Opioid-Induced Bowel Dysfunction
Pathophysiology and Potential New Therapies

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Abstract

Opioid treatment for postoperative or chronic pain is frequently associated with adverse effects, the most common being dose-limiting and debilitating bowel dysfunction. Postoperative ileus, although attributable to surgical procedures, is often exacerbated by opioid use during and following surgery. Postoperative ileus is marked by increased inhibitory neural input, heightened inflammatory responses, decreased propulsive movements and increased fluid absorption in the gastrointestinal tract. The use of opioids for chronic pain is characterised by a constellation of symptoms including hard dry stools, straining, incomplete evacuation, bloating, abdominal distension and increased gastroesophageal reflux.

The current management of opioid-induced bowel dysfunction among patients receiving opioid analgesics consists primarily of nonspecific ameliorative measures. Intensive investigations into the mode of action of opioids have characterised three opioid receptor classes – μ, δ and κ – that mediate the myriad of peripheral and central actions of opioids. Activation of μ-opioid receptors in the gastrointestinal tract is responsible for inhibition of gut motility, whereas receptors in the central nervous system mediate the analgesic actions of opioids. Blocking peripheral opioid receptors in the gut is therefore a logical therapeutic target for managing opioid-induced bowel dysfunction.

Available opioid antagonists such as naloxone are of limited use because they are readily absorbed, cross the blood-brain barrier, and act at central opioid receptors to reverse analgesia and elicit opioid withdrawal. Methylnaltrexone and alvimopan are recently developed opioid antagonists with activity that is restricted to peripheral receptors. Both have recently shown the ability to reverse opioid-induced bowel dysfunction without reversing analgesia or precipitating central nervous system withdrawal signs in non-surgical patients receiving opioids for chronic pain. In addition, recent clinical studies with alvimopan suggest that it may normalise bowel function without blocking opioid analgesia in abdominal laparotomy patients with opioid-related postoperative ileus.

Opioid analgesics are effective for the management of moderate to severe pain.[1-3] However, adverse effects can compromise the usefulness of these agents for analgesia. Bowel dysfunction is among the most important and distressing adverse effects associated with opioid administration. This adverse effect, which is characterised by abdominal distension, pain, constipation, nausea and vomiting, leads to the accumulation of gas and secretions, and the retention of gastrointestinal contents.[2]

Postoperative ileus is the impairment of gastrointestinal motility after abdominal or other surgery, and is considered an inevitable response to abdominal surgery that involves manipulation of the intestines. Surgical stress and postoperative use of opioid analgesia further contribute to ileus. Delayed return of gastrointestinal function postoperatively increases morbidity, prolongs hospitalisation and increases costs;[3,4] rapid restoration of postoperative bowel function is therefore an important component of postsurgical management. Although several nonpharmacological and pharmacological options are frequently used to accelerate postoperative re-

covery, reduced gastrointestinal motility remains a significant healthcare problem.[5,6]

Postoperative ileus is usually defined as an uncomplicated inhibition of gut motility which occurs after surgery and resolves spontaneously in 2–3 days.[2] Paralytic ileus, by contrast, is defined by prolonged stasis and usually results from factors other than surgical trauma.[3] Prolonged, severe ileus may be associated with bacterial overgrowth, translocation of bacteria and endotoxin into the blood stream, and even development of multiple organ failure.[3] Besides causing significant discomfort, ileus prolongs hospital stay, delays early enteral nutrition and increases medical costs. The annual cost of ileus in postoperative patients was estimated to be $US750 million in 1986.[4,7]

Opioid-induced bowel dysfunction is the term ascribed to the constellation of symptoms characterised by hard dry stools, straining, incomplete evacuation, bloating, abdominal distension and increased gastroesophageal reflux.[8] Not only is opioid-induced bowel dysfunction distressing, it also leads to physical and functional deterioration among patients given opioids long-term.[9,10] Despite aggressive use of laxatives and other therapies to improve bowel function, many patients continue to experience the effects of opioid-induced bowel dysfunction. In some patients, the presence of opioid-induced bowel dysfunction is severe enough to be a dose-limiting adverse effect that prevents adequate pain control.

Cancer-related pain affects approximately 9 million people worldwide.[11] The prevalence of moderate to severe pain among cancer patients is 51%, ranging from 43% in stomach cancer to 80% in gynecological malignancies.[12] The WHO has devised guidelines for the treatment of cancer pain based on a sequential 3-step analgesic ladder: (i) aspirin, paracetamol (acetaminophen) or nonsteroidal anti-inflammatory drugs (NSAIDs) for mild pain; (ii) addition of an oral opioid such as codeine or dihydrocodeine to the non-opioid analgesics for moderate pain; and (iii) potent opioids such as morphine, methadone, oxycodone, buprenorphine, hydromorphone or fentanyl for severe pain.[13] Therapy using these guidelines is effective in the vast majority of patients with cancer pain.[14] As cancer progresses, an increasing fraction of patients require treatment with potent oral or parenteral opioids.[15] More than 50% of cancer patients admitted to palliative care units experience opioid-induced bowel dysfunction[11] and the symptom is more frequent in the elderly.[16]

This article discusses the impact of opioid receptor activation on gastrointestinal function, with emphasis on the pathophysiology and management of postoperative ileus and opioid-induced bowel dysfunction, and examines the therapeutic opportunities offered by newer agents in treating opioid-induced bowel motility disorders.

1. Physiological Control of Gastrointestinal Motility

Normal bowel function requires the co-ordination of motility, mucosal transport and defecation reflexes.[17] Gastrointestinal motility is dependent on the electrophysiological activity of smooth muscle cells, neural input from the intrinsic and autonomic nervous systems, hormonal interactions and co-ordinated smooth muscle contraction.[2,4,17,18] Various other factors (see section 1.2.1) are involved in an inhibitory effect on gastrointestinal motility.

1.1 Stimulation of Gastrointestinal Contractions

The smooth muscle of the gastrointestinal tract is subjected to continuous electrical activity characterised by slow waves and spikes. Slow waves present as undulating changes in the resting membrane potential that elicit muscular contraction only in the stomach. Spikes, in contrast, are superimposed action potentials that actually cause most contractions.
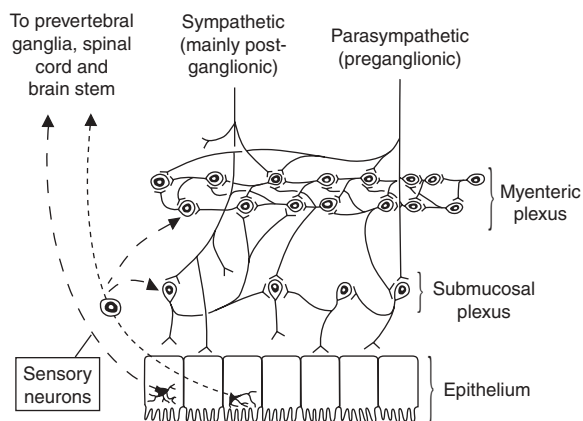
Fig. 1. Neural control of the gut wall (reprinted from Guyton and Hall,[18] with permission from Elsevier Science).

