Opioid antagonists and their therapeutic role in anaesthesia and chronic pain management

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Introduction

“I should not like to be a doctor without Morphin at my disposal”, said by an unknown nineteenth century German physician, certainly holds as true today as when it was said. One of our primary aims as anaesthetists is to relieve the pain and suffering of our patients, and to do this effectively without the aid of opioids is unthinkable.

The use of opioids is often associated with less pain but more suffering in terms of unwanted side effects, some of which may lead to significant morbidity and even mortality. In an attempt to address this problem, numerous alterations were made to the original molecules found in the opium plant. Among others, heroin, methadone and the phenylpiperidine derivatives (fentanyl, pethidine, etc.) were synthesised and all claimed advantages over morphine, although they had the same degree of side effects as the original drug. A notable example is pethidine, which was synthesised in the 1930s and claimed less respiratory depression than morphine (an opinion that is still held by some of our colleagues).1

The synthesis of molecules with partial agonist activity on opioid receptors (buprenorphine), and agonist-antagonist molecules (nalbuphine), represented a significant advance in the avoidance of opioid-mediated side effects in that they could reverse some unwanted effects of the pure agonists, but were analgesic in their own right.

The pure opioid antagonists (naloxone, naltrexone, nalmefene, methylnaltrexone and alvimopan) have the advantage of fully reversing opioid-induced side effects, but they also reverse the analgesia produced by opioids to a greater or lesser degree, depending on the drug. Recent work has shown surprisingly beneficial effects of the antagonists as a group, as well as certain of the drugs in particular, which reveal these drugs as potentially valuable tools in the management of pain and the avoidance of side effects in the acute and chronic setting. In addition, they have certain beneficial antagonist effects on the endogenous opioid system.

This review will focus on the pharmacokinetic actions of opioids and the opioid-receptor antagonists. It will also discuss potential therapeutic roles for the antagonist drugs.

The opioid receptor antagonists

Structure-activity relationships

Antagonists of any ligand-mediated receptor system are classified as molecules that bind specifically with those receptors, but do not elicit an intracellular response, as an agonist would do. Hydroxylation of carbon atom 14 in the basic morphine molecule yields compounds that have either antagonist or no agonist activity at all the opioid receptors.3

The tertiary opioid receptor antagonists, naloxone, naltrexone and nalmefene, are similar in structure and have equal lipophilicity, which enables them to cross all membranes with ease, including the blood-brain barrier.

The quaternary antagonist, methylnaltrexone, was synthesised by adding an alkyl substituent to the nitrogen atom of a tertiary antagonist (naltrexone). This makes the drug more polar and hydrophilic, which prevents it from crossing membranes with ease (see Figure 1).28

Alvimopan (ADL 8-2698) was synthesised from the basic phenylpiperidine structure, is moderately large and has a high polarity, which prevents it from crossing membranes (see Figure 2).

Naloxone (Narcan®)

This drug is a potent antagonist of all known opioid receptors, but has a

Figure 1: Synthesis of the major opioid antagonists from the morphine molecule

Figure 2: Alvimopan synthesised from the phenylpiperidine structure
stronger affinity for mu receptors. It antagonises central and peripheral opioid effects due to its high lipophility.

It has an acute onset of action and thus can precipitate opioid withdrawal symptoms more than other antagonists. These symptoms include hypotension, tachycardia, cardiac arrest, irritability, restlessness, tremulousness, seizures, nausea, vomiting, diarrhoea, dyspnea and pulmonary oedema. All these symptoms are likely to occur in opioid overdose in opioid-dependent patients, and are thought to be due to acute stimulation of the sympathetic nervous system. It is therefore recommended that the drug be avoided in patients with severe hypertension, ischaemic heart disease, a history of cerebrovascular disease, or in any patient where sympathetic stimulation would be detrimental.

Its duration of action is much shorter than its half-life, which demonstrates its fast dissociation from opioid receptors (see Table I). This short duration of action may be problematic if used to reverse the effects of longer acting opioids, due to the problem of “renarcotisation”. Repeated dosing, intravenous infusion or intramuscular administration is recommended in these patients.

IM absorption is adequate, but prolonged, and therefore an IV dose is recommended in the acute setting. Oral bioavailability is less than 3% due to extensive first-pass metabolism. In life-threatening situations the drug can be given endotracheally.

