerance in group A, and of cross-tolerance to morphine in group B, were demonstrated on the 16th day of the experiment. The experiment showed that in the case of buprenorphine, nalbuphine, and cyclorphan, the difference between pupil diameter before and 30 min after the injection of the examined agent was not statistically significant *s* the control groups. This phenomenon did not occur in groups A and B of butorphanol (Table 1, Fig. 1), i.e., tolerance of butorphanol to itself and cross-tolerance to morphine did not develop.

Discussion

Pure opioid agonists and the new group of agonist-antagonist opioids have become more and more popular in clinical practice due to their excellent analgesic effect. Buprenorphine, butorphanol, and nalbuphine produce a dose-dependent mydriatic and analgesic effect in mice [3] like morphine [2] and other pure opioid agonists [1,2]. A strong correlation between the mydriatic and analgesic effects was demonstrated by the pure opioid agonists [1] and the agonist-antagonist [3] opioid derivatives. This fact suggests that the analgesic property of those drugs are also identical.

Table 1. Diameter of pupil (mm) during the evaluation of four agonist-antagonists

	Buprenorphine			Butorphanol			Nalbuphine			Cyclorphan		
Group	A	B	C	A	B	C	A	B	C	A	B	C
Baseline (1st day of experiment)[a]												
PD_{bi}	0.39	0.39	0.39	0.38	0.38	0.34	0.38	0.39	0.39	0.34	0.34	0.34
	(0.06)	(0.06)	(0.06)	(0.07)	(0.07)	(0.07)	(0.07)	(0.06)	(0.06)	(0.07)	(0.07)	(0.07)
PD_{30ai}	0.61	0.64	0.62	0.48	0.48	0.44	0.47	0.49	0.50	0.44	0.44	0.44
	(0.17)	(0.15)	(0.10)	(0.10)	(0.08)	(0.08)	(0.10)	(0.10)	(0.08)	(0.11)	(0.13)	(0.08)
p^{ANOVA}	0.001	$2{\cdot}10^{-4}$	$3{\cdot}10^{-25}$	0.02	0.006	0.01	0.03	0.01	0.004	0.03	0.04	0.01
$p^{bi\&ai}$	0.002	$3{\cdot}10^{-4}$	$6{\cdot}10^{-24}$	0.02	0.001	0.001	0.02	0.009	0.001	0.01	0.001	0.001
	S	S	S	S	S	S	S	S	S	S	S	S
16th day after chronic treatment[a]												
PD_{bi}	0.40	0.40	0.39	0.38	0.39	0.38	0.38	0.39	0.39	0.35	0.34	0.35
	(0.05)	(0.05)	(0.06)	(0.07)	(0.06)	(0.07)	(0.07)	(0.06)	(0.06)	(0.07)	(0.07)	(0.07)
PD_{30ai}	0.44	0.41	0.64	0.50	0.50	0.50	0.39	0.41	0.51	0.37	0.38	0.47
	(0.05)	(0.09)	(0.23)	(0.10)	(0.08)	(0.12)	(0.09)	(0.06)	(0.08)	(0.12)	(0.13)	(0.14)
p^{ANOVA}	0.18	0.92	0.004	0.007	0.003	0.02	0.68	0.38	0.001	0.73	0.50	0.03
$p^{bi\&ai}$	0.17	0.92	0.006	0.003	$7{\cdot}10^{-4}$	0.03	0.34	0.18	$2{\cdot}10^{-4}$	0.56	0.33	0.003
	NS	NS	S	S	S	S	NS	NS	S	NS	NS	S

[a] Injection of 3 mg·kg^{-1} of evaluated agent.

PD_{bi}, pupil diameter before injection; PD_{30ai}, pupil diameter 30 min after injection; p^{ANOVA}, probability following production analysis of variance for single factor; $p^{bi\&ai}$, probability following producing the paired *t*-test for comparison of the pupil diameter before and 30 min after injection of examinated agent in each examined group; NS, no statistically significant difference between groups; S, statistically significant difference between groups.