Spike potentials occur automatically when the resting membrane potential of gastrointestinal smooth muscle exceeds a given threshold (thresholds and resting membrane potentials vary by location within the gastrointestinal tract).[19] The resting membrane potential, and hence spike wave activity, can be modulated by neurotransmitters, hormones and pharmacological agents. Membrane excitability is increased (depolarisation) by stretching of the muscle, acetylcholine or parasympathetic stimuli. Inhibitory stimuli reduce resting membrane potential (hyperpolarisation), and include noradrenaline (norepinephrine) and sympathetic stimuli.[18,19]

The myocytes of the stomach and small intestine are provided with numerous gap junctions that allow current to pass from one cell to the next. This organisation results in large sheets of interconnected cells that produce regular oscillations of uniform amplitude and thus well-ordered contractions.[4] Colonic smooth muscle cells differ in lacking gap junctions and thus fail to intrinsically function as an organised unit. Colonic contraction and motility are, thus, dependent on extrinsic neural input to integrate smooth muscle activity.[5]

1.2 Neural Control

1.2.1 Enteric Nervous System

The gut contains as many nerve cells as the spinal cord. The enteric nervous system lies entirely within the wall of the gut from the oesophagus to the anus, and is organised into two major plexuses: the myenteric plexus and the submucosal plexus (figure 1).[18] Because the myenteric plexus lies between the longitudinal and circular muscle layers and extends the length of the intestine, it is involved primarily with control over motor activity within the gut. Stimulation of the myenteric plexus increases the tone of the gastrointestinal wall, intensity and rhythm of contractions, and conduction velocity.[18] The submucosal plexus controls local secretory and absorptive activity. The plexuses consist of an organised network of motor and sensory neurons, and are also innervated with sympathetic and parasympathetic fibres. Sensory neurons, with nerve endings in the gastrointestinal epithelium or gut wall monitor wall tension and changes in intraluminal content, and activate motor neurons to release neurotransmitters that modulate motility patterns.

More than a dozen neurotransmitters are released from nerve endings of enteric neurons. Acetylcholine is an established physiological excitatory agent of colonic motor activity that acts at muscarinic

receptors on smooth muscle cells. As might thus be expected, administration of the muscarinic receptor antagonist atropine blocks colonic contractions,[20] whereas cholinesterase inhibitors such as neostigmine increase gut activity. Noradrenaline (norepinephrine) produces gut relaxation. Neurotransmitters such as dopamine, serotonin, vasoactive intestinal peptide (VIP), substance P, leu-enkephalin and met-enkephalin have excitatory or inhibitory activity. Several agents that affect these neurotransmitter pathways, including dopamine and serotonin, have been investigated and used for the management of gastrointestinal motility disorders (e.g. domperidone and cisapride). Other substances, including nitric oxide, carbon monoxide, amines and purines also have an inhibitory influence on gastrointestinal motility.

Gastrointestinal hormones also affect motor activity in the gut via various endocrine, paracrine and neural pathways. Gastrin, cholecystokinin, motilin and substance P stimulate smooth muscle contractions, whereas somatostatin, glucagon and gastric inhibitory peptide have inhibitory effects.[6,18] The multiplicity and complexity of interactions between gastrointestinal hormones and neural pathways has made it difficult to define roles for individual hormones.

1.2.2 Autonomic Control

Parasympathetic input to the oesophagus, stomach, small intestine and the proximal half of the large intestine is provided by the vagus nerve, whereas the distal portion of the colon is innervated by the pelvic nerves via the sacral parasympathetics from the second, third and fourth sacral segments. Neurons of the parasympathetic system are located in the myenteric and submucosal plexuses; stimulation of the parasympathetic nerves causes a general increase in activity of the enteric nervous system and an enhancement of gastrointestinal motility.

Sympathetic fibres located in the thoracic and lumbar regions of the spinal cord (between T5 and L2) reach the gut through the splanchnic nerves, and synapse with neurons in the myenteric plexus.[2] Sympathetic nerve endings release noradrenaline (norepinephrine) and exert an inhibitory motor effect in the gastrointestinal tract. The major inhibitory action of noradrenaline (norepinephrine) is on enteric neurons and, to a lesser degree, on smooth muscle cells. Stimulation of the sympathetic system can block the movement of food through the gastrointestinal tract, whereas sympathectomy enhances colonic propulsion.[17]

1.3 Functional Movements

The alimentary tract exhibits two types of movement: propulsive and mixing. The basic propulsive movement is peristalsis, in which co-ordinated contractions of the circular and longitudinal muscles cause gastrointestinal contents to be pushed distally. The usual stimulus for peristalsis is distension of the gut; when a food bolus stretches the gut wall, the enteric nervous system stimulates the gut to contract proximally, thus pushing the bolus distally. In the small intestine, stretching of the wall elicits regularly spaced localised contractions that segment the intestine and mix food with intestinal (e.g. digestive) secretions. Both segmentation and propulsive contractions are weakened when the excitatory activity of the enteric nervous system is blocked by atropine.

The proximal segment of the colon functions in both a mixing and absorptive capacity: segmental mixing movements maximise the surface exposure and fluid absorption, whereas slow contractions propel the luminal contents distally. The distal colon functions primarily in a storage capacity.

During fasting and after feeding, the stomach, small intestine and colon exhibit intermittent organised contractions, of which the best characterised is the interdigestive migrating motor complex. The migrating motor complex is a pattern of activity observed between feedings that sweeps luminal contents distally.[2,19] The migrating motor complex re-

curs approximately every 90 minutes in the stomach and small intestine, and is characterised by four phases. The first phase, which occurs approximately 2–3 hours after a meal, is a silent period lasting about 1 hour, and is characterised by one or two contractions every 5 minutes. The contractions gradually increase in power and frequency over the second phase, and in the third phase, maximum contractile frequency of the gastrointestinal tract is reached. This is a short period of intense contractile activity during which luminal contents are swept distally. The contraction migrates in an orderly fashion, beginning in the stomach and spreading all the way through the ileum. When a migrating motor complex reaches the ileum, a new organised contraction is initiated in the upper gastrointestinal tract. The fourth phase is a short period of transition between the contractions of phase 3 and the inactivity of phase 1. Since postoperative patients are usually not fed, the migrating motor complex remains as the only stimulant of bowel contraction.

2. Effect of Opioid Analgesics on Gut Motility – Pathophysiology

2.1 Opioid Receptors

That opioids suppress bowel function is well known; however, opioids are highly effective analgesics. Opioid analgesics have actions similar to those of endogenous opioids, which are comprised of a family of peptides, including met- and leu-enkephalins, β-endorphin, endomorphin and dynorphin.[21] The enkephalins, β-endorphin and dynorphin are present in neurons and nerve fibres of the myenteric and submucosal plexus, and in endocrine cells of the intestinal mucosa.[22] They exert their effects by activating membrane-bound receptors in the central nervous system (CNS), gastrointestinal and vascular smooth muscle cells, musculoskeletal structures, and at the terminals of sympathetic and sensory peripheral neurons.[23] Although

the endomorphin subtypes (1 and 2) have the highest specificity and affinity for the μ-opioid receptor, β-endorphin exhibits the strongest actions among the endogenous opioids.[24]

The interaction between endogenous opioid peptides and opioid receptors mediates a broad spectrum of physiological effects. Receptor-binding studies and molecular cloning techniques have led to the identification of three classic types of opioid receptors – μ, δ and κ – along with a variety of subtypes within each class.[25] Recently, another opioid receptor (ε) has been identified as having a role in analgesia.[26] Although the role of σ-receptors in analgesia and gastrointestinal physiology has been postulated, this receptor class is generally no longer included in the opioid family.[27-29] The opioid-binding sites first described were the μ-receptors and their two subtypes. Activation of μ_1-receptors in the brain is responsible for analgesia induced by morphine and most other clinically used opioids. The μ_2-receptors are present in the spinal cord and gastrointestinal tract, and their activation produces adverse effects such as respiratory depression and bowel dysfunction.[21,25] Studies of opioid effects in mutant knockout mice that lack specific receptor subtypes confirm the involvement of μ-receptors in regulating analgesia and gastrointestinal motility.[30]

