The Useage of Opioids and their Adverse Effects in Gastrointestinal Practice: A Review

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ABSTRACT

Opium is one of the oldest herbal medicines currently used as an analgesic, sedative and antidiarrheal treatment. The effects of opium are principally mediated by the μ-, κ- and δ-opioid receptors. Opioid substances consist of all natural and synthetic alkaloids that are derived from opium. Most of their effects on gastrointestinal motility and secretion result from suppression of neural activity. Inhibition of gastric emptying, increase in sphincter tone, changes in motor patterns, and blockage of peristalsis result from opioid use. Common adverse effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, dependency and tolerance, and respiratory depression. The most common adverse effect of opioid use is constipation. Although stool softeners are frequently used to decrease opioid-induced bowel dysfunction, however they are not efficacious. Possibly, the use of specific opioid receptor antagonists is a more suitable approach. Opioid antagonists, both central and peripheral, could affect gastrointestinal function and visceromotor sensitivity, which suggests an important role for endogenous opioid peptides in the control of gastrointestinal physiology. Underlying diseases or medications known to influence the central nervous system (CNS) often accelerate the opioid's adverse effects. However, changing the opioid and/or route of administration could also decrease their adverse effects. Appropriate patient selection, patient education and discussion regarding potential adverse effects may assist physicians in maximizing the effectiveness of opioids, while reducing the number and severity of adverse effects.

KEYWORDS
Opium; Analgesic ; Opioid; Gastrointestinal motility

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INTRODUCTION

Opioid substances comprise all natural and synthetic alkaloid derivatives of opium. Opium is one of the oldest medicines in use as an analgesic and sedative. The root of the word opium is derived from "opos", a Greek word which means a liquid collected from the opium poppy.[1]

Opium has been clinically used for many years. Original documents regarding the use of opium drugs have been found as early as 3000 BC. In the first century, for the first time, the anesthetic and sedative effects of opiates have been described in "De Materia Medica". Because of its euphoric effects, opioid substances have been

used in different cultures and religions. There are numerous documents regarding opioid use in traditional Iranian medicine.[1,2] Morphine, the first opium alkaloid was introduced in 1805 by Friedrich Wilhelm Serturner. Later, different alkaloid components have been introduced of which all have analgesic effects on the central or peripheral nervous systems. These analgesic effects are due to decreased perception and reaction to pain, and increased pain tolerance.[1]

The alimentary canal might be has the largest neurological network after central nervous system (CNS). This neurological network is called the enteric nervous system (ENS). This nervous system has a vital role in all activities of the digestive system, of which it's activities are performed by different receptors and substances. The most important substances include acetylcholine, vasoactive intestinal polypeptides, nitric oxide, tachykinins, adenosine triphosphate, opioid peptides, and neuropeptide Y,5-hydroxy trypticon.[1-3]

Because of the frequent use of opium and its prevalence of gastrointestinal adverse effects, in this review article we discuss the physiology of opioids and clinical aspects that relate to the adverse effects of opium use on the alimentary tract.

OPIOID RECEPTORS

Pharmacologically, the opiates activate specific receptors along the nervous system. There are three major receptor subtypes, μ, κ, and δ, of which subtype μ seems to be more common. The δ receptor is another opiate receptor that does not influence mesenteric excitatory motor neurons. Recently a new receptor, the opioid receptor–like 1 (ORL-1) or nociceptin/orphanin (FQ) has been isolated. The activation or blockage of opioid receptors allows for important changes in the gastrointestinal tract's clinical presentation.[4] The receptors bind to opioids that originate from plants, either synthetic or endogenous (dermophins and deltorphins), and amphibian skin.

