Turk J Anaesthesiol Reanim 2018; 46: 191-6 DOI: 10.5152/TJAR.2018.87519

Original Article / Özgün Araştırma

Comparison of *In Vitro* Effects of Opioid Analgesics on Spontaneous Proximal and Distal Colon Contractions in Healthy Rats and Rats with Peritonitis

Normal ve Peritonitli Rat Proksimal ve Distal Kolon Spontan Kontraksiyonlarına Opioid Analjeziklerinin *İn Vitro* Etkilerinin Karşılaştırılması

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Cite this article as: Erşan İ, Gürsoy S, Avcı O, Altun A, Bağcıvan İ, Düger C, et al. Comparison of *In Vitro* Effects of Opioid Analgesics on Spontaneous Proximal and Distal Colon Contractions in Healthy Rats and Rats with Peritonitis. Turk J Anaesthesiol Reanim 2018; 46: 191-6.

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Abstract / Öz

Objective: The goal of this study was to investigate and compare the effects of opioids on proximal and distal colon contractions in normal rats and rats with peritonitis, with and without the presence of naloxone in the environment.

Methods: The study was approved by Cumhuriyet University Ethics committee. In this study, 16 Wistar Albino male rats were used. Rats were divided into two groups. Peritonitis was induced using a cecum ligation and perforation method, 24 h before the tissues of rats in the peritonitis group were collected, and sham surgery was performed 24 h before the tissues of rats in the control group were collected. Twenty-four hours after the surgery, rats' organs were harvested and hung in organ baths. Concentration-dependent inhibitory effects of morphine and meperidine on spontaneous intestinal movements were observed. Any differences between the groups were tested using the Kruskal–Wallis test, and any differences between the groups were tested using the Tukey test.

Results: No significant difference was observed between the proximal and distal colon smooth muscle contraction responses in both groups after 80 mM Potassium Chloride (KCl) injection ($p>0.005$). In the peritonitis group, amplitudes and frequencies of spontaneous contractions in proximal and distal colon significantly increased ($p<0.05$). Drugs decreased the amplitude and frequency responses in the control group ($p<0.05$). In the peritonitis group, whereas morphine decreased the amplitude and frequency responses in comparison with the control group ($p<0.05$), meperidine did not cause any significant changes ($p>0.05$). In both groups, adding naloxone to the organ baths before adding opioids completely blocked the morphine's inhibitory effect on the amplitude and frequency ($p<0.05$), but it could not completely block the inhibition caused by meperidine.

Conclusion: Morphine and meperidine exhibit an inhibitory effect on the intestinal motility in both groups. This effect can be blocked by naloxone completely in morphine, and partially in meperidine.

Keywords: Peritonitis, opioid, intestinal motility, naloxone

Amaç: Bu çalışmada, opioidlerin normal ve peritonitli sıçan proksimal ve distal kolon kontraksiyonları üzerine olan etkilerinin, ortamda naloksan varlığında ve yokluğunda araştırılması ve karşılaştırılması amaçlandı.

Yöntemler: Çalışmamız Cumhuriyet Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylanmıştır. Çalışmada 16 adet Winstar Albino türü erkek sıçan kullanıldı. Sıçanlar iki gruba ayrıldı. Dokular alınmadan 24 saat önce peritonitli gruptaki sıçanlara çekal ligasyon ve perforasyon ile peritonit oluşturuldu, kontrol grubu sıçanlara ise sham operasyonu yapıldı. Operasyonlardan 24 saat sonra sıçanların dokuları alınıp organ banyosuna asıldı. Daha sonra morfin ve meperidin'in barsak spontan hareketleri üzerine konsantrasyona bağlı inhibitör etkilerine bakıldı. Gruplar arasında fark olup olmadığı Kruskal Wallis testi ile grup içi fark olup olmadığı Tukey testiyle test edildi.