Opioids used clinically in pain management are not fully selective for the μ-receptor subtypes, but maintain relative selectivity compared with the δ- and κ-receptors at normal therapeutic doses.[1] The effects of κ-receptor stimulation include analgesia, bowel dysfunction, diuresis and sedation, with dynorphin A (1-13) as the prototypic endogenous ligand.[31] Several κ-receptor subtypes have been identified but their physiological effects are poorly characterised.[21] The δ-receptors, which are located in the CNS, also mediate analgesia and the enkephalins are their endogenous ligand. Recently, the role of a novel opioid (OP4) receptor in the physiol-

ogy of gastrointestinal motility has been postulated, and the endogenous opioid peptide for this receptor is nociceptin/orphanin FQ. Activation of the OP4-receptor results in increased intestinal motility and gastric motor excitation; however, the pharmacological profile of the OP4-receptor is still being investigated and its role as a therapeutic target currently is not clear.[32,33]

Localisation studies of opioid receptors in the rat gastrointestinal tract using immunohistological staining have revealed a substantial density of μ- and κ-receptors in the intestinal wall.[34] In particular, μ-receptors predominate on neurons in the submucosal plexus, whereas a higher number of neurons expressing κ-receptors are present in the myenteric plexus. Both μ- and κ-positive neurons are present in the myenteric plexus of the stomach and the proximal colon. In general, μ-receptors predominate in the submucosal and mucosal layers, and are localised to nerve terminals and somatodendritic synaptic elements. In the muscular layers, μ-receptors are present on nerve terminals, and κ-receptors on both nerve terminals and somatodendritic synaptic elements.

2.1.1 Classification of Opioids

Opioids can be classified by receptor affinity and by their pharmacological action as agonists, agonist-antagonists or antagonists.[25] Pure opioid agonists act in a dose-dependent manner; as their dose is increased, analgesia and adverse effects also in-crease. These are the agents most commonly used in clinical practice for pain management. Opioid agonists can excite or depress the CNS in a dose-dependent fashion. The major limitations of opioid agonists are the adverse effects, which increase proportionately with dose and often limit the usefulness of a particular agent.

Other opioids produce a sub-maximal response at a particular receptor type even at high doses and also have a ceiling effect. These drugs are classified as partial agonists. Opioids that have divergent effects at the various receptor types, for example, those that act as an agonist at one receptor and as an antagonist at another, are called agonist-antagonists. Antagonists are agents such as naloxone that bind, but do not activate, opioid receptors. Of the known endogenous opioids, the two endomorphin subtypes (endomorphin-1 and -2) have the highest selectivity and affinity for μ-opioid receptors.[35]

2.2 Opioid Effects on the Gastrointestinal Tract

Opioids have been used for the treatment of diarrhoea for centuries because they decrease gastrointestinal neural activity, reduce propulsive activity, delay transit of contents through the small and large bowel, and enhance absorption of fluids (table I).[8,11] Morphine, for example, appears in the intestinal lumen of rats within 10–20 minutes after intravenous administration and persists for hours; concen-

Table I. Actions of opioids on the gastrointestinal tract[8,11]

Site of action	Pharmacological action	Clinical effect
Stomach	Decreased gastric motility	Anorexia
	Decreased pyloric tone	Nausea and vomiting
Small intestine	Decreased pancreatic and biliary secretion	Delayed digestion
	Reduced propulsion	Delayed absorption of medications
	Increased fluid absorption	Hard, dry stool
Large intestine	Decreased propulsion	Straining, incomplete evacuation, bloating, abdominal distension, constipation
	Increased non-propulsive contractions	Spasm, abdominal cramps, pain
	Increased fluid absorption	Hard, dry stool
	Increased anal sphincter tone	Incomplete evacuation

trations in intestinal longitudinal muscle correlate well with gastrointestinal transit, whereas brain or plasma concentrations do not.[36]

2.2.1 Decreased Neural Output

The electrically stimulated longitudinal muscle myenteric plexus preparation of guinea pig ileum is a commonly used model for evaluating intestinal neurotransmission.[22,37] In this model, morphine decreases acetylcholine release at low stimulation frequencies, although its effect at higher frequencies remains variable. This action of morphine is attributed to activation of μ-receptors on cholinergic nerves. Stimulation of κ-receptors with the κ-agonist ethylketocyclazocine similarly decreases transmitter release in guinea pig ileum.[37,38] Interspecies differences in opiate receptor subtype densities, however, must be considered when determining the contribution of opiate receptor subtypes to the mechanism of opioid-induced bowel dysfunction. For example, in rats, a δ-receptor-selective agent was a potent inhibitor of the cholinergic contractile response, whereas κ-receptor agonists had no effect and even morphine showed an inhibitory effect at exceptionally high concentrations.[37] Nevertheless, a common feature in all species is that receptor activation inhibits acetylcholine release.[37]

2.2.2 Delayed Transit

Opioid analgesics inhibit intestinal transit in all species, although the magnitude differs substantially among species. However, it is likely that variance is largely a function of widely differing experimental conditions and the resting condition of the tissue. Both μ- and κ-receptor antagonists have inhibitory effects on the peristaltic reflex in guinea pigs,[39,40] whereas in rats, μ- and κ-receptor stimulation abolishes this reflex.[41] Increased propulsive peristalsis by morphine in the isolated dog intestine suggests dual opioid effects on *in vivo* gut motility and strongly supports the concept of functionally contrasting opioid systems in the gut.[22]

In humans, a morphine-induced delay in gastrointestinal transit was observed by using colonic transit scintigraphy.[42] In this double-blind, crossover study, six healthy volunteers were given subcutaneous injections of morphine, naloxone or saline every 6 hours for 48 hours. Morphine significantly delayed colonic transit and decreased the number of bowel movements, whereas naloxone accelerated transit but did not affect bowel movements. The presence of peripheral opioid receptors in the gastrointestinal tract, the acceleration of transit by naloxone and inhibition of transit by exogenous opioids all support an inhibitory role for endogenous opioids in regulating normal colonic movements in humans.

2.2.3 Altered Propulsion

Morphine has an excitatory effect on colonic electrical activity and induces phasic, stationary (non-migrating) spike bursts in the colon. When colonic myoelectric activity was measured in primates, clinically relevant doses of morphine (50–200 μg/kg) increased the frequency of random, non-propagating spike bursts and contractions, and inhibited colonic electrical and contractile activity at higher doses.[43] All doses of morphine inhibited the migrating spike bursts associated with propulsion and defecation. Similarly, in humans recovering from abdominal surgery, intramuscular or intravenous morphine induced phasic stationary, non-migrating colonic spike bursts and disrupted the normal pattern of recovery of colonic motility electrical activity.[44]

Other stimulatory effects of opioids in the gastrointestinal tract have also been reported. For example, opioids act via opioid receptors to stimulate maximal duodenal contractility by inducing phase III-like (migrating motor complex) activity.[45] Furthermore, β-endorphin increases pyloric phasic and tonic activity, suggesting that β-endorphin may play a role in the stimulation of fed pyloric contraction.[46]

2.2.4 Fluid Absorption

Decreased peristalsis delays gut transit and lengthens contact between intestinal contents and the mucosa which leads to increased absorption of fluid and harder stools.[17,47] Additionally, opioids stimulate mucosal sensory receptors to activate a reflex arc that further increases fluid absorption.[17] The antisecretory effect of opioids is mediated in a rather indirect manner through μ-receptors on neurons in the myenteric plexus, submucosa, villi and crypts. The end result is the release of noradrenaline (norepinephrine), which acts on α_2-adrenoceptors to antagonise the secretory mechanism in enterocytes.[37]