The dose for suspected opioid overdose is 0,4 to 2 mg repeated every two minutes until response is obtained. For the periparative reversal of side effects, increments of 0,1 mg iv can be given every two to three minutes. However, it is not always possible to reverse the side effects without reversing the analgesia.28

Naltrexone (Revia®)

Naltrexone is a non-specific opioid receptor antagonist, but with the advantage over naloxone that it has a half-life of four hours, with a significantly longer receptor dissociation constant (see Table I). It also undergoes less first-pass metabolism and is therefore effective in its oral form.

An oral dose of up to 300 mg/day is well tolerated. It may cause transient elevation of liver transaminase levels at higher doses, but this resolves with discontinuation of the drug. Naltrexone may cause stimulation of the sympathetic nervous system, but there are no reports of serious cardiovascular adverse effects associated with the drug. It is only available in oral form and its main indication for use is during opioid withdrawal, and to maintain abstinence. The recommended dose range is from 50 to 300 mg/day po.28

Nalmefene (Revena®)

This antagonist has a greater affinity for mu receptors, like naloxone, but also antagonises opioids at other receptors. It is four times as potent as naloxone in antagonizing mu receptor agonist effects. Its duration of action is at least four hours at lower doses (dose dependent), given parenterally, but its effects may last up to 48 hours if given orally (see Table I). Its oral bioavailability is 40 to 50%.

Nalmefene has a relatively slow onset of action, and no serious adverse reactions were noted in studies where four times the normal dose was given.27 There is one case report in the literature of a healthy patient developing acute postoperative pulmonary oedema after a very low dose (75 µg) of nalmefene.29

It is available in oral and intravenous form. The dosage for opioid overdose is 1 ml (100 µg) per 1 mg of opioid iv. For the reversal of postoperative respiratory depression, 25 µg increments are given every two to five minutes.28

Methylnaltrexone

Being a methylated analogue of naltrexone, this drug does not cross the blood-brain barrier when administered systemically (iv). It has been shown in a number of trials that it does not reverse the centrally-mediated effects on opioids, but is a potent antagonist of peripheral opioid side effects. Its oral bioavailability is less than 1%.

It is well tolerated even in the higher dosage ranges (1,25 mg/kg), apart from transient orthostatic hypotension that has been reported.31 The usual therapeutic dose for the reversal of opioid-induced bowel dysfunction is 0,3 mg/kg every six hours IV.32

Table I: Pharmacokinetic characteristics of the opioid antagonists

| Antagonist          | Onset | Duration               | Metabolism      | Half-life | Elimination | Dissociation rate constant (µ receptor) minutes |
|---------------------|-------|------------------------|-----------------|-----------|-------------|-----------------------------------------------|
| Naloxone            | 2-5min| 20–60min               | Hepatic         | 1–1,5h    | Renal       | 0,82                                          |
| Naltrexone          | 60min | 24h (dose dependant)   | Hepatic (6-beta-naltrexol) | 4h         | Renal       | 2,0                                           |
| Nalmefene           | 1–2h  | 4–8h iv/dose dependant | Hepatic         | 8,5–10,8h | Renal       | 2,4                                           |
| Methylnaltrexone    | 3min (iv) | 48–72h oral         | Hepatic (Nalmefene glucuronide) | 2h         | Renal       | 0,46                                          |
| Alvimopan           | 1h    | 12h oral               | Hepatic         | 10min     | Renal       | 30                                            |
Alvimopan (Entereg®)

This complex synthetic molecule does not antagonise the central effects of opioids, but it is very effective for treating peripheral side effects. It is a mu-selective antagonist. It has a long duration of clinical effect due to its slow dissociation from mu receptors. (see Table 1.) Its oral bioavailability is 0.03%, and it is almost undetectable in plasma after oral administration.