In 1975, for the first time, Hughes and Kosterlitz isolated an endogenous opioid receptor antagonist (leucine–enkephalin,methionine–enkephalin).[5,6] These researchers discovered the interaction between these substances and the ENS. In addition, the gut is not a unique site for opioid receptor antagonist function; these antagonists may additionally function via their receptors in the brain.[7] Opiate-induced effects possibly have a greater association due to their concentration in the ENS rather than the CNS.[8,9]

The opioid receptors belong to the family of metabotropin membrane receptors that act by binding to the GI/GO sites of the G-protein. Opioid receptors decrease intracellular cyclic adenosinenmonophosphate(cAMP) by inhibiting adenylate cyclase. Transduction pathways that include potassium channel activation, membrane hyperpolarization and inhibition of calcium channels are involved in this mechanism.[10,11] However, the action of opioid receptor–like-1 and opioids nociceptin/orphanin (ORL1-N/OFQ s)different. The ORL-1 receptor is expressed by reduction of calcium channels and cAMP activity, however potassium channel activation is also seen.[12]

Effects of opioid agonists on the alimentary tract

As mentioned earlier, the antagonistic effect of opioids occur via opioid receptors in which the μ receptor participates more in their clinical effects. Opioid receptors in the brain and gastrointestinal tract affect pain regulation. Opioids possibly influence both the inhibitory and excitatory neural system of alimentary muscles.[11,13]

Most opioid effects on gastrointestinal motility and secretion occur via suppression of neural activity (Table1). The inhibitory effects of morphine on intestinal peristalsis in guinea pigs has been demonstrated by Trendelenberg in 1917. Later studies have shown that morphine-like medicines reduce the frequency of peristaltic waves and maximal ejection pressure. Inhibition of the acetylcholine and non-adrenergic non-cholinergic (NANC) neurotransmitter release of ENS might be involved in this phenomen.[13,14]

According to a recent investigation, κ receptors

Table 1: Opioid receptors and their functions.

Receptor	Clinical effects	Location
μ	Analgesia Changes smooth muscle tone Sedation Mood alteration Nausea/vomiting	Mesenteric plexus Brain Spinal cord Sub-mucosal plexus
δ	Decreases colonic transit time	Mesenteric plexus Brain
κ	Central analgesia Decreases colonic transit time Visceral nociception antagonist	Mesenteric plexus Brain Spinal cord

have an important effect on pain management. Stimulation of κ receptors in animals has shown an increase in pain threshold and a reverse in peritoneal irritation that induced ileus and visceral pain.[15-17] The antinociceptive effects of κ receptor agonists such as fedotozine and asimadoline are observed at the terminal ends of afferent pelvic nerve fibers.[18-20] Because of the association between these receptors with enteric and ENS neurons, it has been proposed that peripheral receptor agonists might be useful in managing chronic visceral pain. Fedotozine has been shown to reduce irritable bowel syndrome (IBS) symptoms by increase the threshold of perception.[20,21] In addition, studies on asimadoline in humans have shown that this agent caused a reduced sensation of gastric and colonic distention.[22] The effects of these types of medications on the ENS with regards to chronic or acute use are not same. Both in vivo and in vitro studies have shown that chronic exposure of these agents causes reduced neuronal sensitivity.[14] Naloxan, an opioid antagonist, elevates both neuronal excitability and pain threshold the ENS.[23]

Gut

Most opioid agonists, including morphine, cause decreases in gastric motility in humans that are independent of their routes of administration.[14,24,25] These agents cause increased contraction of the antrum and pylorus along with decreased resting tone in the musculature of the gastric reservoir. Their contraction is mediated by activation of both inhibitory and excitatory motor neurons which consequently re-establishes contractility tone. Stimulation of μ receptors enables the opioid to decrease gastric motility. In contrast, opioids cause increased tonic contractions of the antral muscles and upper duodenum.[26,27]

Intestine

In the intestine, opioid agonists block peristaltic reflex by stimulation of receptors along the ENS in addition to the inhibition of nicotinic post-synaptic receptors.[28,29] Opioid agonists cause increased resting tone in circular(spherical) muscles of the small and large intestine along with enhanced rhythmic contractions.[30] Opioids, as morphine, in addition to their effects on the ENS, also act on the spinal cord and brain to suppress intestinal motility.[31] On the other hand, opioids have inhibitory effects on motor neurons at the level of the submucosal plexus, causing suppression of the secretion and liquidity of intestinal contents resulting in the formation of hard stools. Administration of opioids inside CNS has the same effect by causing an elevation in sympathetic activities of ENS.[32,33]