2.3 Postoperative Ileus

Clinically, postoperative ileus is characterised by bowel distension, lack of bowel sounds, accumulation of gastrointestinal gas and fluids, and delayed passage of flatus and stools. Symptoms include nausea, vomiting and stomach cramps. Pulmonary complications, acute gastric dilatation and aspiration may also occur under certain circumstances.[48]

Postoperative ileus affects all segments of the gastrointestinal tract but in humans the colon is most severely affected. The average paralytic state persists less than 24 hours in the small intestine, 24–48 hours in the stomach and 48–72 hours in the colon. The return of colonic motor function is frequently the factor limiting resolution of postoperative ileus.[49] Postoperative ileus occurs most commonly following abdominal or pelvic procedures, but can occur after thoracic, orthopaedic or even neurosurgery. The duration also is related to the anatomic location of surgery, with colonic operations causing the longest ileus.[50]

There is considerable debate about how to characterise termination of ileus and resumption of normal gastrointestinal motility. The return of bowel sounds probably results from resumption of only small bowel motility and the passage of flatus is an equally insensitive measure. An objective indicator of resolution in gastrointestinal motility is the return of migrating motor complexes but these do not always correspond with clinical resolution of ileus. Thus, resolution of ileus is best defined functionally by normalisation of food intake and bowel function.[50]

2.3.1 Pathophysiology

Postoperative neurohormonal signalling and intestinal motility are influenced in complex fashion by various physiological responses to surgical stress, intraoperative anaesthetics and postoperative analgesics.

Sympathetic Hyperactivity

Extrinsic neural pathways undoubtedly play an important role in postoperative ileus. Studies conducted more than 20 years ago demonstrated an increase in circulating catecholamines following laparotomy in experimental models;[51] however, sympathetic pathways also have a probable role in the inhibition of bowel function after surgery that does not involve the peritoneum. As discussed earlier, stimulation of sympathetic fibres inhibits motility and sympathetic hyperactivity associated with surgery is predominantly responsible for the development of ileus. The influence of sympathetic reflexes on ileus has been demonstrated in several experimental models in which sectioning of the splanchnic nerve, abdominal sympathectomy, or spinal anaesthesia were shown to prevent or reduce development of ileus.[4,50] The contribution of the sympathetic nervous system in the development of postoperative ileus has substantial clinical implications as these reflexes can be largely blocked by epidural anaesthesia.

Laparotomy increases production and release of noradrenaline (norepinephrine) from noradrenergic neurons in the gastrointestinal tract of rats.[52] However, circulating catecholamines apparently contrib-

ute less to control of intestinal motility than sympathetic nerves.

Inflammatory Response

The cellular mechanisms of postoperative ileus remain elusive, but recent findings suggest a role for inflammatory cells and their products in the pathogenesis of ileus. Kalff and co-workers,[53] for example, established a causal link between bowel manipulation, leucocyte infiltration of the muscularis and impaired contractile activity. Increasing the intensity of surgical manipulation increased the accumulation of several leucocyte populations, including neutrophils, macrophages, mast cells, T cells, natural killer cells and dendritic cells. Concurrently, smooth muscle contraction was attenuated and shown to correlate with the intensity of inflammation (figure 2).[48] A subsequent temporal study indicated that the paralytic response was biphasic and consisted of a short temporary initial paralysis followed by a longer-lasting impairment of muscle activity that correlated with activation and infiltration of inflammatory cells.[54] The target of leucocyte action remains undefined, but neutrophil-derived mediators, such as oxidants, may directly interfere with local neurotransmission or smooth muscle contractility.[49]

Myoelectric Activity

Migrating motor complexes appear to be suppressed in the postoperative period. Anaesthetic agents such as ether and halothane disrupt migrating motor complexes and opening of the peritoneum can completely abolish migrating motor complexes. In dogs, migrating motor complexes were lost for 24 hours after laparotomy and activity did not return to normal until 3–7 days after surgery.[2] As mentioned previously (section 1.3), migrating motor complexes are important in ileus because they are the only impetus to bowel contraction in fasted postoperative patients.
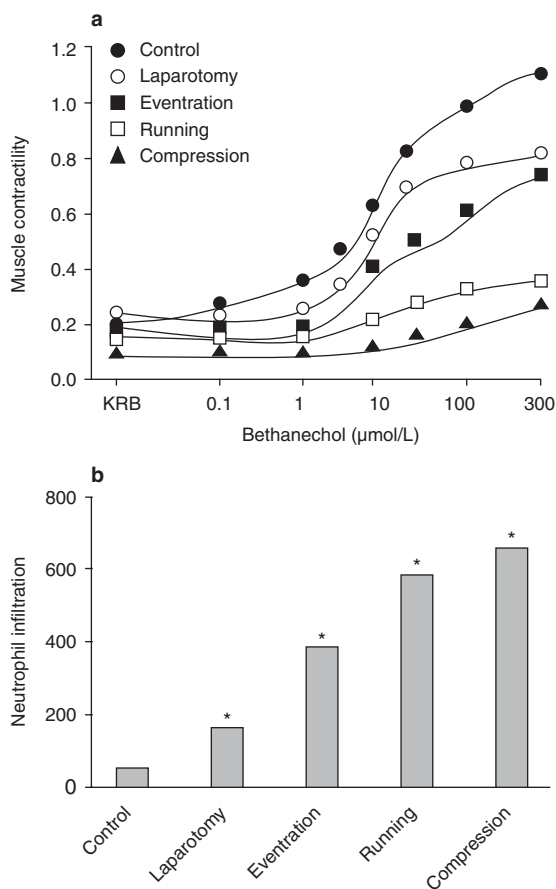

Fig. 2. Effect of surgical manipulation on (**a**) muscle contractility (bethanechol stimulation) and (**b**) neutrophil infiltration in rat bowel (reprinted from Kehlet,[48] with permission from BMJ Publishing Group Ltd). **KRB** = Krebs buffer; ***** indicates $p < 0.05$ compared with control.

The effect of laparotomy on migrating motor complexes depends on the extent and duration of the surgical procedure. Skin incision has no effect on migrating motor complex activity; however, division of abdominal muscles transiently inhibits migrating motor complex and opening of the peritoneum completely abolishes migrating motor complex activity. The duration of this inhibition is prolonged if the bowel itself is manipulated during the surgical procedure.[2] Although it was long accepted that the duration of postoperative ileus is related to the length of the procedure and the degree of intestinal

manipulation, numerous studies demonstrate that the duration of dysmotility does not depend on the duration of surgery, extent of handling or extent of dissection.[55]

Impact of Opioids

Opioids have a profound inhibitory effect on posttraumatic gastrointestinal motility, and their use for postoperative analgesia delays recovery from postoperative ileus. A recent study evaluated the effect of opioid use and incision length on bowel function after colectomy.[55] Colonic motility correlated with postoperative morphine use: there was a significant relationship between the amount of morphine administered and resolution of ileus as measured by time to return of bowel sounds, passage of first flatus and bowel movement. In contrast, incision length failed to correlate with either morphine use or return of bowel function.

The inhibitory effects of morphine on postoperative gastrointestinal motility are observed during systemic opioid administration with patient-controlled anaesthesia, conventional intramuscular opioid administration or epidural opioid administration. Epidural opioids delay gastric emptying, prolong oral-cecal transit time and delay colonic transit. When used for postsurgical pain treatment, they are associated with delayed recovery of bowel function compared with epidural local anaesthetics.[56]

There is evidence to suggest endogenous opioids also inhibit gastrointestinal motility. Levels of endogenous opioids are increased following surgery[57-59] and naloxone administration (in normal volunteers) accelerates colonic transit.[42] However, the role of these endogenous compounds in developing postoperative ileus remains poorly defined.