Alvimopan is well tolerated, with a safety profile comparable to placebo, with the most serious side effect being abdominal cramping. The doses range from four to 12 mg po b.i.d. for treatment, and for the prevention of opioid-induced bowel dysfunction. 2,3

The opioid receptors, their mechanisms of action, and side effects associated with their stimulation

Opioi-mediated analgesia

The opioid receptor family can be divided into mu (μ1 & μ2), kappa (κ1-4) and delta (δ1 & δ2) subgroups according to their differing effects when stimulated, as well as their locations within the central and peripheral nervous system.2

Ligand (endogenous and exogenous opioids) binding to the opioid receptors in the dorsal root ganglia (spinal cord) stimulate either Gi / Go or Gs proteins to mediate their intracellular effects. Gs protein stimulation increases cAMP levels and underlies the mechanism of hyperalgesia and tolerance (see below). Go stimulation leads to hyperpolarisation of cell membranes (via increased potassium conductance) or to direct inhibition of neurotransmitter release presynaptically (via inhibition of N-type calcium channels). Gi stimulation leads to decreased intracellular concentrations of cAMP, which facilitates the modulation of neurotransmitter release (substance P, CGRP, glutamate).

Two types of opioid-sensitive cells in the rostral ventromedial medulla (RVM) and the periaqueduct grey nuclei (PAG) exist at the supra spinal level. Opioids stimulate “off” cells to increase descending inhibition of the DRG, and inhibit “on” cells to decrease descending facilitation of nociceptive stimuli.4

In response to chronic noiceptive stimuli in the area of primary afferent nerve endings in the periphery, DRG neurons transport opioid receptors from the cell body to the afferent nerve endings, which respond to endogenous opioids released by macrophages and lymphocytes, or to exogenous opioids.

These mechanisms underlie the antinociceptive and analgesic actions of opioids at supraspinal, spinal and peripheral levels.5 (See Figure 3.)

Naloxone, naltrexone and nalmefene, in higher concentrations, reverse all the analgesic effects of opioids at supraspinal, spinal and peripheral level.24 This effect is obviously undesirable in the acute perioperative setting. These same antagonist drugs, however, may actually contribute to analgesia in ultra-low concentrations.25 (See below.)

Methyltrexone and alvimopan, by virtue of their inability to cross the blood-brain barrier when administered systemically, do not, however, reverse the central analgesic effects of opioids, which offers clear advantages in the perioperative setting and in opioid-dependent patients.26,27 These same inhibitory effects of opioid ligand binding are also responsible for the wide array of sideeffects seen with opioid administration.

Nausea and vomiting

These very common side effects are both difficult, and costly, to treat in patients who received opioids.5 All opioids in current practice may induce these effects, with no difference in incidence among different drugs.6

Opioids induce nausea and vomiting by stimulation of the δ-receptors in the CTZ in the area postrema of the medulla.7 In addition, their effects on gastric emptying, and on the upper GI tract, play a contributory role. Unfortunately, tolerance to this side effect of opioids does not develop.7

Opioid receptors have a particularly high concentration in the gastric antrum and proximal duodenum,4 and the stimulation of these receptors (most importantly μ-receptors) may induce or worsen nausea and vomiting.7 Central nervous system (CNS) opioid receptors also contribute to nausea and vomiting, as evidenced by the fact that intracerebroventricular administration of morphine results in gastric distension, increased retrograde pressure in the duodenum and vomiting in dogs.54

It should be remembered that pain per se stimulates the vomiting centre and that there is a central anti-emetic, receptor-mediated opioid effect.4 (See Figure 4.) The centrally-acting opioid antagonists given

Figure 3: Mechanism of opioid mediated analgesia

(Dotted red arrows – inhibition; solid red arrows – stimulation; M – macrophage; L – lymphocyte)
Orally administered alvimopan (6 mg) reduced the incidence of PONV from 23% in the placebo group to 0% in the alvimopan group in 79 patients undergoing TAH or colectomy, which compares favourably with the administration of ondansetron. Central analgesia mediated by large doses (71 mg cumulative) of morphine was not affected by the drug.4 In a recent large randomised controlled trial (RCT) of the effects of alvimopan (6 mg or 12 mg) on postoperative bowel dysfunction in hysterectomy patients, the incidence of nausea and vomiting was similar to the placebo and alvimopan groups, although opioid consumption was not mentioned in the study.15

These results taken together suggest that the direct inhibition of mu-opioid receptors in the upper GIT plays a major role in treating opioid-induced nausea and vomiting. It seems that low-dose centrally-acting antagonists, and the peripheral-acting antagonists, especially when given orally, are effective in treating these side effects without reversing centrally-mediated opioid analgesia.

