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Differential effect of indomethacin and ketorolac on postoperative ileus in rats

Benedicte Y. De Winter [a], Guy E. Boeckxstaens [b], Joris G. De Man [a], Tom G. Moreels [a], Arnold G. Herman [a], Paul A. Pelckmans [a,*]

[a] *Division of Gastroenterology and Pharmacology, Faculty of Medicine, University of Antwerp, Universiteitsplein 1, 2610 Antwerp-Wilrijk, Belgium*
[b] *Division of Gastroenterology and Hepatology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

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Abstract

The effect of two prostaglandin biosynthesis inhibitors and their interaction with the L-arginine/nitric oxide (NO) pathway was investigated in a rat model of experimental ileus. The gastrointestinal transit was measured as the migration of Evans blue after three different operations. Indomethacin completely reversed the additional inhibition of the transit induced by mechanical stimulation of the gut. Ketorolac completely reversed the inhibition of the transit induced by the laparotomy, but had no additional effect on the inhibition induced by mechanical stimulation of the gut. Administration of indomethacin plus L-nitroarginine or L-arginine could not enhance or prevent the effect of indomethacin alone. Administration of ketorolac and L-nitroarginine completely reversed the transit after the laparotomy plus manipulation whereas ketorolac plus L-arginine had no additional effect as compared to ketorolac alone. From these findings we conclude that in addition to NO, prostaglandins are involved in the pathogenesis of postoperative ileus in the rat. However, indomethacin and ketorolac differentially affect postoperative ileus suggesting that prostaglandins are involved in different pathogenic mechanisms leading to postoperative ileus. © 1998 Elsevier Science B.V.

Keywords: Gastrointestinal transit; Nitric oxide (NO) synthase; Prostaglandin; Ileus; Analgesia; NSAID (non-steroidal anti-inflammatory drug)

1. Introduction

Postoperative ileus is a common complication after abdominal surgery of which the pathogenesis is still debated. It is generally accepted that ileus involves the activation of an inhibitory nervous reflex pathway with the efferent limb consisting of adrenergic inhibitory fibers and the afferent limb consisting of capsaicin sensitive fibers (Dubois et al., 1973; Furness and Costa, 1974; Holzer et al., 1986; Livingston and Passaro, 1990; Holzer et al., 1992). However, other mechanisms such as the activation of inhibitory non-adrenergic non-cholinergic (NANC) nerves (Abrahamsson et al., 1979; Glise and Abrahamsson, 1980) may contribute as well. Nitric oxide (NO) is generally accepted as one of the main inhibitory NANC neurotransmitters in the gastrointestinal tract (Rand and Li, 1995; Boeckxstaens and Pelckmans, 1998). We previously showed the involvement of both adrenergic and nitrergic NANC nerves in the pathogenesis of postoperative ileus in the rat. In these experiments it was shown that the additional inhibitory effect of mechanical stimulation of the gut resulted from an enhanced release of NO by the constitutive NO synthase (De Winter et al., 1997).

There is recent evidence for an interaction between NO and prostaglandins. NO and prostaglandins are synthesised by NO synthase and cyclooxygenase, respectively. Both enzymes consist in a constitutive and an inducible isoform: constitutive NO synthase and cyclooxygenase 1 are the constitutive isoforms and inducible NO synthase and cyclooxygenase 2 the inducible isoforms (Di Rosa et al., 1996). In physiological conditions there is a stimulation of prostaglandin biosynthesis by NO produced by the constitutive NO synthase (Sautebin et al., 1995). In inflammatory conditions, inducible NO synthase and cyclooxygenase 2 are co-expressed in many cells and there is a NO-driven activation of cyclooxygenase resulting in an increased production of pro-inflammatory prostaglandins (Salvemini et al., 1995). The data concerning the actions of prostaglandins on NO synthase are conflicting, reporting