2.4 Opioid-Induced Bowel Dysfunction

Morphine is the mainstay of treatment for cancer-related pain. A long-term survey of pain management among cancer patients showed that morphine was used during more than 40% of treatment time and by more than 50% of patients with advanced cancer.[46] Morphine is generally the drug of choice for chronic cancer pain because of its effectiveness, tolerability, flexibility of use and low cost.[11]

Opioid-induced bowel dysfunction, nausea, vomiting, urinary retention, pruritus and sedation are classic adverse effects of opioid therapy.[16] Among these, bowel dysfunction is considered the most common and often the most debilitating adverse effect reported by patients (figure 3).[60,61]

Clinically, opioid-induced bowel dysfunction is a constellation of symptoms characterised by hard dry stools, straining, incomplete evacuation, bloating, abdominal distension and increased gastroesophageal reflux (table II).[8,17,62] Uncontrolled, opioid-induced bowel dysfunction can lead to complications including: (i) faecal impaction with overflow diarrhoea and incontinence; (ii) pseudo-obstruction of the bowel causing anorexia, nausea and vomiting; (iii) inadequate absorption of oral drugs; (iv) urinary retention and incontinence; and (v) confusion.[17,63]

Persistent symptoms associated with opioid-induced bowel dysfunction severely impair quality of life measures.[9] Opioids undoubtedly improve pain control; however, initiation of morphine therapy often increases the likelihood of bowel dysfunction
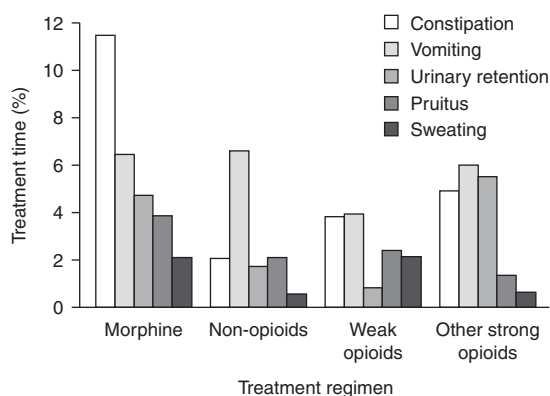

Fig. 3. Duration spent with specific adverse effects after analgesic therapy (reprinted from Schug et al.,[60,61] with permission from Elsevier Science).

Table II. Manifestations of opioid-induced bowel dysfunction[8,17] (reprinted from McMillan,[62] with permission from Cancer Control: Journal of the Moffitt Cancer Center)

Abdominal distention
Abdominal growling
Abdominal mass
Abdominal pain
Blood with stool
Change in abdominal size
Change in flatus
Change in frequency
Decreased appetite
Dry, hard stool
Headache
Inability to pass stool
Increased abdominal pressure
Indigestion
Oozing liquid stool
Rectal fullness
Rectal mass
Rectal pain with stool
Rectal pressure
Small volume of stool
Straining at stool
Swollen rectal veins

and vomiting. Consequently, quality-of-life score may not improve, suggesting that the adverse effects undermined the value of pain relief.[10,64] In certain patients, opioid-induced bowel dysfunction may be sufficiently severe that patients prefer to discontinue analgesic therapy rather than experience the discomfort associated with this adverse effect. A recent survey quantified the impact of adverse effects associated with opioid treatment for chronic non-malignant pain; it showed that severe opioid-induced bowel dysfunction reduced the value of effective pain relief by more than 30%.[65] Importantly, many patients expressed a preference for uncontrolled pain over well-controlled pain with severe adverse effects. Optimal management of chronic pain thus hinges on balancing pain control with treatment tolerability.

Unlike other adverse effects of narcotic administration, such as sedation and nausea and vomiting which improve and often resolve with continued use, tolerance to bowel symptoms develops slowly, if at all.[9,66] Opioid-induced bowel dysfunction thus generally persists throughout treatment.[61,67]

The role of opioid analgesics for the management of non-malignant pain has been controversial, but several recent studies in patients with chronic musculoskeletal pain have allayed fears of addiction and show that morphine treatment can reduce pain intensity; hence, the use of opioids to treat pain of non-malignant origin has increased in the past decade.[68] The prevalence of opioid-induced bowel dysfunction among patients with non-malignant pain was assessed from a survey of 76 patients with chronic musculoskeletal or neuralgic pain who had received opioid analgesics for a median of 2 years. The results showed that patients receiving opioids had significantly more constipation-related symptoms, were using more treatments to relieve bowel dysfunction and were less satisfied than the general population.[8]

2.4.1 Pathophysiology

Both central and peripheral opioid receptors are involved in the slowdown of gastrointestinal transit after opioid use. However, evidence suggests a predominantly peripheral action of opioids. Subcutaneously administered morphine inhibits intestinal transit in vagotomised animals,[69] and anti-diarrhoeal opioids such as loperamide and diphenoxylate, which generally are not absorbed systemically, produce constipating effects at peripheral sites.[70] The ability of loperamide to delay intestinal transit in normal animals and humans, an activity that can be reversed by narcotic antagonists, attests to an exclusively peripheral, anti-propulsive opioid action.

Quaternary narcotic antagonists are useful in differentiating between central and peripheral opioid effects on the gut. Because of their low lipophilicity, these agents do not cross into the CNS; their actions are therefore confined to peripheral sites. The N-methyl quaternary analogues of naltrexone and naloxone attenuate morphine-induced spike poten-

tials in canine duodenum at doses that do not elicit signs of narcotic withdrawal in animals, demonstrating that opioid-mediated effects on the bowel could be reversed solely by blocking peripheral opioid receptors.[71]

Studies with intracranial injection of opioid drugs nonetheless provide evidence for a role of central opioid receptors in the control of gastrointestinal motility. A delay in intestinal transit was observed in several animal models after subdural injection of morphine at doses considerably lower than intravenous doses required to produce a comparable degree of bowel dysfunction.[70] Another study suggested that the site of action of morphine depends on the dose: at sub-analgesic doses, morphine acts through peripheral μ-receptors to inhibit transit, but at analgesic doses both central and peripheral sites are involved.[72] Gut hypomotility correlates better with opioid concentrations in the enteric nervous system than with concentrations in the CNS.[73] Overall, the central sites involved in mediating gastrointestinal motility have yet to be defined, and the relevance of centrally elicited gastrointestinal effects following direct injection into the CNS to the mechanism of opioid action after systemic administration remains questionable.

3. Management of Opioid-Induced Bowel Dysfunction

Evaluating the effectiveness of therapeutic agents for postoperative ileus and opioid-induced bowel dysfunction is challenging because the definitions of ileus and bowel dysfunction, and the methods for assessment, are not clearly defined.[50] Endpoints that are frequently used in clinical trials, such as bowel sounds, passage of flatus and stool, are controversial and do not correlate well with resolution of postoperative ileus. The resolution of ileus is also poorly correlated with more technical variables, such as intraluminal pressure, migration of radio-opaque markers and electrical activity.[50] Because

there is no single objective variable that correlates with resolution of postoperative ileus or opioid-bowel dysfunction, the most adequate measures probably involve a combination of functional outcomes (e.g., normalisation of food intake and bowel function).[50]

3.1 Postoperative Ileus

Lack of specific therapy renders postoperative ileus an important clinical problem. Nasogastric suction effectively reduces accumulation of gas and fluids, and was initially reported to reduce postoperative mortality. Consequently, the technique rapidly became standard practice after abdominal surgery. However, subsequent studies suggested that nasogastric suction does not shorten time to first bowel movement or time to effective oral intake, and may even promote aerophagia and thus worsen abdominal distension.[74,75] A meta-analysis of more than 30 trials suggested that gastrointestinal suction should not be used routinely and that unnecessary use could impair recovery from ileus by leading to atelectasis, pneumonia and fever.[74] Similar conclusions were derived in a recent systematic review of the literature.[50] Gastrointestinal suction nonetheless remains the only proven effective therapy for clinically evident ileus.[2]

Oral feeding after laparotomy is traditionally delayed until ileus has resolved spontaneously. Patients undergoing major abdominal procedures are often starved or semi-starved for 4–5 days, resulting in catabolism, fatigue, poorer immune function and increased susceptibility to infections. Recent practice, though, suggests that early enteral feeding, either nasoenterically or orally, hastens recovery from postoperative ileus by preserving gastrointestinal function and stimulating the small intestine.[50] Several clinical trials show early enteral feeding can be safely and effectively used in reducing the duration of ileus. In general, patients who are fed early tolerate a regular diet sooner and are discharged

from the hospital earlier than those in whom feeding is delayed.