Respiratory depression
This is the most serious adverse effect of opioids, with a postoperative incidence of 0,1 to 1%. The incidence is independent of the route of administration or the type of opioid, but the duration of depression is related to the duration of the effect of a specific drug (e.g. morphine vs. alfentanil).13

Opioid agonists depress ventilation via central stimulation of mu2, kappa and delta receptors, the most important of which are the mu2 receptors in the medulla. The role of the mu1 receptors in this effect is controversial. Certainly, all opioids with mu-agonist activity depress respiration in a dose-dependent manner.14,15

The overall effects on respiration induced by opioids are primarily mediated via effects on the medullar respiratory centres, although other areas of the CNS and chemoreceptor areas might also be involved. Opioids decreases respiratory rate more than tidal volume (which might actually increase), primarily through an increase in expiratory time and a prolonged expiratory pause. The minute ventilatory response to pCO2 is decreased (shifted to the right), the apnoeic threshold and resting ET CO2

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Figures

**Figure 4:** Mechanisms of opioid-induced emesis and anti-emesis

*+ denotes stimulation or emetic effects; - denotes inhibition or anti-emetic effects; note that the CTZ lies outside the BBB*

Naloxone infusion regimens have been used to determine the efficacy of the drug. In this study, lower-dose infusions (0,25 µg/kg/hr) and higher-dose infusions (1 µg/kg/hr) of naloxone were administered to patients receiving opioid analgesia. The incidence of nausea and vomiting was comparable between the two regimens and significantly less than in the placebo group. All other indices were similar between groups, including pain ratings.35

Infusion of nalmefene in morphine PCA patients revealed a reduction in nausea and vomiting from 63% (placebo) to 33% (nalmefene groups). Very low dose ranges were used (15–25 µg), and this could explain the absence of increased pain scores in the nalmefene group.36

Methylnaltrexone administration does reduce nausea and vomiting in dogs,37,38 and two studies in humans also attest to its efficacy in reducing this side effect, without affecting analgesia.39,40 However, in a double-blind placebo controlled study of postoperative nausea and vomiting (PONV) after gynaecological surgery, 20 mg of methylnaltrexone did not have any beneficial effect on PONV, although the morphine doses used were small (6 mg) and methylnaltrexone did reduce nausea by 45%, although it was not regarded as significant because the study was powered to detect a 50% reduction in nausea and vomiting.41

**Figure 5:** Opioid-induced minute ventilatory response to pCO2

(Note the increase in the apnoeic threshold)
A series of studies on methylnaltrexone have demonstrated that the drug prevents opioid effects on gastric emptying and improves oral-cecal transit time without affecting analgesia, even when given parenterally, and regardless of the plasma concentration of the drug.

Alvimopan has been shown to be effective in preventing acute postoperative bowel dysfunction and, in patients on chronic opioid therapy for chronic pain, without reversal of analgesia, withdrawal symptoms or serious adverse effects.

Other therapeutic applications of opioid receptor antagonists

**Chronic therapy for promoting abstinence in opioid and alcohol dependence**

Opioid receptors in the CNS and specifically the mesolimbic system are involved in the euphoria mediated by alcohol consumption and opioid abuse. The rationale behind using antagonists is that, by preventing this euphoria, the pleasure motivation of using these substances is removed.

Naltrexone has shown similar characteristics if administered orally or in low IV doses. As can be expected, the peripherally-acting antagonists do not exhibit an effect on tolerance or hyperalgesia.

Recent work suggests that there may be differences in the development of tolerance and hyperalgesia between different strains of rats and between male and female rats (difference in GM1 levels). There is also evidence of involvement of adenosine in the mechanism of inhibition of tolerance by low-dose antagonists.

**Opioid induced bowel dysfunction**

Opioid-induced constipation and delayed gastric emptying lead to significant morbidity in both the acute postoperative patient and in the long-term opioid-dependent patient. These drugs reduce gastrointestinal propulsion and inhibit intestinal fluid secretion, even in low doses. Tolerance does not develop to these effects of opioids.