Bulgular: Kontrol ve peritonit grubunda proksimal ve distal kolon düz kaslarının 80 mM Potassium Chloride (KCl) ile kasılma cevapları arasında anlamlı fark bulunamadı ($p>0,05$). Peritonitli grupta,proksimal ve distal kolonda spontan kontraksiyonların amplitüd ve frekansı anlamlı derecede arttı ($p<0,05$). Kontrol grubunda ilaçlar amplitüd ve frekans yanıtlarını anlamlı şekilde azalttı ($p<0,05$). Peritonit grubunda ise morfin amplitüd ve frekans yanıtlarını kontrole göre anlamlı şekilde azaltırken ($p<0.05$), meperidin istatistiksel olarak anlamlı bir fark meydana getirmedi ($p>0,05$). Her iki grupta, organ banyolarına opioid eklenmesinden önce naloksan uygulanması, morfinin amplitüd ve frekans üzerinde oluşturmuş oldukları inhibitör etkiyi tamamen engelledi ($p<0,05$). Meperidinin neden olduğu inhibisyonu tam olarak engelleyemedi.

Sonuç: Morfin ve meperidin her iki grupta barsak motilitesi üzerinde inhibitör bir etki yapmakta, bu etki naloksan ile morfinde tamamen, meperidinde ise kısmi olarak engellenebilmektedir.

Anahtar Kelimeler: Peritonit, opioid, intestinal motilite, naloksan

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Received / Geliş Tarihi : 06.12.2016
Accepted / Kabul Tarihi : 02.04.2018

Introduction

Opioids have been used by humans for approximately 4000 years. Since Friedrich Wilhelm Serturner achieved the crystallization of morphine in 1805, these substances have been greatly studied. Opioids are frequently used as analgesics and sedatives in the treatment of patients with severe acute and chronic pain, in postoperative pain, anesthetic practice, and intensive care patients. However, side-effects such as nausea, emesis, and decreased intestinal motility limit the use of opioids (1). These effects related to opioid use may result in a prolonged hospital stay and increased hospital bills (2).

Opioid agents activate the same receptors as natural opioids (3). They inhibit gastrointestinal transit by inhibiting neurotransmitter release and changing neuronal excitability.

Gastric emptying can be delayed, and enteral nutrition tolerance may decline due to opioid use in intensive care patients (4). The aim of this study was to compare in vitro effects of morphine and meperidine, which are frequently used agents in intensive care and anesthetic practice, on proximal and distal colon spontaneous contractions in healthy rats and rats with peritonitis.

Methods

This study was conducted in Cumhuriyet University Medical Faculty Experimental Animals Research Laboratory and Pharmacology Department Laboratory after the approval of the ethics committee (Date: 12.02.2009 No: 294). Sixteen Wistar albino male rats (8 in control and 8 in the peritonitis group) weighing between 250 and 350 g were used for this study. Peritonitis was induced through cecum ligation, and perforation method (CLP) 24 h before the tissues of rats in the peritonitis group were collected (5). Sham surgery was performed 24 h before the tissues of rats in the control group were collected.

As anesthetic agents, 3 mg kg^{-1} intramuscular (IM) Xylazine hydrochloride (Basilazin®) and 90 mg kg^{-1} IM ketamine (Ketalar®) were administered. Next, the rats were laid down in a supine position, and rats' abdomens were opened with a 2 cm midline abdominal incision. The cecum of the rats in the peritonitis group was opened (n=8) and tied over the ileocecal valve using 4/0 silk suture, so a closed section was created inside the intestines without disrupting the intestinal integrity. After ending the procedure, the cecum was placed back into the abdomen, and the incision was sutured as two layers. Anesthetics were applied to the control group in the same way (n=8). Laparotomy was performed, and the cecum was manipulated, but ligation and perforation were not performed. After these procedures, the cecum was placed back into the abdomen and sutured as two layers. 4 mg kg^{-1} subcutaneous carprofen (Rimadyl®) was applied as an analgesic in both groups.