* Corresponding author. Tel.: +32-3-8213323; fax: +32-3-8254678; e-mail: pelckman@uia.ua.ac.be

either an inhibition or an enhancement of the NO production in different models (Salvemini et al., 1995; Sautebin et al., 1995; for review see Di Rosa et al., 1996). Prostaglandins are produced throughout the gastrointestinal tract and influence gastrointestinal secretion, motility and inflammation. Prostaglandins are able to contract or relax intestinal smooth muscle depending on the type of prostaglandins administered and depending on the type of muscle layer involved, longitudinal or circular (Ferreira et al., 1976; Frantzides et al., 1992; for review see Eberhart and Dubois, 1995). Administration of indomethacin, an inhibitor of the prostaglandin biosynthesis, increased intestinal motility in dogs and increased gastric emptying of a hyperosmolar test meal in rats, indicating that endogenous prostaglandins are important in the physiological control of intestinal motility (Thor et al., 1985; Stein et al., 1994). Indomethacin induced duodenal and jejunal contractions after abdominal surgery in the rat and the cat (Gustafsson and Delbro, 1993; Sababi et al., 1996). Non-steroidal anti-inflammatory drugs (NSAID) are known for their ability to block the prostaglandin biosynthesis and they are widely used to control postoperative pain mainly for their analgesic activities. Pre-treatment with these drugs could interfere with the initiation of pain in the periphery and minimise the activation and sensitisation of peripheral nociceptors, thereby minimising the noxious input into the central nervous system and attenuating the response normally observed after surgical trauma (Dahl and Kehlet, 1991). Both indomethacin and ketorolac are NSAID's acting preferentially on cyclooxygenase 1 (Pallapies et al., 1995; Frölich, 1997). Ketorolac is proposed as a more potent analgesic reducing the postoperative need for opioid analgesia (Sampson et al., 1996). As NSAID's were shown to be beneficial in the treatment of postoperative ileus in rodents (Pairet and Ruckebusch, 1989; Kelley et al., 1993; Sababi et al., 1996), we investigated the effect of indomethacin and ketorolac in our rat model of postoperative ileus. As we previously demonstrated that NO is involved in postoperative ileus in rats, we also investigated the interaction between NO and prostaglandins in postoperative ileus in the rat.

2. Materials and methods

2.1. Operation protocol

All procedures received approval from the Commission for Medical Ethics from the University of Antwerp (U.I.A.). Male Wistar rats (150–220 g) were fasted for 48 h with free access to water. The operation protocol was previously described in detail (De Winter et al., 1997). Briefly, the rats were divided in three groups in a randomised way and underwent an operation under ether anaesthesia. Ether anaesthesia was chosen as, in contrast to pentobarbital, its effect on gastrointestinal motility approximately lasted for only 1 h after the induction of the anaesthesia (Bueno et al., 1978; De Winter et al., 1997). The first group underwent an abdominal skin incision after shaving and disinfecting of the abdomen. The second group underwent a laparotomy consisting of the incision of the abdominal skin, the abdominal muscle layers and the peritoneum. The third group underwent a laparotomy followed by the evisceration and manipulation of the small intestine and caecum (laparotomy plus manipulation). Therefore the small intestine and caecum were gently pulled out of the abdominal cavity and unfurled like a fan on two sterile gauzes covering the abdomen of the rat. After 5 min of gentle manipulation the small intestine and caecum were replaced in the abdominal cavity and the surgical wound was sutured. After the operations the rats were allowed to recover for 1 h. Then they received an intragastric injection of 0.1 ml Evans blue (50 mg in 1 ml 0.9% sodium chloride; Tanila et al., 1993) via a specially designed orogastric cannula introduced through the mouth. The rats were killed 20 min later by a cardiotomy after ether anaesthesia and the intestinal transit was measured from the pylorus to the most distal point of migration of Evans blue and expressed in cm.

2.2. Experimental protocol

In a first series of experiments the effect of indomethacin (3 mg/kg), a prostaglandin synthase inhibitor, was tested on the intestinal transit of Evans blue. This dose of indomethacin was previously shown to inhibit prostaglandin synthesis in the rat (Salvemini et al., 1995). The rats were randomly divided in four groups. The first group served as control group and received an intravenous (i.v.) injection of sterile water in the tail vein. Then the rats underwent a skin incision, laparotomy or a laparotomy followed by the evisceration and manipulation of the small intestine and caecum. The second group received an i.v. injection of indomethacin (3 mg/kg) 1 min before the operations. The third group received an i.v. injection of indomethacin immediately followed by an i.v. injection of the NO synthase inhibitor, L-nitroarginine (5 mg/kg), 1 min before the operations. The fourth group was injected i.v. with indomethacin, followed by the NO substrate, L-arginine (300 mg/kg), 1 min before the operations.

