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Opioids In Pain Therapy

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Abstract

I. TRANSMISSION OF PAIN

Pain is transmitted via pathways which ascend from the periphery to the central nervous processing areas in the brain. There are different inhibiting control mechanisms on various levels of these ascending pathways but there is no defined morphologic area for processing the perception of pain [1] .

The original physical or chemical pain trigger is perceived by specialized receptors. Generated action potentials are sent to the dorsal horns by A(- and C-fibers . The frequency of these are proportional to the intensity of the original trigger.

The dorsal horn contains a complex circuitry of neurons that permits not only reception and transmission of nociceptive input but also a high degree of sensory processing . It is subdivided into six laminae where the lamina I is the most dorsal one. Before the nociceptive fibers end in the laminae I and II (substantia gelatinosa) they usually ascend or descend one or two segments. When the nociceptive information has been transmitted through interneurons to the neurons of the lamina V, long axons in the anterolateral tract will transmit it to the higher integrating centers. Usually the 1st neuron of this pathway is located in the spinal ganglia or the ganglia of the cranial nerves. The 2nd neuron is located in the dorsal horn or the rhombencephalon .

The synaptic transmitters of sensoric afferent transmission are neuropeptides like Substance P. After synaptic processing in the dorsal horns the nociceptive information together with the peripherally perceived information about temperature is channeled to the contralateral ascending tracts. In contrast propioceptive information is transmitted via the ipsilateral dorsal ascending tracts to the thalmo-cortical system.

Depending on the intensity of the incoming nociceptive information there is direct activation of specific flexor and extensor motor neurons via interneurons. The direct activation of autonomic sympathetic neurons by the processing of nociceptive information on the segmental spinal level can lead to immediate changes in the perfusion of defined areas. Referred pain (phenomena of Head`s Zones) can be explained by interneuronal processing on a spinal level where there is a summation of different incoming signals at the first neuronal ganglion in the dorsal horn. By the way of convergent processing in neurons which receive visceral and peripheral information, nociceptive signals below threshold for localized pain perception may cause referred pain. This is only one example of the complex processing of nociceptive signals through the neuronal circuitry in the dorsal horn of the spinal cord .

On the spinal level nociceptive sensory input can be modulated not only by the phenomena of central convergence and summation but also through excitatory and inhibitory influences coming from the periphery, local interneurons, the brainstem and the cortex. So afferent signals from C-fibers are usually modulated by inhibitory signals transmitted via A(- and A(-fibers. Descending non-nociceptive pathways also influence the further processing by the localized secretion of enkephalins ($_6$(. This phenomena of segmental inhibition for example is the basis for many alternative treatment regimens as acupuncture or acupressure, since there is a significant modulation of pain perception by activation of related afferent sensory fibers.

I.1. OPIOID RECEPTORS

The different pharmacological action of morphine and the other natural and synthetic opioids led to the assumption that there is a heterogeneous group of opioid receptors which was proven by Martin in 1976. Depending on the classification three to five major receptor subtypes are recognized today, but a further extension and subdivision of

receptor subtypes is ongoing.

Opioid receptors exist throughout the CNS, with particular high concentrations in the periaqueductal gray area and the dorsal horn of the spinal cord. The greatest abundance of opioid receptors is in the substantia gelatinosa , where they are located at the presynaptic terminals of primary afferent sensory neurones and on the dendrites of the postsynaptic inter-neurones that modulate spinothalamic transmission. The presynaptic receptors inhibit the release of substance P, glutamate and other neurotransmitters and postsynaptic receptors decrease the evoked excitatory postsynaptic potential (EPSP).

Euphoria and anxiolytic effects are most probably elicited by receptor stimulation inside the limbic system. The neuroendocrine structures inside the CNS are also rich in opioid receptors, while there is only a restricted receptor density in the cortex and the cerebellar system may lack any opioid receptors. Opioid receptors are also present outside the CNS and this may account for some of the adverse effects such a gastrointestinal effects. Their peripheral existence is for example proven in sites of the musculoskeletal system, in autonomic ganglia, in the submucosal and myenteric plexus of the gastrointestinal tract and in the adrenal medulla [16].

The analgesic effects of opioids are based on the interference at different opioid receptors. At the moment these, through bioassays classified, receptor subtypes are called : ? (delta), µ (mu=µ1, µ2), ? (sigma), ? (epsilon) and ? (kappa) receptors with the ?-receptor not being recognized as a pure opioid receptor.

The binding of pure antagonists at opioid receptors ellict no pharmacological action but at a sufficient concentration will reverse the action of agonists. A pure antagonist is naloxone with a high affinity for µ-receptors and only little affinity for -receptors. Therefore naloxone reverses the respiratory depression and analgesia of opioids and precipitates withdrawal in opioid addicts. It is also effective in alleviating the pruritus and urinary retention of intrathecal and epidural opioids.

All known pure opioid receptor subtypes have now been cloned and their amino acid sequence defined. At the same time a new classification has gained importance. The so called OP-classification contains the receptors of the subtype ((OP1), ((OP2) and ((OP3). The (receptor is no longer classified as an opioid receptor as it does not meet the full criteria because it has a high affinity binding for phencylidine derivatives, the (mediated effects are not fully reversed by naloxone and especially because (receptors are stereo-specific for dextrorotatory isomers, and not for laevorotatory isomers of opioids as the other receptors included in the OP-classification are.

