Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 3, pp. 561–563, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00140-9

Oxymorphone-Induced Analgesia and Colonic Motility Measured in Colorectal Distension

SHANNON L. BRIGGS,[1] DONALD C. SAWYER, RICHARD H. RECH AND JAMES J. GALLIGAN

Department of Pharmacology, Michigan State University, East Lansing, MI 48824

Received 29 August 1994

BRIGGS, S. L., D. C. SAWYER, R. H. RECH AND J. J. GALLIGAN. *Oxymorphone-induced analgesia and colonic motility measured in colorectal distension.* PHARMACOL BIOCHEM BEHAV **52**(3) 561–563, 1995.—Changes in colonic motility in rats following intravenous (IV) oxymorphone (0.1 mg/kg), atropine (0.1 mg/kg), or saline were monitored to determine whether opioid-induced changes in colonic motility affect antinociceptive measurements when using colorectal distension (CRD) as a nociceptive assay. Polygraph recordings of colonic pressures, contraction frequencies, and the pressure-volume relationship of the stimulus showed that oxymorphone produced a transient increase in contraction frequencies when compared to atropine- and saline-treated rats. The transient increase in contraction frequency caused by oxymorphone declined to baseline levels at 30 min after administration, the time at which the nociceptive threshold for CRD was tested. Neither oxymorphone nor atropine changed baseline pressures or the pressure-volume curve for the balloon stimulus. Antinociceptive results from CRD at 30 min posttreatment showed that only oxymorphone produced significant antinociception. We conclude that oxymorphone does not produce changes in colonic motility that complicate antinociceptive measurements in CRD and that CRD is an effective means of testing opioid-induced visceral antinociception.

Colorectal distension Visceral antinociception Oxymorphone Atropine

DISTENDING hollow organs, such as the colon, is a means of studying visceral nociception in a variety of species (1,5,8–10,13–15). Studies using CRD in testing opioids or other antinociceptive agents generally have not included data regarding how colonic motility may affect meaurements of antinociception. Mu opioids are known to produce effective antinociception as well as powerful effects on gastrointestinal motility (3,9,12,16). Thus, when using CRD as a nociceptive assay in testing opioids, especially μ opioids, it is important to know how these agents affect the distensibility of the colon, i.e., elastic and contractile properties of the colon. If opioids relax the colon and increase distensibility at the time when antinociceptive measurements are taken, then those measurements may be misleading. In addition, an increase in the threshold pressure stimulus following opioid treatments could be due to the increased distensibility of the colon and not a true antinociceptive effect. If the colon is affected by μ opioids in this manner, then CRD may not be appropriate as a nociceptive assay, because opioids may be creating an apparent antinociceptive effect by increasing the colonic diameter. On the other hand, if colonic motility is not changed by opioids, then CRD would be useful as a nociceptive assay. These studies were done to assess changes in colonic motility caused by oxymorphone to determine whether oxymorphone had changed colonic motility at a time when antinociceptive measurements were made.

METHODS

Subjects

Five Harlan Sprague-Dawley rats (480–590 g), trained for the CRD protocol, randomly received one IV dose of each of the following treatments: atropine sulfate (0.1 mg/kg; The Butler Company, Columbus, OH), oxymorphone hydrochloride (0.1 mg/kg; Numorphan; Dupont Pharmaceuticals, Manati, Puerto Rico), and saline (control). All drugs were administered in a blinded manner. The dose of atropine was selected for its gastrointestinal effects (4,17) and the dose of oxymor-

[1] Requests for reprints should be addressed to S. L. Briggs, B-300 Life Sciences, Michigan State University, East Lansing, MI 48824-1317.

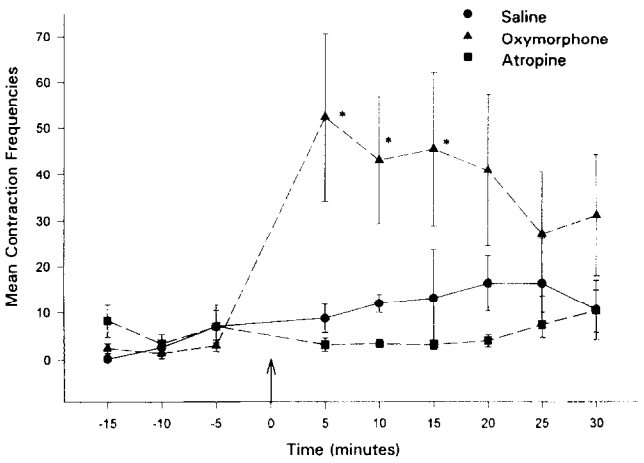

FIG. 1. Mean contractions per 5-min periods as measured for 15 min before drug injection and 30 min after drug injection. Each point represents the mean ± SE of data from five rats. Only oxymorphone-treated rats showed a significant (*$p < 0.05$) difference from control.