Colon

Delayed colonic transit due to opioids causes prolonged contract time of the colon, which in turn enhances liquid absorption. Studies have suggested that all types of opioid receptors have this effect.[34] Colonic transit time in the cecum and ascending colon in addition to the frequency of defecation are decreased by morphine–like derivatives. Several studies have suggested that these substances affect anorectal function which increases pain threshold volumes for minimal perception and the sensation of defecation.[34,35] Musial has demonstrated that loperamid increased internal anal sphincter tone and improved continence mechanisms.[36]

Biliary system

Opioids also impact the biliary system and sphincter of Oddi. Administration of opioids results

in relaxation of the sphincter of Oddi, subsequently resulting in biliary stasis.[1,34,37] On the other hand, opioid peptides cause decreased gallbladder contractions that have been induced by cholecystokinin (CCK)which in turn assists with bile saturation and cholelithiosis.[38-40]

Immune function

The effects of opioids during inflammation on nociception, motility and secretion are increased,[39-41] which could be attributed to changes in permeability and integrity of the perineurium that results in easier access to opioid agonists.[42,43] In a study on mice that lacked μ receptors, it was observed that these mice were more susceptible to induced colitis which emphasized the effects of this receptor on intestinal inflammation.[44,45] In addition, this might be related to up-regulation of μ and κ receptors.[46] Endogenous opioids also influence immune cells, enhance cytokine production and T-cell proliferation.[43.45]

Visceral Sensation

Opiates have been shown to reduce somatic and visceral pain sensation. Their effects possibly act via either the central (spinocerebellar) or peripheral (spinal) nervous systems, which influence the perception of visceral pain.[47] Morphine-like derivatives act by increasing the nociceptive threshold via μ receptors primarily in CNS.[48] Meanwhile, κ receptor agonists such as fedotozine could increase the threshold of the discomfort sensation associated with gastric and colonic distention in IBS patients and healthy volunteers.[21,49] The same result was observed with asimadoline (a κ receptor agonist that does not cross the blood brain barrier) administration in healthy subjects. Possibly, the κ agonist acted on the peripheral afferent pathway.[50,51]

Secretion

Opioids such as lopramid and diphenoxylate are usually used as antidiarrhea drugs because of their anti-secretory properties. The mechanism of morphine-like derivatives on gastrointestinal secretions is mainly indirect; possibly they act on receptors located on the mesenteric plexus and sub-mucosa[13,22] which induct serotonin secretion. Serotonin consequently stimulates noradrenalin release which has inhibitory effects on enterocyte secretion by activation of alpha-2-adrenoceptors. Data have revealed that endogenous opiates are involved in gastric acid regulation. Morphine-like derivatives could decrease bicarbonate, fluid and electrolyte secretions in the intestine. They also reduce inflammatory fluid secretion during cholecystitis which contributes to pain relief. In addition, opioids primarily increase fluid absorption by delaying colonic transit.[13,52,53]

ADVERSE EFFECTS OF OPIOID USE

Common side effects of opioid medicines are dependency, tolerance, constipation, sedation, dizziness, vomiting, and respiratory depression. These effects sometimes cause discontinuation of the medication. Although constipation and nausea are considered the two main complications of opioids that rarely develop tolerances against them, other less common side effects include delayed gastric emptying, hyperalgesia, immunologic effects and hormonal dysfunction (Tables 2 and 3). Flushing, pruritus and anaphylaxis are also adverse effects of opioid use and are the result of histamine release that involves the μ and κ receptors.[54] Some studies have reported that fentanyl and its analogs do not cause histamine release.[54,55]

Immunologic Effects

Opioids affect the immune system by decreasing resistance to bacterial infections, which are mostly due to exogenous opioids. It has been demonstrated that exogenous opioid administration, either acute or chronic, suppresses antibody and cellular immune responses. Mechanisms of this suppression involve the central and peripheral nervous systems(CNS&PNS) where the hypothalamic–pituitary–adrenal axis and autonomic nervous system are involved.[17,56,57]

Constipation

Constipation occurs in approximately 90% of patients who take opioids and can occur with a single dose.[58,59] Long-term constipation causes substantial morbidity with reduced quality of life in patients. The μ receptors are possibly more involved in this phenomenon.[34,59] Studies have shown that intestinal motility is not influenced by morphine administration within the spinal cord.[13,59]