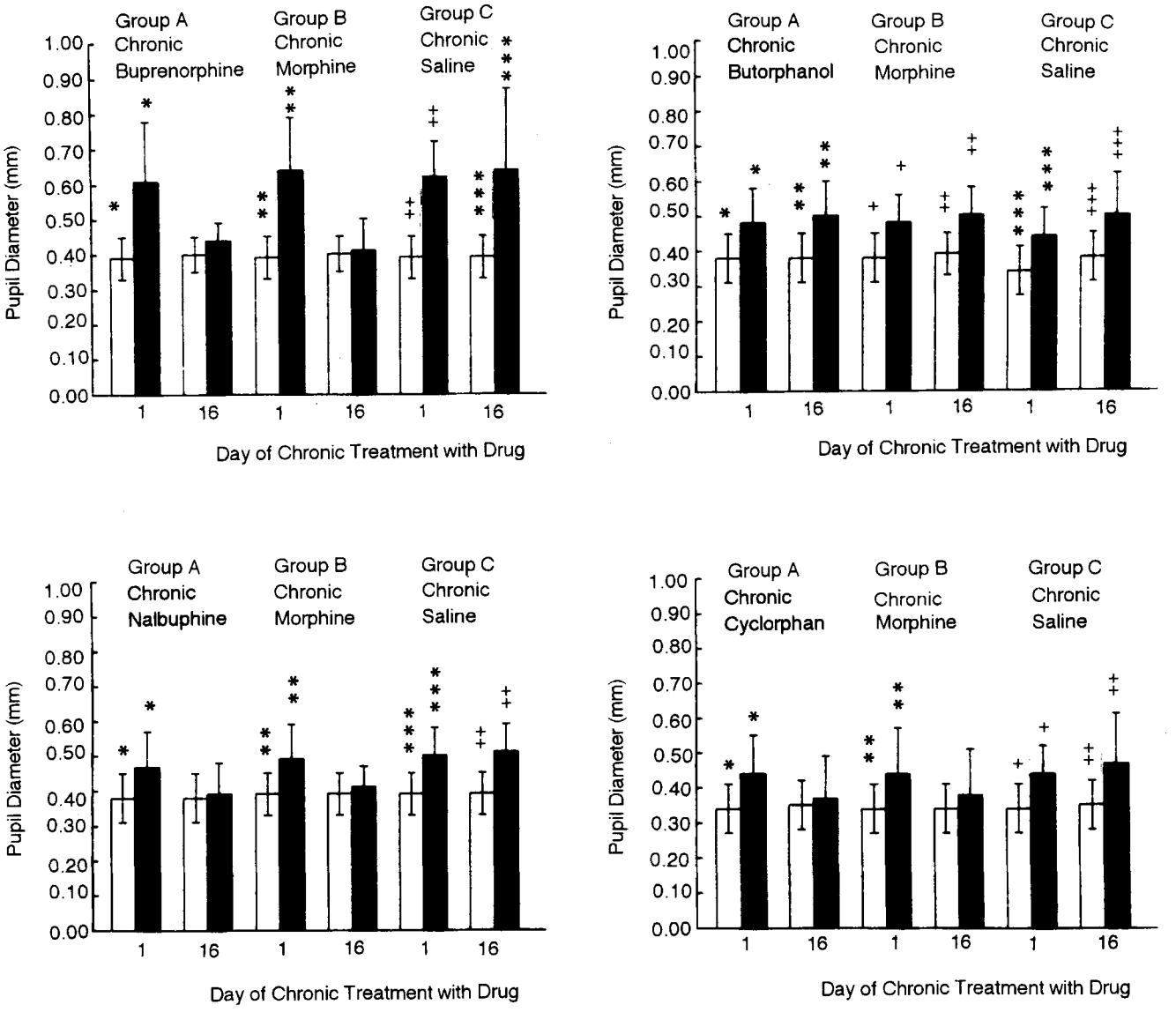

Fig. 1. Pupil diameter changes following the evaluation of tolerance and cross-tolerance development to morphine of four agonist-antagonist opioids: buprenorphine, butorphanol, nalbuphine, and cyclorphan. *Open bars* indicate pupil diameter before injection of the agent; *shaded bars* indicate pupil diameter 30 min after injection of the agent. A statistically significant difference between pupil diameter before and after injection of the evaluated agent is marked similarly, for example * & * , + & +, etc. Butorphanol does not develop tolerance and cross-tolerance to morphine

The evaluation of tolerance and cross-tolerance of pure opioids and agonist-antagonists is of considerable practical importance because of the increased attention that is being focused on the problem of acute and chronic pain, especially in cancer patients [5,6]. The side effects and tolerance to the analgesic effect of morphine and other pure opioid agonists have prompted the search for other, better drugs.