Twenty-four hours after these operations, the rats were killed with a high dose (200 mg kg^{-1}) of intraperitoneal thiopental (Pentothal®) injection, and their abdomens were opened with a midline incision. Proximal and distal colon tissues were removed immediately and cleaned from the adjacent connective tissues and intestinal contents inside also are removed by using pre-gassed Krebs bicarbonate solution. Then tissues are cut into 1 cm whole layer preparations. These preparations were hung crosswise on two ends of a 10 mL organ bath, which was heated to 37°C and gassed with 95% O_2 and 5% CO_2 to test the agents. The inferior clip was hung to the bottom of the bath, and the superior clip was hung to the Force-Displacement Transducer with 4/0 silk. Next, 1.5 g of pre-tensioning was applied to the tissues, and they were left in for 1-hour resting to reach equilibrium while being washed every 15 minutes with a fresh solution. Tissue contractions were recorded with Grass FT 03 polygraph, Quincy, MA. After the balance period, 80 mM Potassium Chloride (KCl) was applied to the tissues to evaluate the amplitudes of spontaneous contractions, and the tissues were washed after contractions reached a plateau. After 30 minutes of balance period, concentration-related inhibitory effects on spontaneous contractions of morphine and meperidine were observed by administering agents to the organ baths in a cumulatively increasing manner from 10^{-8} to 10^{-4} [M] (mol L^{-1}, molar). After administering morphine alone and recording the alteration in contractility, tissues were washed with Krebs solution and incubated for 30 minutes to reach another equilibrium state. Then, meperidine was administered in the same manner. After evaluating the effects of morphine and meperidine on the amplitude and frequency of proximal and distal colon, the same experiments were repeated in the presence of 10^{-5} [M] (mol L^{-1}, molar) naloxone to see the role of opioid receptors in the observed effect.

At the beginning of each experiment, 80 mmol L^{-1} KCl was added to the organ bath, and the contraction was considered to be the reference response. After the application of morphine or meperidine alone and in the presence of antagonists, the amplitude of spontaneous contractions of the isolated proximal and distal colon muscle segments was calculated as a percentage of contractions induced by KCl (80 mmol L^{-1}) in both control and peritonitis groups. Changes in the frequency (number/min) of spontaneous contractions were expressed as the number of contractions for 10 min intervals.

Statistical analysis

The data acquired from this study were statistically evaluated using Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 15.0. Data were expressed as mean±standard error of the mean (SEM). Any differences between the groups were tested using Kruskal-Wallis test, and any differences between the groups were tested using Tukey test. A p-value <0.05 was considered significant.

Results

No significant difference was observed between the proximal and distal colon smooth muscles contraction responses in the

Table 1. Proximal and distal colon contraction values with KCl

	Contraction (gr)	
	Control	**Peritonitis**
Proximal colon	2.98±0.40	2.89±0.32
Distal colon	2.92±0.43	2.84±0.27

Data were expressed as mean±standard error of the mean (SEM)
KCI: Potassium Chloride

Table 2. Proximal and distal colon spontaneous contraction amplitudes percentages (as KCl percentage)

	Contraction (gr)	
	Control	**Peritonitis**
Proximal colon	32.7±7.2	58.1±6.1*
Distal colon	60.6±6.3#	112.4±6.2*#

*Statistically different when compared to the control group, p<0.05
#Statistically different when compared to the proximal colon amplitudes, p<0.05
Data were expressed as mean±standard error of the mean (SEM)

Table 3. Morphine's and meperidine's effects on proximal and distal colon amplitudes

Proximal colon	**Control**	**Peritonitis**
Morphine	78.8±8.8*	77.7±8.7*
Meperidine	75.2±5.0**	101.7±5.0
Distal colon		
Morphine	86.6±11.4*	80.2±12.5*
Meperidine	86.9±10.5**	98.6±9.4

*Statistically different when compared to the meperidine group, p<0.05
**Statistically different when compared to both meperidine and peritonitis group, p<0.05
Data were expressed as mean±standard error of the mean (SEM)

control and peritonitis groups after 80 mM KCl injection (Table 1).

Peritonitis significantly increased spontaneous contraction amplitudes in the proximal and distal colon. In the control group, the amplitude of the proximal colon was significantly lower compared with that of the distal colon (p=0.015). Amplitudes were significantly high both in the proximal and distal colon in the peritonitis group compared with the control group (Table 2).