Table 2: The effects of opioids on numbers of hormones

Hormone	Effect	Symptom
Testosterone	Decrease	Decreased libido, energy, erectile dysfunction
Estrogen	Decrease	Sexual dysfunction Reduced bone mineral density and osteoporosis
Cortisol	Decrease	Hormonal alteration
LH	Decrease	Decreased androgen level Hypomenorrhea Amenorrhea
Gonadotropin Releasing Hormone	Decrease	Decreased androgen level Hormones levels

Table 3: Immunological effects of opioids.

Receptor	Effects
μ	↓ NK cell activity ↓ Macrophage activities ↓T-cell proliferation, NO release
Δ	↑ NK cell activity ↓ Plaque-forming cell
δ, antagonists	↓ Delayed hypersensitivity reaction
K	↓ Humoral immunity
κ antagonists	↑ Plaque-forming cell ↓ Humoral immunity

Although it is not completely clear whether the effect of opioids develop by stimulation of the central or peripheral nervous system, however it is generally accepted that morphine and its extracted drugs change autonomic outflow via the CNS[18,19,59] and by stimulating opioid receptors within the ENS. Unlike other opioid complications, constipation is not tolerated overtime, necessitating monitoring and treatment. The severity of constipation can be evaluated by the patient assessment constipation system and patient assessment of constipation quality of life questionnaire (PAC-SYM and PAC–QOL), among others.[21] Based on studies of patients who suffer from cancer pain, the transdermal patch fentanyl may cause less constipation compared to morphine. Fentanyl is a lipophilic substance; transdermal fentanyl absorption is dependent on body weight and body fat mass.[60-62] To manage constipation, in addition to changing the narcotic drug and treatment with anti-constipation medications (Table 4), the administration of opioid receptor antagonists is important. Currently, methylnaltrexone and alvimopan are under clinical trials. Both are μ receptor antagonists whose efficacies have not been completely proven (Table 5).

Nausea and Vomiting

Opioid administration induces nausea and vomiting, which in turn could lead to the development of patient dissatisfaction with treatment. In this situation, other etiologies should be excluded. Mechanisms of this side effect involve both central and peripheral nervous system . Opioids mainly stimulate the chemoreceptor trigger zone (CTZ), inhibit gut motility and stimulate the vestibular apparatus.[63,64] Studies show that the neurokinin-1 (NK-1) and serotonin receptor in post rema area (is a medullary part at the inferoposterior of the fourth ventricle that controls vomiting)may be involved in opioid-induce emesis.[65] In this situation, new medications such as palonosetron (serotonin receptor antagonist) and aprepitant (NK-1 antagonist) might be beneficial.[66,67] Switching from one opioid to another in addition to the use of sustained-release opioids might assist patients. Adding a prokinetic agent may also be of benefit to patients. The American College of Physicians recommendations for ill and terminal patients are illustrated in Table 5.

Narcotic Bowel Syndrome (NBS)

Narcotic bowel syndrome (NBS) is a subset of opioid–induced bowel dysfunctions accompanied by chronic, frequent abdominal pain that worsens by taking or escalating the dose of opioids. NBS symptoms include abdominal pain, intermittent vomiting, weight loss and occasional ileus-like symptoms.[68,69] These symptoms cause the patient to take more narcotics, however after a short period of relief the pain returns and is stronger, which causes the patient to take additional narcotics. This condition causes a vicious cycle. Patients, who for first time have received high doses of narcotics, tend to report this problem.[68] The key to diagnosing NBS is chronic use or escalating dose of narcotics that lead to continued or worsening problems for the patient. This problem has been initially reported two decades ago in the United States, after which other countries also observed cases of NBS.[70] Treatment of NBS involves early diagnosis of symptoms, with effective psychological consulta-