In a second series of experiments we investigated the effect of ketorolac (1 mg/kg), a prostaglandin synthase inhibitor with more potent analgesic properties, on the intestinal transit of Evans blue after the three operations. The dose we used was previously shown to inhibit prostaglandin synthesis in the rat (Pallapies et al., 1995). The rats were randomly divided in four groups. The first group served as control group and received an i.v. injection of sterile water. The second group was injected i.v. with ketorolac (1 mg/kg) 1 min before the operations. The third group received an i.v. injection of ketorolac followed by an i.v. injection of L-nitroarginine, the NO synthase

inhibitor (5 mg/kg). The fourth group received an i.v. injection of ketorolac followed by an i.v. injection of the NO synthase substrate L-arginine (300 mg/kg).

2.3. Drugs used

The following drugs were used: diethyl ether (Merck, Darmstadt, Germany), Evans blue, L-arginine hydrochloride, N^{ω}-nitro-L-arginine (Sigma, St. Louis, MO), indomethacin sodium trihydrate (Merck Sharp and Dohme, Rahway, NJ), ketorolac tromethaminum (Taradyl®, Syntex, Roche, Brussels), sodium chloride 0.9% (Plurule®) and sterile water (Baxter, Lessines, Belgium). Indomethacin and ketorolac were dissolved in sterile water, L-nitroarginine and L-arginine were dissolved in 0.9% sodium chloride.

2.4. Presentation of results and statistical analysis

The total length of the small intestine was not statistically different between the groups. Therefore, results are expressed as cm migration of Evans blue, the measurements were from the pylorus to the most distal point of migration of Evans blue. Group differences were assessed by simple factorial analysis of variance (ANOVA) and one way analysis of variance followed by the Bonferroni test for multiple comparisons. Values are shown as mean ± S.E.M. for n indicates the number of rats used. *P*-values ≤ 0.05 were considered to be significant. All data were analysed with the SPSS for Windows software (SPSS, Chicago, IL).

3. Results

3.1. Effect of indomethacin on intestinal transit

The total length of the small intestine was not statistically different between the different groups. In control rats, treated with sterile water, the transit after skin incision was 61.3 ± 2.1 cm of 99.9 ± 1.5 cm ($n = 9$). The transit was not influenced by the skin incision as previously shown (De Winter et al., 1997). The transit was significantly delayed by laparotomy to 40.7 ± 3.8 cm of 99.2 ± 2.0 cm ($n = 9$). This inhibition was even more pronounced when the laparotomy was followed by evisceration and manipulation of the small intestine and caecum; the transit was 18.0 ± 2.7 cm of 96.8 ± 1.3 cm ($n = 9$) (Fig. 1).

Treatment of the rats with indomethacin (3 mg/kg) alone, with indomethacin plus L-nitroarginine (5 mg/kg) or with indomethacin plus L-arginine (300 mg/kg), had no effect on the transit after skin incision or laparotomy as compared to control rats ($n = 9$) (Fig. 1). However, the transit after the laparotomy plus manipulation was significantly increased by indomethacin, from 18.0 ± 2.7 cm in control rats to 34.3 ± 4.7 cm in indomethacin treated rats ($n = 9$) (Fig. 1). Indomethacin plus L-nitroarginine or indomethacin plus L-arginine could not enhance or prevent the effect of indomethacin alone on the transit after the laparotomy plus manipulation; the transit was respectively 30.8 ± 2.2 and 32.6 ± 2.5 cm ($n = 9$) (Fig. 1).