Changes in amplitude responses were assessed by adding morphine and meperidine to the organ baths. All drugs in control group significantly lowered amplitude responses in proximal and distal colon tissues, compared to control (p=0.026). In the peritonitis group, while morphine significantly reduced amplitude responses compared to control (p=0.019), meperidine did not make any significant differences (Table 3).

Table 4. Opioid agonists' effects on proximal and distal colon amplitudes, both alone and following naloxone application

Proximal colon	**Control**		**Peritonitis**	
VEH	32.7±2.2	32.7±2.2	58.1±6.2	58.1±5.4
Morphine	25.8±2.5	32.9±2.2	45.2±2.5	56.9±4.2
Meperidine	24.6±2.8	29.6±3.8	59.1±2.8	59.0±4.7
Distal colon				
VEH	60.6±7.2	60.6±7.2	112.4±6.2	112.4±5.4
Morphine	52.5±2.5	60.8±3.9	90.2±5.5	112.4±4.8
Meperidine	52.7±2.8	54.7±4.6	110.9±5.8	112.4±4.2

Data were expressed as mean±standard error of the mean (SEM). VEH: vehicle

Table 5. Frequency counts (count/10 minutes)

	Control	**Peritonitis**
Distal colon	10.8±1.4	20.4±2.9*
Proximal colon	9.2±1.6	17.4±2.0*

*Statistically different when compared to the control group, p<0.05
Data were expressed as mean±standard error of the mean (SEM)

Table 6. Opioid agonists' effects on frequencies in the proximal and distal colon in the control and peritonitis group

Proximal colon		
Morphine	35.0±3.1	55.7±3.9
Meperidine	37.1±3.8	57.6±3.3
Distal colon		
Morphine	13.3±1.8	23.7±2.7
Meperidine	14.3±2.2	24.6±2.9

Data were expressed as mean±standard error of the mean (SEM)

In proximal and distal colon control tissues, the inhibitory effect of morphine on proximal and distal colon amplitude was entirely blocked in the presence of naloxone (p=0.035). In the tissues exposed to meperidine, however, while the inhibition decreased, it did not fully disappear. In proximal and distal colon peritonitis tissues. The inhibitory effect of morphine on proximal and distal colon amplitude was fully blocked in the presence of naloxone (p<0.05). On the contrary, meperidine did not have any effects on proximal and distal colon amplitude responses; therefore, adding naloxone before meperidine did not result in any significant changes in the amplitudes (Table 4).

A significant increase in frequencies was observed when the control and peritonitis groups were compared to smooth muscle spontaneous contraction frequencies in the proximal and distal colon (Table 5).

Table 7. Opioid agonists' effects on proximal and distal colon frequencies, both alone and following naloxone application

Proximal colon	**Control**		**Peritonitis**	
Vehicle	40.7±2.6	40.7±2.6	62.8±2.8	62.8±2.8
Morphine	32.9±1.1	40.5±1.6	55.7±1.9	63.5±1.7
Meperidine	35.1±1.8	38.9±1.5	57.6±1.3	60.9±1.4
Distal colon				
Vehicle	17.7±1.4	17.7±1.4	28.1±1.8	28.1±1.8
Morphine	13.3±0.8	18.9±0.8	23.7±1.7	29.2±1.5
Meperidine	14.3±1.2	16.7±1.2	24.6±1.9	27.9±1.4

Changes in frequency values were investigated by adding opioid agonists to the environment, morphine, and meperidine. Adding morphine and meperidine to the environment significantly decreased the contraction frequencies of proximal and distal colon tissues in both the control and peritonitis group. But there were no significant differences between the effects of the opioid agonists on the frequency (Table 6).

In proximal and distal colon control and peritonitis tissues, adding naloxone to the organ baths before the addition of opioids completely blocked the inhibitory effect on the distal colon frequency ($p<0.05$). In the tissues that were exposed to meperidine, however, while the inhibition decreased, it did not fully disappear (Table 7).