Table 4: **Novel medications for the treatment of opioid-induced constipation.**

Name	Class	Efficacy	Clinical effects
Naloxone	Non-selective opioid antagonist	Reverses opiate-induced delay in orocecal and colonic transit.	Naloxone PR formulation prevents OIC in patients who received PR oxycodone.
Methylnaltrexone	Opioid antagonist	Reverses effects of opiates in health and of chronic methadone treatment on orocecal transit; no effect on small intestinal or colonic transit delayed by codeine (30 mg q.i.d.) in opiate-naive healthy subjects.	S.c. methylnaltrexone (0.15 mg/kg) on alternate days was effective in inducing laxation in patients with advanced illness.
Alvimopan	PAMORA	8 mg oral dose accelerated colonic transit and Reversed the effects of codeine in opiate-naive healthy volunteers who received codeine, 30 mg q.i.d.	0.5 mg Alvimopan dose efficacious in treating OIC; rare instances of ischemic heart disease.
Tapentadol	Narcotic analgesic plus norepinephrine reuptake inhibitor	ND	Tapentadol ER 100-250 mg b.i.d. equally effective for moderate to severe chronic steoarthritis-related knee pain compared to oxycodone HCl (CR) 20 – 50 mg b.i.d., given daily with less bowel dysfunction symptoms.
NKTR-118	PAMORA; PEGylated naloxol conjugate	Normalized morphine-induced delay in orocecal transit.	25 and 50 mg NKTR-118 had increased numbers of SBM during the first week and during 4 weeks of treatment of OIC patients.
TD-1211	PAMORA	ND	5 and 10 mg/day TD-1211 increased average SBM/week over 2 weeks in OIC patients.

CR, Controlled release; ER, Extended release; ND, Not done; OIC, Opiate-induced constipation; PAMORA, Peripherally-restricted –opioid receptor antagonist; PEG, Polyethylene glycol; PR, Prolonged release; SBM, Spontaneous bowel movement; s.c., Subcutaneous administration

tions and gradual withdrawal of the narcotics during a specific program. Clonidin, an alpha adrenergic agonist, is indicated for this problem.[71,72] Clonidin works at the alpha-2-receptors in the CNS and gut wall.[73] Lofexidine, another alpha-2-adrenergic agonist with less side effects is more suitable for outpatient programs.[72,74]

Pruritus

The rate of pruritus due to opioids ranges from 2% to 10%.[75] Histamine release appears to be the mechanism for developing pruritus. Management of pruritus includes antihistamines, switching opiates, changing the dose of opioides and supportive treatment.[75-77]

Central Nervous System (CNS)

CNS adverse effects from opioids are primarily sedation and decreased cognition. Although some patients need additional treatment for these effects, most often they are transient. Sedation and decreased cognition usually present during the onset of opioid treatment or with increasing doses. A psycho-stimulant might be used for their management. Administration of antipsychotics could be considered in cognitive side effect.[78,79]

Tolerance and Dependency

Tolerance and dependency are common side effects of opioid treatment that are primary or acquired.[80] Tolerance and dependency primarily have a genetic origin and could be present from the first dose. Acquired tolerance and dependency is divided into pharmacokinetic, pharmacodynamic and learned categories. Repeated administration leads to pharmacokinetic tolerance, whereas pharmaco-dynamic tolerance results from decreased effectiveness of the drug over time. Learned tolerance is results in decreased effectiveness by incorporation use of the opioid medication. Although the mechanisms of tolerance are not unclear some studies have indicated an increased neuropeptide activity such as the calcitonin

Table 5: Antiemetics based on recommendations by the American College of Physicians.

Drug	Cause of nausea	Dose
Prochlorperazine	Initiation of opioid therapy	10 mg orally or 25 mg rectally, 2 or 3 times daily
Haloperidol	Stimulation of chemoreceptor	1.5–5 mg, orally 3–4 times daily; 2–10 mg Intramuscularly, 2 or 3 times daily
Prochlorperazine	Trigger zone by chemotherapy	10 mg orally or 25 mg rectally, 2 or 3 times daily 2–6.25 mg intramuscularly, 3 times daily;
Methotrimeprazine		6–25 mg, over 24 h
Scopolamine (transdermal patch)	Vertigo	Apply 1 patch every 2–3 days
Meclizine		50 mg orally or 25–50 mg intramuscularly, 3 times daily
Metoclopramide	Delayed gastric emptying	10–20 mg, 2–3 times daily; 1–3 mg h intravenously
Octreotide	Bowel obstruction	50–100 lg subcutaneously 2 or 3 times daily or 300 lg During 24hours subcutaneously
Ondansetron	Multiple causes, refractory	4–8 mg orally, 2 or 3 times daily
Dexamethasone		2–4 mg orally, 2 or 3 times daily

gene-related peptide (CGRP) and substance P.[80-82]