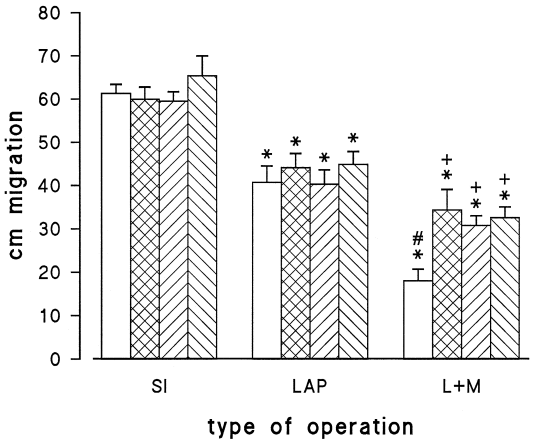

Fig. 1. Effect of skin incision (SI), laparotomy (LAP) or laparotomy plus manipulation of the small intestine and caecum (L + M) on the intestinal transit in control rats (open bars, $n = 9$) and in rats treated i.v. with indomethacin 3 mg/kg (cross-hatched bars, $n = 9$) or with indomethacin plus L-nitroarginine 5 mg/kg (right-rising hatched bars, $n = 9$) or with indomethacin plus L-arginine 300 mg/kg (left-rising hatched bars, $n = 9$). Results are expressed as cm migration of Evans blue and shown as mean ± S.E.M. $^{*}P \leq 0.05$, significantly different from the transit after skin incision (SI) in rats with the same treatment; $^{\#}P \leq 0.05$, significantly different from the transit after laparotomy (LAP) in rats with the same treatment; $^{+}P \leq 0.05$, significantly different from the transit of control rats that underwent the laparotomy plus manipulation (L + M); one way analysis of variance followed by the Bonferroni test.

After treatment of the rats with indomethacin alone, with indomethacin plus L-nitroarginine or indomethacin plus L-arginine, the transit after laparotomy plus manipulation was no longer significantly different from transit after laparotomy alone.

3.2. Effect of ketorolac on intestinal transit

There was no statistical significant difference in total length of the small intestine between the groups. In control rats, treated with sterile water, the transit after skin incision was 65.9 ± 3.3 cm of 100.9 ± 1.9 cm ($n = 9$). The transit after laparotomy was significantly delayed to 41.9 ± 2.5 cm of 98.8 ± 1.9 cm ($n = 9$). After the laparotomy plus manipulation, the transit was 18.6 ± 2.1 cm of 96.1 ± 1.7 cm ($n = 9$) (Fig. 2).

Treatment of the rats with ketorolac alone (1 mg/kg), with ketorolac plus L-nitroarginine (5 mg/kg) or with ketorolac plus L-arginine (300 mg/kg) had no effect on the transit after skin incision ($n \geq 9$) (Fig. 2). However, in contrast to indomethacin, ketorolac completely reversed the transit after laparotomy from 41.9 ± 2.5 cm in control rats to 60.6 ± 4.2 cm in ketorolac treated rats ($n = 9$). Ketorolac plus L-nitroarginine or ketorolac plus L-arginine

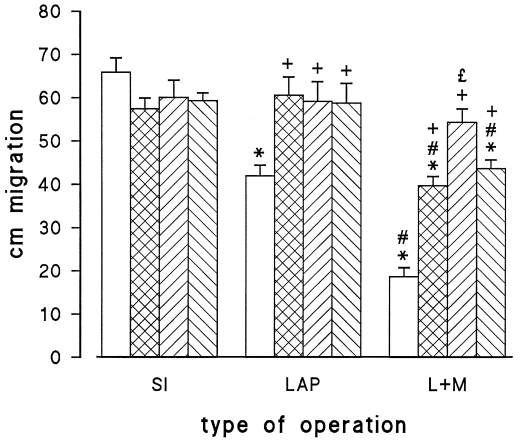

Fig. 2. Effect of skin incision (SI), laparotomy (LAP) or laparotomy plus manipulation of the small intestine and caecum (L + M) on the intestinal transit in control rats (open bars, $n = 9$) and in rats treated i.v. with ketorolac 1 mg/kg (cross-hatched bars, $n \geq 9$) or with ketorolac plus L-nitroarginine 5 mg/kg (right-rising hatched bars, $n = 9$) or with ketorolac plus L-arginine 300 mg/kg (left-rising hatched bars, $n = 9$). Results are expressed as cm migration of Evans blue and shown as mean ± S.E.M. $^{*}P \leq 0.05$, significantly different from the transit after skin incision (SI) in rats with the same treatment; $^{\#}P \leq 0.05$, significantly different from the transit after laparotomy (LAP) in rats with the same treatment; $^{+}P \leq 0.05$, significantly different from the transit of control rats with the same operation; $^{£}P \leq 0.05$, significantly different from the transit in the other treatment groups that underwent a laparotomy plus manipulation (L + M), one way analysis of variance followed by the Bonferroni test.