The duration of ileus is shortened after less invasive surgical procedures, which is one reason laparoscopic procedures are increasingly favoured over more invasive abdominal procedures. Reduced surgical trauma leads to less sympathetic activation and inflammation,[50] and patients undergoing laparoscopic procedures progress to a solid diet earlier and are hospitalised for fewer days compared with those undergoing laparotomy.[76] However, the superior results following laparoscopy may also be the result of treatment bias that favours earlier feeding and less reliance on opioid analgesia.[3,50] More recent studies have questioned the value of laparoscopic surgery in reducing the duration of postoperative ileus.[50,77]

Prokinetic agents such as metoclopramide (which increases motility probably by enhancing the response to acetylcholine), erythromycin (a motilin agonist) and cisapride (which increases motility by increasing the release of acetylcholine from the myenteric plexus and binding at $5HT_4$ receptors) have been used to reduce the duration of postoperative ileus. However, their efficacy remains unsubstantiated. There are no data to support the routine use of metoclopramide or erythromycin for postoperative ileus.[5,78] Although clinical trials have suggested cisapride offers some benefit in the postoperative period,[50] it has been withdrawn from the US market because of cardiac adverse effects.

Hyperactive sympathetic reflexes can be blocked by epidural anaesthesia, thereby substantially reducing the duration of postoperative ileus. Several randomised studies in patients undergoing abdominal procedures have compared the effect of epidural thoracic anaesthesia with systemic opioids and shown that epidural local anaesthetics reduce gastrointestinal paralysis.[56,79] The efficacy of epidural local anaesthesia is related to the location of the catheter, with thoracic application generally being more effective than lumbar or low-thoracic epidural administration.[80] Because of the minimal effects on gastric emptying and intestinal propulsive activity, epidural anaesthesia with local anaesthetics is probably the best method for relieving pain following abdominal surgery. Patients treated with an epidural protocol not only have their gastric tubes removed sooner and tolerate solid foods earlier, but they also have a lower incidence of nausea and vomiting after their first exposure to a liquid diet.[81] Epidural local anaesthetics and local anaesthetic-opioid combinations are more effective at reducing ileus than epidural opioids alone.[79,80]

Given the concentration of opioid receptors in the dorsal horn of the spinal cord and the involvement of these receptors in transmitting afferent nociceptive signals to the CNS, spinal administration of opioid analgesics makes intuitive sense. The precise mechanism of spinal opioid analgesia is not entirely clear, but it is thought that opioid agonists prevent the release of peptide neurotransmitters from afferent nociceptors. It was proposed that spinal administration would avoid some of the adverse CNS effects associated with systemic administration. Although spinal analgesics are widely used, particularly in combination with local anaesthetics, respiratory depression remains a significant problem associated with this administration technique.[82]

Various opioid-sparing techniques have been developed to circumvent the undesirable sequelae of opioid use in the postoperative period. NSAIDs represent one means of providing analgesia without affecting bowel motility. The analgesic action of these drugs results from inhibition of prostaglandin synthesis. In a small clinical trial, postoperative analgesia with ketorolac led to faster resolution of ileus compared with morphine plus ketorolac analgesia.[7,83] However, ketorolac is not a powerful analgesic so it is not surprising that several patients required supplemental morphine analgesia. Tramadol, a centrally acting analgesic with low affinity

for µ-receptor affinity, is another potential option for postoperative analgesia. However, despite the low affinity for opioid receptors, this analgesic is not entirely devoid of gastrointestinal effects.

With the exception of epidural local anaesthesia, no individual technique has led to major improvement of postoperative ileus. A recent promising approach has been to use a multimodal approach that combines treatments which are most likely to be effective. Standardised postoperative care protocols that include combinations of continuous thoracic epidural blockade with local anaesthetics, opioid-sparing analgesia, avoidance of nasogastric tubes and early oral nutrition hasten the return of normal bowel function and reduce hospital stay.[50,84-86]

3.2 Opioid-Induced Bowel Dysfunction

The objective of management is to prevent symptoms rather than treat established opioid-induced bowel dysfunction. Because opioid-induced bowel dysfunction is an almost inevitable consequence of opioid use, initiating a bowel regimen early in the course of treatment is standard practice. Both nonpharmacological and pharmacological measures are usually needed to reduce opioid-induced bowel dysfunction. There have been few comparative trials of agents for the management of chronic opioid-induced bowel dysfunction, and strategies are largely based on the needs, capabilities and preferences of individual patients.[47,87]

3.2.1 Nonpharmacological Methods
Nonpharmacological treatments focus on increased intake of fluids and dietary fibre. Increasing fluid intake is similar to using a natural stool softener. Retention of water by fibre leads to increased bulk, which stimulates peristalsis and decreases transit time.[47,88] Regular exercise and establishing a regular bowel routine (preferably after breakfast when propulsive movements are strongest) are additional helpful interventions. However, these measures are generally insufficient and most patients

receiving long-term opioid therapy require more aggressive pharmacological treatment.

3.2.2 Pharmacological Therapy
The role of laxatives for the management of opioid-induced bowel dysfunction has been outlined elsewhere.[89] However, it is important to point out that laxative regimens often do not provide sufficient relief from the symptoms of opioid-induced bowel dysfunction. Furthermore, routine ingestion of numerous pills or a large volume of liquid makes compliance difficult because chronic nausea, anorexia and dysphagia are common in this population. Of course none of the laxatives address the opioid receptor-mediated mechanism of bowel dysfunction.

3.2.3 Transdermal Administration
Transdermal fentanyl is a relatively new alternative to morphine for the treatment of malignant and non-malignant pain. Patients treated with transdermal fentanyl experience less constipation and required fewer laxatives than when taking morphine.[90,91] Patients also expressed a preference for transdermal fentanyl over sustained-release morphine.[91] A similar finding emerged when patients with non-malignant pain showed a strong treatment preference for fentanyl over morphine.[92]

4. Selective Antagonism of Gastrointestinal Adverse Effects

Because endogenous and exogenous activation of opioid receptors in the gut contributes to the pathophysiology of both opioid-induced bowel dysfunction and postoperative ileus, receptor blockade with opioid antagonists would seem to be a rational therapeutic approach.[93] However, the challenge with opioid antagonists is to reduce the adverse effects and morbidity conferred by opioid use without compromising analgesic efficacy. The experience with traditional opioid antagonists has been disappointing, but with new understanding of gas-

trointestinal neurophysiology and improved opioid receptor pharmacology, promising new therapies have emerged. Two approaches have been taken to achieve this goal: opioids antagonists with limited systemic absorption and peripherally restricted μ-receptor antagonists.