phone was selected for its analgesic effects (2). Oxymorphone at 0.1 mg/kg produced sedation, but not to an extent that prevented ambulation. Rats were trained to lie quietly while wrapped in a towel with a balloon catheter inserted into the colon per rectum. To obviate stress during the study, IV catheters were implanted into tail veins at least 15 min before each study. Nociceptive thresholds were established using an air-filled colonic balloon catheter. Air was used to distend the balloon to designated pressures and then released into a volume displacement system in which the volume of liquid displaced by the pressurized air was measured. When the pressure stimulus distended the balloon sufficiently to reach the minimum nociceptive threshold, the rat responded with an increased tone of abdominal muscles, also referred to as a guarding response. These contractions activated an abdominal belt equipped with a strain gauge (Omega Engineering, Stamford, CT), which caused significant deflections of an oscillograph trace. An oscillograph trace deflection denoting a nociceptive response is at least six times larger than that of background deflections in the absence of a stimulus (2). Nociceptive threshold data were represented graphically as a percent of the maximum possible effect (MPE) by subtracting the predrug control (C) from the postdrug pressure at time = n (PDn), and dividing that value by the difference of the maximum pressure (M) and the control pressure (C), and multiplying by 100 (7):

$$\text{MPE} = \frac{(\text{PDn} - \text{C})}{(\text{M} - \text{C})} \times 100$$

Next, the air-filled balloon catheter was removed and replaced with a water-filled balloon catheter to measure pressures and the contraction frequency of the colon. Colonic pressures and contractions were recorded for 15 min using a pressure transducer connected to a polygraph (model 7D; Grass Instruments Co., Quincy, MA). Only contractions producing at least a 5 mm Hg change in pressure were considered significant; these recorded deflections were later counted manually. After 15 min, IV catheters were flushed with 0.2 ml saline, the coded drug was administered, and catheters were again flushed with 0.2 ml saline. Pressures and colonic contractions were recorded for 30 min after drug administration. The water-filled balloon was then removed and replaced with the air-filled balloon and the CRD threshold was again measured.

A one-way repeated-measures analysis of variance (ANOVA) was performed on data from colonic pressures and the pressure-volume relationship of the stimuli. A two-way repeated measures ANOVA on two factors was used to test for differences between groups for frequency of contractions, and Student-Newman-Keuls test was used to determine differences between pairs. The criterion for a significant difference was $p < 0.05$.

RESULTS

Oxymorphone, (0.1 mg/kg, IV) produced a significant antinociceptive effect at 30 min postinjection (MPE mean ± SE = 100 ± 0%, $p < 0.05$), whereas neither atropine nor saline injections produced antinociception (MPE mean ± SE = 0 ± 0%, $p < 0.05$). Atropine or saline did not alter colonic motility following IV administration. However, oxymorphone did cause a transient increase in the frequency of phasic contractions. The increase in contraction frequency reached a peak at 5 min and declined toward baseline levels over the next 25 min (Fig. 1). Colonic pressures from oxymorphone-, atropine-, and saline-treated rats were compared, and there were no significant differences among groups. Also, colonic pressures for each treatment recorded for 30 min after drug injection were not different from pressures recorded for 15 min before drug injections. The stimulus pressure producing a guarding response during predrug trials (control pressure) was

TABLE 1

VOLUME (ml) DISPLACEMENT FROM CONTROL PRESSURE (mmHg) STIMULI, MEAN ± SE

	Before Drug Administration			After Drug Administration		
	Volume	Control Pressure		Volume	Control Pressure	
Treatment	(ml)	(mm Hg)	(n)	(ml)	(mm Hg)	(n)
Saline	7.8 ± 0.2	242 ± 6.6	5	6.8 ± 0.6	244 ± 6.7	5
	7.7 ± 0.4	242 ± 6.6	5			
Oxymorphone	8.1 ± 0.4	256 ± 13.6	5	7.7 ± 0.5	256 ± 13.6	5
	7.7 ± 0.5	256 ± 13.6	5			
Atropine	8.0 ± 0.2	244 ± 8.1	5	7.3 ± 0.2	244 ± 8.1	5
	7.5 ± 0.2	244 ± 8.1	5			

presented again 30 min after drug administration. Volumes of water displaced by the control pressure at 30 min did not differ from those displaced by those same pressures during predrug trials. Furthermore, volumes of water displacement were not changed by oxymorphone, atropine, or saline (Table 1).

DISCUSSION

μ Agonists have potent analgesic and gastrointestinal effects including profound changes in gastrointestinal motility. When using CRD to study opioid induced antinociception, it is necessary to establish that the analgesic effect is pharmacologically induced and not the result of an alteration in colonic distensibility. Because μ agonists can affect phasic and tonic contractions of the colon, measurements were made of the frequency of phasic contractions and of the baseline pressure or tone of the colon in oxymorphone-, atropine-, and saline-treated rats. Results showed that oxymorphone did not alter the tone of the colon compared to saline- and atropine-treated rats. This is indicated by the data in Table 1, which shows that drug treatment did not alter the pressure–volume relationship of the colon. Oxymorphone produced an increase in contraction frequency, as has been previously demonstrated (3,4,6,9). However, contraction frequency returned to levels similar to that of saline-treated rats at 30 min, at which time a maximum antinociceptive effect was observed. Furthermore, the pressure–volume relationship of the stimulus observed in all three treated groups did not change in this study, indicating that colonic distensibility was not affected by any treatment including oxymorphone. A similar observation was reported by Diop et al. (1), who found that morphine did not affect the tone of the colon. Thus, the observed "antinociception" of this study appeared to be due to pharmacologic alteration of nociceptive mechanisms rather than physiologic changes in colonic motility. From this study we conclude that CRD is a reliable nociceptive assay and oxymorphone-induced changes in colonic motility do not confound measurements of antinociceptive drug effects.

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