Opioids inhibit GIT function primarily through mu receptors at supraspinal, spinal and peripheral sites, although of the three sites the peripheral action on the intestines is probably the most important. All three opioid receptor types have been isolated in the intestines, with mu receptors predominant in the myenteric plexus. The submucous plexus and circular muscle layer contain delta receptors. The longitudinal muscle layer is devoid of opioid receptors.

Alvimopan and methylnaltrexone are ideally suited to treat opioid-induced bowel dysfunction because of their very low systemic bioavailability when given orally, which preserves the analgesic benefits of opioids and prevents withdrawal reactions.

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The long-term application of opioids leads to increased spinal expression of the pronociceptive neuropeptides – cholecystokinin (CCK), neuropeptide F and nociceptin – and dynorphin A, which results in increased activation of the NMDA receptor system and decreased opioid activation of the RVM “off-cells”, with a resultant decreased descending inhibition. In addition, the increased pronociceptive intracellular mechanism (specifically dynorphin A increases) stimulates the “on-cells” in the RVM to increase descending facilitation of nociceptive input, which leads to hyperalgesia. (See Figure 7.)

According to Crain and Shen, low concentrations (pM) of opioid antagonists completely block the excitatory Gs/GM1/PKA opioid receptor mode and thus prevent tolerance and the development of hyperalgesia, whilst enhancing the antinociceptive effects of opioids. A higher concentration (nM) of antagonists, in contrast, completely blocks the inhibitory G0/Gs/PKC opioid receptor mode and thus may enhance the excitatory mode, apart from decreasing the antinociceptive effects of opioids.

The above phenomenon has been validated in clinical studies. The most compelling evidence is provided by the study by Gan et al. Infusion of an ultra-low dose of naloxone (0.25 μg/kg/hr) in post-hysterectomy patients reduced the cumulative morphine PCA dosage over a period of 24 hours from 60 mg to 40 mg. The difference in dose requirements increased progressively as time progressed, and showed that the placebo group was becoming progressively more tolerant to morphine. In contrast, in the group that received the higher dose of naloxone (1μg/kg/hr), no opioid-sparing effect and slight attenuation of morphine analgesia were observed.

Nalmefene, given at very a low dose of 15 or 25 μg IV pre-surgery for hysterectomy, significantly reduced pain scores (3.5 and 2.3 respectively, compared to 5.5 for placebo) over a 24-hour period. Nalmefene might be a more suitable drug in this setting, as a single injection has an effect over a 24-hour period.

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Figure 7: Bimodal receptor theory of opioid-induced tolerance, hyperalgesia and dependence.

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are increased, and the hypoxic drive and carotid body chemoreception are blunted by relatively low doses of opioids.3 (See Figure 5.)

In order to reverse the respiratory depression induced by opioids, the antagonist administered must reach the CNS, but this has the potential to evoke unwanted sympathetic stimulation and reversal of analgesia. To achieve the balance between reversing respiratory depression while preserving analgesia and avoiding side effects associated with higher doses of antagonists, low-dose infusions of naloxone and nalmefene are employed.

Continuous infusion of 5 µg/kg/hr and 10 µg/kg/hr of naloxone respectively were evaluated after 4 mg of morphine or 200 µg of fentanyl epidurally. Both dosing regimens prevented respiratory depression, but the higher dose infusion was associated with a 25% reduction in analgesia.4,5 A useful regimen is a continuous infusion of 1 µg/kg/hr for the first 24 hours, followed by 0.25 µg/kg/hr for the next 12 hours. This dose of naloxone is effective in reversing depression without affecting analgesia.5

Nalmefene has been used for the same indication, but unfortunately had adverse effects on analgesia in all studies. It has the advantage of a much longer reversal effect on respiratory depression. An oral dose of 50 mg of nalmefene preoperatively reverses depression and analgesia due to fentanyl for up to 48 hours,6 while IV nalmefene can be expected to inhibit depression for at least four hours. It does not have the acute onset of action of naloxone.7 The newer peripherally-acting antagonists, methylaltrexone and alvimopan, do not have any significant effect on the reversal of respiratory depression, as can be expected from their pharmacological profiles. Indeed, a study done on methylaltrexone versus naloxone for the reversal of opioid-induced respiratory depression could not demonstrate a difference between methylaltrexone and placebo.8