Discussion

Potassium channels in colon smooth muscle cells differ from other ion channels similar to other smooth muscle cells (6). In colon smooth muscles, calcium influx via voltage-gated calcium channels and potassium efflux via potassium channels is always required (7). In our study, KCl did not yield different results between both groups and each tissue. After the balance period, 80 mM KCl was applied to the tissues to evaluate the amplitudes of spontaneous contractions. In the peritonitis group, the amplitudes were significantly high both in the proximal and distal colon, when compared to the control group, these sentences are from the text, and so the control and peritonitis groups are not similar in response to KCl. Similar contraction responses of tissues in control and peritonitis groups to potassium chloride indicate that peritonitis does not affect these mechanisms on the cellular level and that physiologic contractile mechanisms of colon smooth muscles in peritonitis are intact.

Peritonitis is the most frequent reason for mortality and morbidity in surgical intensive care units (8). The cecum ligation and perforation technique described by Baker (9), which we used in our study to induce peritonitis, is a hyper-dynamic and normotensive peritonitis model that can cause sepsis in 24 h, and imitate human clinical symptomatology of peritonitis and sepsis the best. Peritonitis can cause many symptoms, primarily small volume diarrhea. Koyluoglu et al. (10) showed that peritonitis does not cause a decrease in the amplitude and frequency of spontaneous contractions in the jejunum and ileum. Similar to the study conducted by Koyluoglu et al. (10), Aydin et al. (11) showed a significant amplitude and frequency decrease of ileum spontaneous contractions. In contrast to this, in the present study, both the amplitude and frequency responses of the proximal and distal colon in the peritonitis group increased significantly. This response difference to peritonitis of two closely related parts of the gastrointestinal system can be explained with embryonic development and innervation difference and shows the importance of the knowledge about gastrointestinal motility changes in pathological conditions.

On the other hand, in a study by Yildiz et al. (12) in 2007, amplitudes and frequencies of proximal and distal colon spontaneous contractions showed a significant decrease in the presence of peritonitis, which is completely contrary to our findings. This difference may be related to the ages of animals used in the experiments or the method used to induce peritonitis. As Mikawa et al. (13) demonstrated in their study, inflammation is a process, and the actors change dramatically during the course of abdominal inflammation. This situation affects the motility of the intestinal system as well. This may explain why to the diarrhea is one of the main symptoms at the beginning of the peritonitis, where constipation and an even ileus can be observed by the time inflammation progresses. Since our study aimed to focus on the hyperactive phase of peritonitis, it seems that we managed to catch the right time frame and reduce the diarrhea-like effects of inflammation by using opioid agents.

Morphine and Meperidine are well-known and frequently used opioid analgesics in the clinic. They show their effects by binding to central and peripheric opioid receptors (mu [μ], kappa [κ], and delta [δ]). Endogenic opioid peptides and opioid receptors are widespread in mammals' gastrointestinal system (14). Tissue injury and peripheral inflammation increase local endogenic opioid peptides and opioid receptor sensitivity (15).

When tissues with and without inflammation were compared, the increased opioid analgesic effect in tissues with inflammation was observed, as a result of opiate's peripheral effect (16). It was reported that in the presence of intestinal inflammation in rats, morphine's inhibitory efficacy tripled (17). The same researchers showed in another study that fentanyl's inhibitory effect on gastrointestinal transit increased during intestinal inflammation (18). Topcu et al. (19) observed that fentanyl prolongs gastrointestinal transit duration of rats while a systemic inflammation was present in 2006.

In 1987, Jacoby et al. (20) came to a conclusion that opioids inhibit intestinal propulsive motility, prolong transit duration, and thereby cause constipation.

The reason for the depressive effect on intestinal motility induced by opioids is contradictive. Parolaro et al. (21) reported in 1977 that morphine changes intestinal autonomic stimulus through the central nervous system. Manara et al. (22) reported in 1986 that morphine also inhibits gastrointestinal motility via intestinal opioid receptors.