had no additional effect on the transit after laparotomy as compared to ketorolac alone: the transit was 59.2 ± 4.5 and 58.8 ± 4.5 cm, respectively ($n = 9$) (Fig. 2). The transit after the laparotomy plus manipulation was only partially reversed by ketorolac from 18.6 ± 2.1 cm in control rats to 39.7 ± 2.1 cm in ketorolac treated rats ($n = 9$) (Fig. 2). Ketorolac plus L-arginine had no additional effect on the transit after the laparotomy plus manipulation as compared to ketorolac alone: transit was 43.6 ± 2.0 cm ($n = 9$) (Fig. 2). However, treatment of the rats with ketorolac plus L-nitroarginine, completely reversed the transit after laparotomy plus manipulation from 18.6 ± 2.1 cm in control rats to 54.4 ± 3.1 cm in rats treated with ketorolac plus L-nitroarginine ($n = 9$) (Fig. 2).

The transit after the laparotomy plus manipulation was significantly different from the transit after skin incision or laparotomy in the rats treated with ketorolac alone or with ketorolac plus L-arginine. However, in the rats treated with ketorolac plus L-nitroarginine there was no difference between the transit after the three operations (Fig. 2).

4. Discussion

Postoperative ileus is a common complication after surgery of which the pathogenesis is still debated. Previously, we demonstrated a role for nitrergic and adrenergic neurons in the pathogenesis of postoperative ileus in rats. In the present study, we provide evidence that also prostaglandins are involved in the pathogenesis of postoperative ileus.

In our rat model we applied three different nociceptive stimuli: skin incision, laparotomy and laparotomy plus mechanical stimulation of the gut, resulting in different degrees of inhibition of the intestinal transit. Skin incision did not affect the intestinal transit, whereas the transit was significantly delayed by the laparotomy. This inhibition was even more pronounced when the laparotomy was associated with mechanical stimulation of the gut. Similar results were shown by Bueno et al. (1978). Previously, we demonstrated that the inhibition of the transit induced by laparotomy resulted from an hyperactivity of adrenergic neurons as we were able to reverse the inhibition of the transit by reserpine, an adrenergic neuron blocking drug (De Winter et al., 1997). We could also demonstrate that mechanical stimulation of the gut triggers an additional non-adrenergic pathway mediated by nitrergic neurons since treatment with L-nitroarginine, a NO synthase inhibitor, did not affect the transit after the skin incision or laparotomy but reversed the additional inhibition of the transit induced by mechanical stimulation. This effect of L-nitroarginine was prevented by concomitant administration of L-arginine, the NO synthase substrate. L-arginine alone had no effect on the transit after skin incision or laparotomy but significantly increased the additional inhibitory effect of mechanical stimulation (De Winter et al., 1997).

Several studies demonstrated that prostaglandins can act as local regulatory agents in the control of digestive motility since indomethacin increased intestinal motility in chronically instrumented dogs and increased gastric emptying of a hyperosmolar test meal in rats that did not undergo surgery (Thor et al., 1985; Stein et al., 1994). However, in the present study, indomethacin and ketorolac had no influence on the gastrointestinal transit in rats that underwent a skin incision, indicating that there is no role for endogenous prostaglandins in the intestine having a normal transit.

Indomethacin had no effect on the transit after laparotomy but reversed the additional inhibition induced by mechanical stimulation of the gut. These results are in accordance with the study of Pairet and Ruckebusch (1989). We previously obtained the same results with the NO synthase inhibitor L-nitroarginine as with indomethacin: they did not influence the transit after skin incision or laparotomy but completely reversed the additional inhibition induced by mechanical stimulation of the gut (De Winter et al., 1997). These results suggest the release of NO and prostaglandins by mechanical stimulation of the gut. Similarly, an increased release of prostaglandins and NO was shown by Sababi et al. (1996) after handling of the rat duodenum. There is recent evidence for an interaction between NO and prostaglandins suggesting that NO increases prostaglandins biosynthesis in physiological and