Pruritus
This troublesome and common effect of all opioids most often manifests as itching of the nose, but may present as generalised pruritus. It is not related to allergic phenomena or to the release of histamine, as the non-histamine-releasing opioids are as likely to cause pruritus as morphine and pethidine.9,20 Tolerance to the pruritus induced by opioids usually develops within 24 to 48 hours.21 The exact mechanism of opioid-induced pruritus is unknown, but probably involves stimulation of the central mu-receptors, possibly in the medulla oblongata (human analog of the “scratching centre” in animals).11,12 This mechanism is further supported by the fact that pruritus is more common after intrathecal (50% incidence) than epidural administration of opioids (10% incidence). Systemic (IV and oral) administration has the lowest incidence of pruritus.1,13,14

Certainly, centrally-acting antagonists in higher doses are effective in the treatment of opioid-induced pruritus, but again, analgesia is adversely affected. Low-dose naloxone infusion (0.25 µg/kg/hr), as well as methylaltrexone orally, is effective in reducing the incidence of opioid-mediated pruritus, without affecting analgesia.15-16 In addition, in Yuan et al’s study, methylaltrexone significantly reduced other subjective unpleasant effects of opioid administration, like flushing, which may point to a common peripheral mechanism underlying pruritus and other effects like flushing.17

There is no data regarding the efficacy of alvimopan in the treatment of pruritus, but owing to its very low systemic availability after oral administration it is unlikely that it will have a beneficial antagonist effect.

Opioid-induced hyperalgesia and development of opioid tolerance
These two phenomena are generally regarded as being interrelated and share the same pathophysiological mechanisms (see Figure 6).

Acute and chronic tolerance and hyperalgesia have been demonstrated to occur with the administration of fentanyl,18,19 alfentanil,20 remifentanil,21 morphine,22 methadone23 and heroin.24

Figure 6: In hyperalgesia there is a leftward shift of the stimulus-pain curve; when tolerance develops there is a rightward shift of the dose-effect curve

Hyperalgesia and tolerance develop via various pronociceptive systems in the CNS that are stimulated in response to opioid administration. With the stimulation of opioid receptors, protein kinase C (PKC) is induced. This leads to increased phosphorylation of the opioid receptors, with a resultant desensitisation of Gi/Go-coupled receptors, in other words down-regulation of the antinoceptive mechanisms.25

Opioid stimulation, even at low concentrations, activates the alternative Gs-coupled receptor system, with the stimulation of protein kinase A (PKA), which is excitatory in that it increases intracellular cAMP levels. This leads, via presynaptic action, to increased excitatory neurotransmitter release (substance P, glutamate, CGPR, etc.) at DRG level.26 In addition, GM1-ganglioside levels are increased with the stimulation of the AC/cAMP/PKA second messenger system. GM1, in turn, increases the conversion of Gi/Go receptors to Gs receptors (hormonadal receptor theory), with a resultant increased excitatory stimulation of opioids and a positive feedback phosphorylation cycle. This is probably the most important mechanism for the development of tolerance, dependence and hyperalgesia in response to opioids.27 (See Figure 7.)

Opioid-induced PKC induction removes the magnesium blockade of the NMDA receptors, with a resultant increased calcium influx and further induction of PKC (central sensitisation and “wind-up”), which leads to predictable tolerance via further-down regulation of the antinoceptive opioid receptors, and to hyperalgesia.28
which promotes abstinence. Both naltrexone and nalmefene have been used for these indications and have been reasonably successful in preventing relapses.\textsuperscript{64,65}

**Treatment of pruritus caused by cholestatic disease**

It is hypothesised that there is an increased endogenous opioidergic tone in patients with cholestatic disease, and this is supported by three observations: administration of opioid agonists aggravates the pruritis, opioid antagonist administration relieves the pruritis and induces an opioid withdrawal-like syndrome.