In this study, morphine's and meperidine's effects on proximal and distal colon spontaneous contractions were evaluated in the peritonitis and control groups. Similar to the studies above, all opioid agonists decreased spontaneous contraction amplitudes and frequencies of the proximal and distal colon in the control group. In the peritonitis group, however, while morphine reduced contractions, meperidine did not make any changes. Our study showed that opioid agonists inhibit intestinal motility, in compliance with the literature. Distinctly in this study, opioid agonists were compared with each other. Based on this result, we can say that opioid agonists can successfully be used for the treatment of diarrhea seen in patients with peritonitis. While morphine inhibits uterus smooth muscle contractions (23), meperidine delays birth without affecting uterus smooth muscle contractions (24). In parallel with this, meperidine inhibited the intestinal smooth muscle contractions the least among opioid agonists in this study. Meperidine inhibiting intestinal motility in the control group and this effect not being present in the peritonitis group indicate that one or more mechanisms in which meperidine shows it effects on intestines may be a defect in the case of peritonitis. In addition, opioid agonists' intestinal motility inhibiting effect was more significant in the control group than in the peritonitis group, which shows that the principal mechanism of action of opioid agonists, opioid receptors, might be affected in the case of peritonitis. These findings also suggest that diarrhea seen in peritonitis may be related to the decrease of opioid receptor density and, as a result, decreased suppressing of the effect of endogenic opioids on intestinal motility.

Shahbazian et al. (25) in 2002 concluded in their studies that the intestinal motility inhibition and peristaltic motor activity depression caused by opioids are related to mu, kappa, and probably sigma opioid receptors.

In this study, opioid receptors were blocked with an opioid receptor antagonist naloxone, to determine their role in intestinal motility before applying opioid agonists. In the control group, naloxone entirely blocked morphine's inhibitory effect on intestinal motility, while only partially blocking meperidine's inhibition. This finding of morphine, in compliance with the literature, proves that its action mechanism only consists of opioid receptors. The finding of meperidine, on the other hand, shows that other action mechanisms may have a role in its inhibitory effect alongside opioid receptors.

Conclusion

Frequently used opioid agonists in postoperative and intensive care patients as an analgesic, morphine, and meperidine, have an inhibitory effect on isolated intestinal spontaneous motility. This effect could be blocked with naloxone fully in morphine and partially in meperidine. Peritonitis, while affecting several tissues and systems, also affects the intestines and causes changes in various segments. This study shows that one of the affected systems is the opioidergic system and that probably an injury or dysfunction of opioid receptors took place. But further research is required to confirm these effects with other methods and to reveal the underlying mechanisms in more detail.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cumhuriyet University School of Medicine (Date: 12.02.2009 No: 294).

Informed Consent: Written informed consent was not obtained because this is an animal study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.E., S.G., O.A.; Design - İ.E., S.G., O.A.; Supervision - A.A., İ.B.; Resources - C.D., İ.Ö.K.; Materials - A.A., İ.B.; Data Collection and/or Processing - K.K., M.C.M.; Analysis and/or Interpretation - İ.E., S.G., O.A.; Literature Search - C.D., O.A., K.K.; Writing Manuscript - İ.E., S.G., O.A.; Critical Review - C.D., İ.O.K.; Other - K.K., M.C.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Cumhuriyet Üniversitesi Tıp Fakültesi'nden (Tarih: 12.02.2009, No: 294) alınmıştır.

Hasta Onamı: Hayvan çalışması olduğu için hasta onamı alınmamıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - İ.E., S.G., O.A.; Tasarım - İ.E., S.G., O.A.; Denetleme - A.A., İ.B.; Kaynaklar - C.D., İ.Ö.K.; Malzemeler - A.A., İ.B.; Veri Toplanması ve/veya İşlemesi - K.K., M.C.M.; Analiz ve/veya Yorum - İ.E., S.G., O.A.; Literatür Taraması - C.D., O.A., K.K.; Yazıyı Yazan - İ.E., S.G., O.A.; Eleştirel İnceleme - C.D., İ.O.K.; Diğer - K.K., M.C.M.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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