pathophysiological conditions and suggesting that there is an up- or down-regulation of NO by prostaglandins (Salvemini et al., 1995; Sautebin et al., 1995; Di Rosa et al., 1996). Although L-arginine, the NO synthase substrate, prevented the effect of L-nitroarginine (De Winter et al., 1997), it did not alter the effect of indomethacin suggesting that indomethacin does not compete or interact with the substrate of NO synthase. Indomethacin could also interact with NO synthase itself independent of substrate availability: it might act directly on NO synthase or affect NO synthase for example by interfering with the calcium homeostasis (Northover, 1977). Gustafsson and Delbro (1993) showed the induction of jejunal hypermotility by indomethacin in the anaesthetised cat. They suggested that the effect of indomethacin was unrelated to the inhibition of prostaglandins but was caused by an inhibition of the inhibitory nitrergic NANC nerves. This is in agreement with our study in which L-nitroarginine could not enhance the effect of indomethacin on the transit after the laparotomy plus manipulation. These results suggest that prostaglandins and NO indeed act in series in the same pathway activated by mechanical stimulation of the gut. However, in order to unravel this pathway measurements of prostaglandins and NO products should be performed.

In contrast to indomethacin, pre-treatment with ketorolac completely reversed the inhibition induced by laparotomy in our model. On the other hand, ketorolac could only partially reverse the inhibition of the transit induced by the laparotomy plus manipulation. The effect of ketorolac on the transit after the laparotomy plus manipulation is comparable to the effect on the transit after the laparotomy alone. Thus, in contrast to indomethacin, ketorolac is not able to reverse the additional inhibition induced by mechanical stimulation of the gut. In a clinical study, Ferraz et al. (1995) reported that ketorolac resulted in a faster resolution but not in the prevention of ileus after elective abdominal operations. Also Kelley et al. (1993) found that ketorolac may be of benefit in the prevention of postoperative ileus in the rat. The consecutive administration of ketorolac and L-nitroarginine completely reversed the inhibition of the transit induced by laparotomy plus manipulation. Treatment of the rats with ketorolac plus L-arginine had no additional effect on the transit as compared to ketorolac alone. These results indicate that ketorolac and L-nitroarginine are affecting complementary pathways. Therefore, the combination of ketorolac and NO synthase inhibition might represent a new approach to resolve postoperative ileus.

The differential effect of indomethacin and ketorolac in our study is difficult to explain. Since both indomethacin and ketorolac are non-selective cyclooxygenase inhibitors acting preferentially on cyclooxygenase 1, we cannot explain their differential activity by a different isoform selectivity (Pallapies et al., 1995; Frölich, 1997). Also the doses of indomethacin and ketorolac we used were previously shown to completely inhibit the prostaglandin synthesis in the rat (Pallapies et al., 1995; Salvemini et al., 1995). The exact origin of the released prostaglandins cannot be determined from our experiments as almost all cells, except non-nucleated erythrocytes, are able to synthesise and release prostaglandins in response to trauma or disturbances of the cell membrane (Ferreira et al., 1976; Dahl and Kehlet, 1991). Nevertheless, several possible mechanisms by which prostaglandins might induce gastrointestinal hypomotility can be put forward. Possibly, prostaglandins affect peripheral nociceptors, thereby lowering the threshold of afferent fibers resulting in hyperalgesia which in turn activates inhibitory reflexes (Dahl and Kehlet, 1991). Alternatively, prostaglandins can also decrease the gastrointestinal motility either by a direct action on intestinal smooth muscle cells (Thor et al., 1985; Frantzides et al., 1992) or by modulating the neurotransmission of myenteric neurons (Gustafsson and Delbro, 1993; Mulholland and Simeone, 1993; Baccari et al., 1996).

In summary, we demonstrated that the prostaglandin synthase inhibitors, indomethacin and ketorolac differentially affect postoperative ileus in the rat. Indomethacin prevents the inhibition induced by mechanical stimulation of the gut, whereas ketorolac prevents the inhibition of the transit induced by laparotomy. Our data suggest an enhanced synthesis of prostaglandins and NO after mechanical stimulation of the gut that is blocked by indomethacin without any additional effect of NO synthase blockade, indicating that NO and prostaglandins are part of the same pathway. However, the observation that ketorolac plus L-nitroarginine completely reversed the transit after the laparotomy plus manipulation, suggests that the action site of ketorolac, in contrast to indomethacin, is complementary to the increased release of NO. The combination of ketorolac plus L-nitroarginine might theoretically represent a new approach for the treatment of postoperative ileus.

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