4.1 Antagonists with Limited Systemic Absorption

Naloxone is a specific μ-receptor antagonist with an oral bioavailability of approximately 2% because of extensive first-pass metabolism.[94] However, because naloxone readily crosses the blood-brain barrier, it can still reverse analgesia despite low systemic bioavailability. In clinical trials with naloxone, a single large daily dose restored laxation during opioid use, but an appropriate oral dose, individual titration of the dose and clinical vigilance were necessary to avoid reversal of analgesia and systemic withdrawal.[95-97] Despite prompt biotransformation, there is a dose-dependent increase in plasma concentrations of unchanged naloxone, which can trigger signs of withdrawal or reduce analgesia at doses that are still insufficient to produce laxation.[95] Thus, oral naloxone has a narrow therapeutic index, and dose administration recommendations are still being investigated. Peak plasma naloxone concentrations are not predictive of laxative function or of withdrawal, and there appears to be a ceiling dose that can be used safely in individual patients but this dose is highly variable among patients.[98]

Nalmefene is a μ-receptor antagonist that is not selective for central versus peripheral effects; nalmefene glucuronide, which is a natural metabolite of nalmefene, has shown peripheral (i.e. intestinal) selectivity in rodent models. However, large doses of nalmefene glucuronide nonetheless precipitate withdrawal in methadone-dependent individuals, possibly because of biotransformation of the glucuronide form back to the parent compound,

nalmefene.[99] Hence, nalmefene does not appear to exert sufficient gut selectivity in humans to be clinically useful for opioid-induced bowel dysfunction.

4.2 Peripherally Restricted μ-Receptor Antagonists

An alternative strategy to prevent reversal of central opioid actions is to use opioid antagonists that are not systemically absorbed and that do not penetrate the blood-brain barrier. Providing these agents as an oral dosage formulation optimises the antagonism of peripheral (i.e. gastrointestinal) opioid receptors with minimal impact on central receptors. Two promising agents in this category are methylnaltrexone and alvimopan. They are able to selectively antagonise the gastrointestinal effects of opioids without affecting pain relief and are undergoing clinical investigation.

4.2.1 Methylnaltrexone

Quaternary derivatives of the tertiary opioid antagonists are poorly lipid soluble, do not penetrate the CNS, and do not antagonise the central effects of morphine or precipitate withdrawal.[71,100,101] Methylnaltrexone is a quaternary N-methyl derivative of the opioid antagonist naltrexone (figure 4).[102] A drawback of many quaternary opioid antagonists investigated has been their relative susceptibility to demethylation to the tertiary form, which then allows ready penetration of the blood-brain barrier. Methylnaltrexone is extensively demethylated in rats but only slightly so in humans.[102,103]
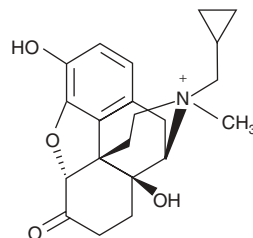
Fig. 4. Chemical structure of methylnaltrexone.[102]

Early experimental studies established that parenterally administered methylnaltrexone is active at peripheral rather than central opioid sites. At doses as high as 50 mg/kg, methylnaltrexone failed to promote withdrawal in morphine-dependent dogs, whereas naltrexone did so at 0.3 mg/kg.[71] Another study examined the ability of several tertiary and quaternary opioid antagonists to induce withdrawal contraction of ilea from opioid-dependent guinea pigs and elicit withdrawal in morphine-dependent monkeys.[104] Methylnaltrexone was the only agent that elicited withdrawal *in vitro* but not *in vivo*, attesting to its superior peripheral selectivity compared with other quaternary compounds. Additional studies demonstrated that methylnaltrexone blocked morphine-induced delay in gastrointestinal transit in rats[105] and dogs[71] at doses that did not elicit signs of withdrawal.

The direct local gut activity of methylnaltrexone was demonstrated by the ability of methylnaltrexone to reverse morphine-induced inhibition of electrically stimulated contraction in isolated guinea pig ileum and human small intestine smooth muscle strips.[106] Methylnaltrexone reversed morphine-induced contractility changes in both preparations in a dose-dependent manner. As demonstrated in previous studies, the antagonist activity of methylnaltrexone was about 10-fold less than that of naloxone. These data provided preliminary information for clinical studies to evaluate the efficacy of methylnaltrexone in preventing or reducing morphine-induced antimotility actions and also suggested that methylnaltrexone might be effective when administered orally.

A preliminary clinical study in healthy volunteers demonstrated that methylnaltrexone could reverse opioid-induced bowel inhibition without reversing analgesia.[107] Oral-caecal transit time and pain intensity scores were assessed in a randomised, double-blind study in which 12 volunteers were given intravenous placebo, placebo and morphine 0.5 mg/ kg, or methylnaltrexone 0.45 mg/kg combined with morphine 0.5 mg/kg. Morphine significantly increased the oral-caecal transit time from a baseline level of 105 ± 31 minutes to 163 ± 40 minutes; methylnaltrexone treatment reversed this morphine-induced delay and normalised transit times to baseline levels in all 12 participants. The pain intensity ratings, which were reduced by morphine, were not significantly altered by concomitant administration of methylnaltrexone, indicating that methylnaltrexone did not antagonise morphine-induced analgesia.

A similar reversal of morphine-induced gastrointestinal transit delay was demonstrated after administration of ascending oral doses of methylnaltrexone to healthy volunteers who were simultaneously given intravenous morphine.[108] Inhibition was dose-dependent, and there was no correlation between changes in transit times and plasma methylnaltrexone concentrations over the 3-hour study period. An enteric-coated formulation of methylnaltrexone has been investigated that prevents gastric absorption and releases active drug only in the small and large intestine.[109] A preliminary comparison between uncoated and enteric-coated methylnaltrexone showed that the enteric formulation was about 6-fold more efficient at preventing morphine-induced oral-caecal transit time. Interestingly, greater efficacy was associated with substantially less bioavailability, providing further evidence of direct and local luminal action.

The previous studies demonstrated the efficacy of methylnaltrexone in reversing gut dysmotility induced by a single dose of morphine. However, receptor physiology may be altered after long-term opioid use, for example in cancer patients or individuals in methadone maintenance programmes. A double-blind, placebo-controlled, randomised trial was conducted in 22 individuals in a methadone maintenance programme to examine the use of methylnaltrexone for treating opioid-induced bowel dysfunction.[110] Participants received four escalat-
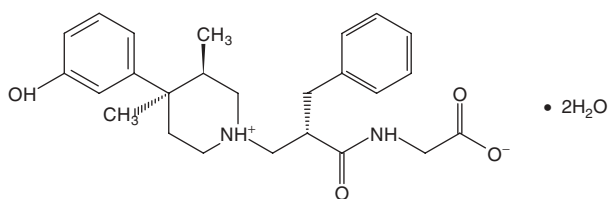
Fig. 5. Chemical structure of alvimopan.[112]

ing doses of methylnaltrexone sequentially over 2 days of the study until a laxation response (elimination of any stool) was obtained. None of the placebo-treated participants experienced laxation, whereas in the methylnaltrexone group, 10 of 11 and 11 of 11 individuals reported laxation on days 1 and 2, respectively. Oral-caecal transit times in all participants were reduced after methylnaltrexone treatment.[110] No opioid withdrawal was reported by the participants.

Oral methylnaltrexone also has potential clinical utility in managing opioid-induced bowel dysfunction. Three groups of patients from a methadone maintenance programme who were experiencing constipation received increasing oral doses of methylnaltrexone.[111] Treatment with placebo did not induce a laxation response in any patient, whereas 11 of 12 patients receiving methylnaltrexone had laxation. The timing of laxation was dose dependent, as was the reduction of oral-caecal transit time. Most patients reported mild abdominal cramping but no symptoms of opioid withdrawal were experienced.