Tolerance to the mydriatic effect of morphine in mice was previously examined [4]. The present work demonstrated on the one hand the development of tolerance of buprenorphine, nalbuphine, and cyclorphan when administered alone, and also cross-tolerance to morphine. On the other hand, tolerance and cross-tolerance of butorphanol has not been demonstrated. It has also been reported that butorphanol exhibited no tolerance [7–9]. This suggests that butorphanol may be used in the treatment of cancer patients without inducing tolerance or cross-tolerance.

What is the explanation for these phenomena? Why do buprenorphine[10], nalbuphine [10], and cyclorphan produce tolerance and cross-tolerance to morphine, but not butorphanol?

The development of the theory of opioid receptors [10–15] provides at least a partial explanation for the action of the side effects of opioid derivatives, but does not explain the present results. Opioids produce miosis in humans and dogs due to an excitatory action on the

Table 2. The affinity of morphine and four investigated agonist-antagonists to opioid receptors [10–16]

Agent	Affinity to the opioid receptors			
	Mu	Kappa	Sigma	Delta
Morphine	+++	+	----	++
Buprenorphine	++	+	+	+
Butorphanol	+++	+++	++	++
Nalbuphine	+	+++	+/−	+
Cyclorphan	++	+	+	+

nucleus of the oculomotor nerve [17], but we do not know which type of opioid receptors are responsible for the mydriatic effect of opioids in mice, cats, and monkeys [1–3]. If the occupation of the μ-opioid receptors of the nucleus region of the oculomotor nerve in the brain produces a mydriatic effect in mice, then we are unable to explain why butorphanol does not produce tolerance like morphine[4], buprenorphine, and cyclorphan. All four agents possess a similar affinity to the μ-opioid receptors (Table 2). If we assume that occupying the κ-opioid receptors produces a mydriatic effect in mice, then it is impossible to explain why butorphanol does not produce a tolerance like nalbuphine because affinity to κ receptors of these two drugs is similar (Table 2), [10–16].

It is known that a high degree of cross-tolerance occurs in drugs with morphine-like actions [18], but "κ-receptor agonists do not induce cross-tolerance to agents that act primarily on the μ-receptors" [18]. This last assertion of the results we got assumes the absence of cross-tolerance of butorphanol to morphine, but it fails to assume the presence of cross-tolerance of nalbuphine to morphine.

We presume that the increased rate of metabolism of buprenorphine, nalbuphine, and cyclorphan (dispositional tolerance) [18], and/or adaptive changes within affected systems (pharmacodynamic tolerance) [18], may be appropriate mechanisms of tolerance and cross-tolerance of these three agonist-antagonists. However, the mechanisms for butorphanol appear to be different.

Conclusions

1. Three agonist-antagonists, buprenorphine, nalbuphine, and cyclorphan, produced a mydriatic effect in mice with developing tolerance and cross-tolerance to morphine.
2. The agonist-antagonist butorphanol produced a mydriatic effect in mice, but it did not induce tolerance or cross-tolerance to morphine.
3. The results of this work cannot be explained by the theory of opioid receptors.
4. From previous work we know that there is a strong correlation between the mydriatic and analgesic properties of agonist-antagonist opioid derivatives. The observation that butorphanol did not induce tolerance suggests that the same phenomenon will also be observed regarding the analgesic effect of butorphanol.
5. If the absence of tolerance to the analgesic effect of butorphanol is confirmed in humans, butorphanol may become the drug of first choice for chronic use in cancer patients for appropriate pain relief.

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