Effect of Opioid Use on the Alimentary Tract

Over 300 analogues of endogenous or exogenous opioid peptides are designed to act on opioid receptors. Numerous research has focused on the provision of new molecules that do not pass the blood-brain barrier that just have peripheral effects. Morphine and morphine-like medications work mostly via the opioid μ receptor, which is responsible for the majority of opioid effects in the brain and periphery. Opioid analogues have unwanted effects on bowel dysfunction such as severe constipation, hard stools, incomplete evacuation, straining, bloating and gastro-esophageal reflux. However many of these medications might be used to manage excessive exertion such as fistula or stomy output. Two popular opiates frequently used are loperamide and diphenoxylate.

Loperamide and Diphenoxylate

Loperamide is a derivate of meperidin which inhibits calcium channels and calmodulin in the intestine's smooth muscles, as well as inhibiting fluid secretion in the colon. Loperamide does not pass the blood-brain barrier. Oral loperamide absorption can be increased by raising the pH in the gut. Therefore gastric hypersecretion theoretically decreases the clinical effects of loperamide. Inhibiting P-glycoprotein, an efflux pump in the intestine, would increase the oral absorption of loperamide. P-glycoprotein is found in different organs such as the brain and kidneys, thus it's inhibition by different medicines could result in the passage of loperamide to the brain and CNS.[83] The elements with inhibitory effects on P-glycoprotein and substances which metabolize cytochrome P450 2C9(CYP2C9) and cytochrome P450 3A4(CYP3A4) can enhance the systemic effects of loperamide. Concurrent use of itraconazole and gemfibrozil increase plasma levels by increasing absorption, and decrease loperamide elimination.[83-86]

Diphenoxylate is a derivate of meperidin which at low doses leads to constipation; at high doses it causes systemic effects such as euphoria. Excessive use of this medication could lead to cardiovascular problems due to its anticholinergic effects. Diphenoxylate is rapidly absorbed following oral administration.[87]

Esophageal Motility

Some studies shows that morphine-like drugs decrease lower esophageal sphincter relaxation, resulting in fewer reflux episodes along with a reduction in the time of contact between decreased pH liquids and the esophageal membrane. The therapeutic use of opioids for gastro esophageal reflux has yet to be established.[88,89]

Dyspepsia

Various forms of dyspepsia are related to neuromuscular and sensory abnormalities. Visceral hypersensitivity in

response to different stimulation could be considered an important mechanism of dyspepsia.[90] κ receptor agonists have been shown to influence visceral perception without changing gastric emptying. Drugs such as fedotozine could be effective in eliminating bloating, abdominal pain and post-prandial fullness in functional dyspepsia.[91] In different studies, asimadoline a selective κ receptor agonist, did not favorite on dyspepsia in one study this drug overall did not significantly alter maximum-tolerated volume, symptoms post nutrient challenge or symptoms over 8 weeks in functional dyspepsia.[51,92]

Irritable Bowel Syndrome (IBS)

IBS is a complex, symptom-based diagnostic problem in which abdominal discomfort, bloating and disturbed defecation are present. Although the etiologies of IBS remain unclear, however a combination of sensory and motor changes to the alimentary tract have been proposed.[93] μ receptor agonists such as morphine, loperamide, diphenoxilate, and mepridin have decreasing effects on circular and longitudinal muscles of the intestine. Of these, loperamide has not effects on CNS.[93,94] Currently, loperamide is mainly used to treat diarrhea-predominant IBS. Loperamide decreases the frequency, urgency and pain in IBS patients. Tremebutin has an affinity for μ, δ and κ receptors without affecting colonic motility, and decrease post-prandial motor activity in IBS patients. Tremebutin also accelerates bowel transit time in patients who have constipation. Asimadoline, a selective κ receptor agonist, is also used in this manner.[94,95]

In constipation-predominant IBS, μ receptor antagonists have been evaluated based on the hypothesis that endogenous opiates might influence motility disorders. Fedotozine, a κ receptor agonist, increases the threshold of perception in the colon and might be useful for IBS patients.[96] In one study, low dose naltreoxone has been shown to improve pain and general feeling in IBS patients. However this result was not confirmed in a case control study.[93] There have not been enough clinical trials to establish the efficacy of opiates antagonist in IBS.