4.2.2 Alvimopan

Alvimopan is a μ-receptor antagonist with a molecular weight of 461 (figure 5),[112] which, along with a zwitterionic structure and polarity, prevents gastrointestinal absorption or crossing of the blood-brain barrier.[113] *In vitro* studies with alvimopan have established that this agent has a high affinity for μ-receptors. In radioligand-binding assays, alvimopan had a higher binding affinity for μ-receptors (K_i <1 nmol/L), compared with δ- (K_i = 4.4 nmol/L) and κ- (K_i = 40 nmol/L) receptors.[112,113]

By comparison, naloxone has a binding affinity for μ-receptors that is approximately 5-fold lower than alvimopan (K_i = 3.7 vs 0.8 mmol/L, respectively). Selectivity for μ-receptors was confirmed in subsequent studies that evaluated the ability of alvimopan to block the effects of select opioid agonists on preparations of guinea pig ileum (for μ- and κ-receptors) or mouse vas deferens (for δ-receptors). The highest antagonist potency was at the μ-receptor, with 10- and 100-fold lower binding affinities at δ- and κ-receptors, respectively (table III).[112,113] No measurable opioid agonist activity was detected for alvimopan in either model. Alvimopan acts specifically at opioid receptors and has no substantial affinity (K_i <100 μmol/L) for non-opioid receptors such as adrenergic, dopaminergic, histaminergic, GABAergic or cholinergic (muscarinic) receptors.[113]

In vivo, alvimopan is a potent and selective antagonist of gastrointestinal μ-receptors, as demonstrated by its ability to precipitate diarrhoea in morphine-dependent mice without reversing morphine-induced analgesia (table III).[112,113] After intravenous administration, alvimopan was 200 times more potent at blocking peripheral than central μ-receptors, attesting to peripheral selectivity.[113] Oral administration with this agent also effectively blocks morphine-induced gastrointestinal inhibition and precipitates diarrhoea or reverses the delay in gastrointestinal transit of a charcoal meal in morphine-treated animals in a dose-related manner. Alvimopan has a rapid onset of action with maximum activity observed within 30 minutes after adminis-

tration in mice and activity lasting for at least 8 hours.[113]

Systemic absorption of alvimopan after oral administration is minimal in animal models. In dogs, the oral systemic bioavailability of alvimopan following administration of doses up to 100 mg/kg was 0.03%.[112] In contrast to its long duration of activity after oral administration in mice, the half-life of parenterally administered alvimopan was estimated to be approximately 10 minutes in dogs and rabbits. Poor systemic absorption after oral administration has been confirmed by whole body autoradiographic studies in rats dosed with ^{14}C-labelled alvimopan. The radioactivity was predominantly located within the gastrointestinal tract, with no evidence of distribution to blood or other tissues.[112,114]

Early clinical studies in human volunteers established the safety and efficacy of alvimopan in reversing opioid-mediated gastrointestinal inhibition without limiting central analgesia.[114] The effect of alvimopan on morphine-induced delay in oral-caecal transit time was assessed in a randomised, double-blind, crossover study in 14 volunteers.[115] Three treatments were administered on 3 separate days: intravenous placebo and oral placebo; intravenous morphine and oral placebo; and intravenous morphine and oral alvimopan. Morphine significantly prolonged gastrointestinal transit time from 69–103 minutes; treatment with alvimopan reversed this delay (transit time 76 minutes), and restored transit

time to baselines levels. In parallel, the ability of alvimopan to affect the central actions of opioids was investigated in 45 healthy patients who underwent dental surgery.[115] Treatment groups were similar to those in the previous study. Pain scores and pupillary constriction, both measures of central opioid effects, remained unchanged in morphine-treated patients after administration of alvimopan. These studies demonstrated that administration of alvimopan during opioid therapy normalises bowel function without reversing analgesia.

Selective postoperative inhibition of gastrointestinal opioid receptors with alvimopan has been reported recently.[116] Recovery of gastrointestinal function and hospitalisation were evaluated in a randomised, placebo-controlled trial involving 79 patients who underwent colectomy or total abdominal hysterectomy. Patients received alvimopan 1 or 6mg or placebo 2 hours before surgery and twice daily after surgery until the first bowel movement, discharge from the hospital or for a maximum of 7 days. Postoperative pain relief was provided by patient-controlled intravenous morphine or meperidine (pethidine).

The time to recovery of gastrointestinal function was significantly shorter among the patients who were treated with alvimopan 6mg than in those given placebo.[116] Treatment with alvimopan also significantly reduced the median time to first passage of flatus by 21 hours, time to the first bowel

Table III. Gastrointestinal effects of opioid antagonists (reprinted from Zimmerman et al.,[112,113] with permission from *Drugs of the Future*)

Opioid antagonist	Opioid receptor antagonist pA$_2$[a] values			Precipitation of diarrhoea in morphine-dependent mice (mg/kg)[d]	Antagonism of morphine analgesia in mice (mg/kg)[e]
	guinea pig ileum		mouse vas deferens		
	μ (DAMGO)[b]	κ (U69,593)	δ (DPDPE)[c]		
Alvimopan	9.7	7.8	8.7	0.04 (IV)	9.0 (IV)
Naloxone	8.5	7.7	7.3	0.31 (SC)	1.5 (SC)

a   Negative log of the equilibrium dissociation constant.

b   Tyr-d-Ala-Gly-MePhe-NH-(CH$_2$)$_2$OH (DAMGO).

c   d-Pen^2-d-Pen^5-enkephalin (DPDPE).

d   Dose that precipitated diarrhoea in 50% of the mice tested.

e   Dose that reduced the inhibition of writhing by 50%.

IV = intravenous; **pA**$_2$ = measure of antagonist potency; **SC** = subcutaneous.

movement by 41 hours and time to readiness for discharge by 23 hours. The median time to actual discharge was approximately 1 day earlier in the group that received the 6mg dose of alvimopan. Another benefit of treatment with alvimopan was a reduction in postoperative nausea and vomiting with the 6mg dose. In general, outcomes in managing postoperative ileus were superior with the 6mg compared with the 1mg dose. In this study, analgesic effects were not inhibited by the administration of alvimopan; pain scores and consumption of opioid were similar in all treatment groups. In addition to shortening the duration of hospitalisation, which has substantial clinical and economic implications, alvimopan offers ease of use and selectivity for gut opioid receptors that is independent of the site of surgery.

5. Conclusion

Opioid analgesics are frequently used for postoperative pain management, and for the treatment of chronic cancer and non-malignant pain. However, endogenous and exogenous opioids alter neural input, inhibit peristaltic contractions and propulsion, and increase fluid absorption; this leads to symptoms of bowel dysfunction. Activation of opioid receptors, particularly μ-receptors within the gastrointestinal tract, contributes to the pathophysiology of ileus after opioid use.

Because opioids contribute to ileus, gastrointestinal complications are likely to be moderated by administration of opioid receptor antagonists. However, use of low doses of currently available oral antagonists such as naloxone has been met with only partial success, mainly because these agents readily cross the blood-brain barrier and thus impair analgesia or even elicit opioid withdrawal.

The peripherally acting agents methylnaltrexone and alvimopan are the first opioid receptor antagonists for which an exclusively peripheral mode of action has been demonstrated in controlled clinical trials. These studies demonstrate the feasibility of selectively antagonising the undesirable peripheral effects of opioids following oral administration (i.e. bowel dysfunction), while preserving desired analgesic effects. Consequently, postoperative patients in whom opioid analgesics are combined with peripherally acting opioid antagonists have less ileus and shortened duration of hospitalisation than those given opioids alone.

Acknowledgements

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