A common treatment regimen for these patients is a low-dose naloxone infusion, which is substituted with oral naltrexone or nalmefene at a later stage, in order to prevent the withdrawal syndrome from developing.\textsuperscript{63}

**Reversing the immunosuppression induced by opioids**

Opioids are known for suppressing phagocytosis, natural killer cell function and B and T cell function. This is particularly important with a disease like HIV, especially because opioid-abusing patients are exposed to the virus, and because of the increasing number of patients who are HIV positive presenting for surgery. The mechanism of suppression is not clear and controversy exists regarding the site of immunomodulation by opioids (central or peripheral).\textsuperscript{66} Methylated naltrexone and naltrexone have been shown to block opioid-induced HIV infection in immune cells.\textsuperscript{65}

**Possible role in gram-negative septic shock**

Lipopolysaccharide (LPS) production by gram-negative organisms induces the production of tumour necrosis factor-alpha (TNF-\(\alpha\)) by macrophages via the binding of endogenous opioids to receptors on the macrophage. This opioid-induced action can be blocked by opioid antagonists. A recent study demonstrated improved survival among mice exposed to LPS that received naltrexone, which blocked the production of TNF-\(\alpha\). Interestingly, methyl naltrexone had no effect on mice exposed to gram-positive organisms or their toxins.\textsuperscript{67}

**Opioid antagonists and their role in angiogenesis**

Angiogenesis is determined by endothelial cell proliferation and migration. It has been found that opioids (endogenous and exogenous) and vascular endothelial growth factor promote endothelial cell migration and proliferation. Methyl naltrexone has been shown to inhibit these effects effectively. This may have clinical relevance in conditions where angiogenesis will be undesirable, as with malignancies.\textsuperscript{67}

**Possible beneficial effects in Alzheimer’s disease**

The opioid system is involved in the pathophysiology of Alzheimer’s disease, possibly through adverse effects on cerebral blood flow to certain regions.\textsuperscript{68} It has recently been shown that naltrexone reverses the age-induced cognitive deficits in rats.\textsuperscript{67}

**Role in the treatment of obesity and hyperinsulinism in polycystic ovar- ian syndrome and in postmenopausal women**

Endogenous opioids could play a role in glucose regulation and in the pathogenesis of obesity. Metabolic abnormalities, such as hyperinsulinemia, insulin resistance and obesity are common features of polycystic ovary syndrome (PCOS), and seem to have a pathogenic role in this disorder. A link between opioids and PCOS-related hyperinsulinism is suggested by the finding of altered central opioid tone and elevated beta-endorphins levels, directly correlated with body weight, in these patients. Furthermore, naloxone and naltrexone significantly reduce the insulin response to glucose load only in hyperinsulinemic PCOS patients. This effect is obtained chiefly through an improvement in insulin clearance.

The postmenopausal period is characterised by a high prevalence of hyperinsulinemia and insulin resistance. In particular, an association between hyperinsulinemia and increased opioid activity was found in postmenopausal women showing a central body fat distribution. Both naloxone and naltrexone ameliorate the metabolic imbalance, also when it appears in the climacteric period, and mainly by increasing insulin clearance. In clinical practice, the benefits of naltrexone may in the future represent a useful tool for the treatment of women with hyperinsulinism.\textsuperscript{70}

**Treatment of amenorrhoea**

Endogenous opioids have been shown to be involved as a causal factor of hypothalamic amenorrhoea. Naltrexone has been shown to effectively treat amenorrhoea of hypothalamic origin.\textsuperscript{71}

**Treatment of erectile dysfunction**

The opioid system plays a significant inhibitory role in non-neurogenic, non-vascular erectile dysfunction in males. In two studies, a significant improvement in erectile function was shown on administration of naltrexone.\textsuperscript{72,73}

**Summary**

Historically, the opioid antagonists were seen mainly as research drugs, and indeed they still play a valuable role in elucidating opioid effects and receptors. For years the only real clinical indication for these drugs was reversal of the respiratory depression caused by opioids. However, with the development of newer, clinically-useful antagonists besides naloxone, a wider application has been found for these drugs, especially in other fields of medicine, where antagonism of the endogenous opioid system enables the treatment of a variety of pathologi- cal conditions not associated with the exogenous administration of opioids.

As far as acute and chronic pain management is concerned, the gener- al message elucidated by recent research is that lower doses of antag- nists have greater clinical efficacy in a variety of side effects caused by opioids, with less adverse effects from the antagonists themselves. The development of the peripherally-acting antagonists, alvimopan and methyl naltrexone, makes it possible to treat common side effects associated with opioids without reversing the beneficial effects.

The opioid receptor antagonists are increasingly being shown to be versatile drugs with a variety of clinical applications. SJAA

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