Diarrhea

Worldwide, the accepted treatments for chronic and acute diarrhea are loperamide and diphenoxylate, in which loperamide is preferred. Mostly these drugs are not used for either palliative or control of acute diarrhea. Opiates are commonly used in short bowel syndrome. These agents act by stimulating the μ receptor by slowing colonic transit. They also have anti-secretory effects.[86,97,98] However, enkephalin, an endogenous opiate present its antisecretory effects by stimulate sigma receptor in basolateral membrane of enterocyte via inhibition of adenylate cyclase.[99] It is degraded by enkephalinase. Racecadotril, an antagonist for enkephalinase favorably affects both the frequency and weight of stool in children and adults and is comparable with loperamide.[86,98] Codeine has an antidiarrheal effect of which approximately 10% of this medication is metabolized into morphine by the CYP2D6 enzyme.[100] Other systemic opiates may be used to treat diarrhea when the patient can not tolerate or respond to the usual agents.

Liver Impairment

Hepatic failure affects the metabolism of a majority of opioid drugs; the activity of some of these drugs is dependent upon hepatic biotransformation to active metabolites. Narcotics possibly have a role in development or even aggravation of hepatic encephalopathy, therefore cautious use and careful monitoring are warranted.[101,102]

On the other hand, hepatic failure may reduce the analgesic effects of these medications. In addition, clearance of opioids (morphine, oxycodone, tramadol and alfentanil) might be impaired during hepatic failure. According to some studies the bioavailability of a number of opiates such as morphine, hydromorphone and oxycodone are enhanced during hepatic failure and adjustment of doses or longer intervals must be considered. Also the elimination of toxic metabolites decreases during liver failure, increasing the risk of toxicity of some narcotics such as pethidine (meperidine) that has a toxic metabolite(Figure 1). Administration of these agents should be performed with caution or otherwise avoided. Hepatic disease is not influence on pharmacokinetic of the phenylpiperidine family (fentanyl).[101-103]

CONCLUSION

Opioid medications are widely used in the management of acute and chronic pain. As with other medications there are potential adverse effects. Serious adverse effects usually develop in patients that use these medi-

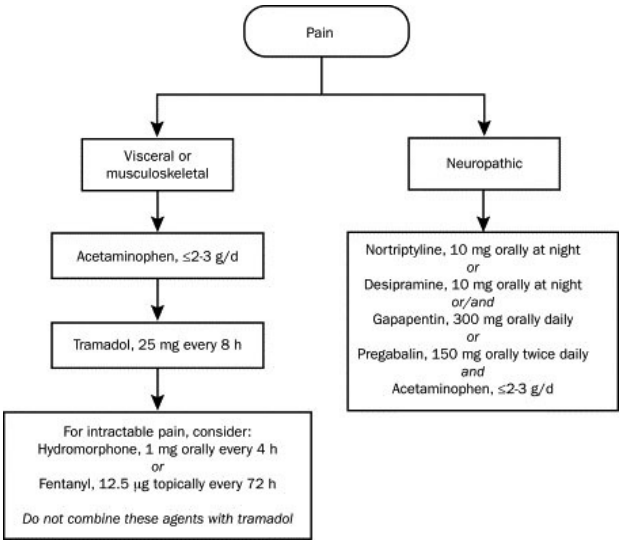

Fig.1: Pain management in liver failure

cations for extended periods. Education of patients and health service staff along with the correct prescription and proper consideration of adverse effects, particularly at the onset, as well as changing the dose of medication could assist in the management of common and uncommon adverse effects

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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