Natural ligands for the opioid receptors include neuropeptides such as enkephalins, endorphins and dynorphins. These endocrine substances not only modulate the pain perception in certain physiologic circumstances (e.g. high impact physical activity, states of emotional arousal as fear and joy, sexual activity etc.) but also regulate autonomic functions as respiratory action, coughing and the regulation of blood pressure. The µ2-receptor plays an important role for the reduction of the respiratory drive [17]. The high density of - and ?-receptors in the substantia gelantinosa reflects their importance for the modulation and depression of pain on the spinal level. The endogenous inhibition of pain at the spinal level is therefore mainly mediated though action of dynorphin and metenkephalin at ?-receptors [5].

II. OPIOID-AGONISTS AND -ANTAGONISTS

Opioids can be divided into pure agonists , antagonists and partial or mixed agonists/antagonists.

The effects of opioids are related to their physical and chemical properties.

The potency, speed of onset, and duration of the opioid analgesics are perhaps the most clinical relevant pharmacodynamic measures.

The specific pharmacological effects of certain opioids can be explained by their characteristic individual action at specific binding site. First of all the affinity to a receptor subtypes explains the individual pharmacological effects of some opioids. Apparently this specific affinity of an opioid to a receptor subtype depends on the size and the steric configuration of its molecular structure. Another important property is the ability to induce a structural change of the receptor complex. This puts the receptor into a functional state which usually means the opening of an ion channel. This property is called Intrinsic Activity.

Antagonists as e.g. naloxone have a high receptor affinity but no or only little intrinsic affinity. Competitive displacement which is the mechanism of their action also plays an important role when pure agonist of different

potency and affinity are used. Agonists/antagonists act antagonistic at a specific concentration or on a specific receptor if a pure agonist has been used beforehand. The duration and power of the antagonistic effect is determined by the pharmacodynamic characteristics (potency and affinity) and the pharmacokinetic determinants (concentration, elimination half-life, volume of distribution etc.) of the opioids used together. Given alone agonists/antagonists usually act as a pure agonist producing analgesia and other opioid effects. This dual effect of the agonists/antagonists can be explained by the interaction with different subgroups of opioid-receptors. Morphine and other opioids with a high potency like fentanyl and alfentanil interact with the (-receptor, which is responsible for the mediation of :

The agonists/antagonists pentazocine and nalbuphine act as antagonists at these (-receptors.

Their analgesic, agonistic effect is mediated through the ????????receptors.

In contrast buprenorphine, the clinically most important partial agonist in the United States and Germany, binds mainly to the (-receptor. Its high affinity to the (-receptor contributes to the relative long duration of action and naloxone's reduced ability to reverse the effects of buprenorphine relative to other opioids. It is called a partial agonist since it demonstrates a ceiling effect where increasing the dose does not increase the respiratory depression. This is thought to be the result of an antagonistic effect at (-2 receptors becoming more apparent at higher concentrations.

In general an opioid reacts with all receptor subtypes in some way. The following basic principle holds for this: Since the binding of an opioid to the different receptor populations is variable, the affinity of an opioid to a subtype of receptor manifest itself in the depending clinical effects.

Figure 1

Function	Receptor				
	μ	κ	σ	δ	ε
Analgesia cerebral	+	-	-	-	+
Spinal	+	+	+	-	-
Vigilance	-	↓	-	↑	-
Respiratory drive	↓	-	-	↑	-
Heart rate	↓			↑	-
Cardiovascular tonus	-	↓	↓	-	-
Endocrine effects	+	-	+	-	-
Diuresis	↓	↑	-	-	-
Constipation	+	-	-	-	-

Figure 2

Euphoria	+	-	-	-	-
Dysphoria	-	+	+	+	-
Pupill size	↓	↓	-	↑	-
Nausea	+	-	-	+	-
Muscular rigidity	↑	↓		↑	-

- = no effect, + = effect, ↑ = increasing, ↓ = decreasing

The analgesic potency of opioids is usually set in relation to the corresponding analgesic potency of morphine. A statement about the absolute analgesia to be reached at most with the specific drug can't be derived from this. For example the analgesic effect of the agonists/antagonists mediated through the ?-receptor can't be compared directly with the μ-receptor mediated strong analgesic effect of the pure agonists and tramadol. In contrast to the beneficial ceiling effect exerted at (-receptors which is characteristic for the partial agonist buprenorphin, with high doses of the agonists/antagonists you will reach an endpoint to the analgesic effect mediated through (-receptors. Only the side effects mediated through (-receptors like nausea and dysphoria will increase further.

II.1. OPIOID ANALGETIC SUBSTANCES

For clinical use analgesic drugs can be divided into three groups :

The concept opioids describes all substances which act on

the OP-receptors and therefore can be antagonized by naloxone . All effects exerted by opioids which can't be antagonized by naloxone to some extent are not mediated through OP-receptors [9].

Natural ligands for the opioid receptors include neuropeptides such as the already mentioned enkephalins, endorphins and dynorphins. They are synthesized through enzymatic splitting of larger precursor peptides. They all have a very short half-life. Logically opioid drugs also interact with their endogenous action and balance.

Today Opiates are called only the natural substances which are directly derived from the opium poppy (papaver somniferum) . The naturally occurring opioids are morphine, its derived analogues (e.g. codeine) and thebaine.

Opioids are powerful, centrally acting analgesic agents which however also have peripheral effects. Besides morphine a number of synthetic and semisynthetic agents belong to the clinically important opioids. The semisynthetic opioids diamorphine, dihydrocodeine and naloxone are all derived from morphine. The synthetic opioids are based on phenylpiperidine (pethidine, fentanyl, sulfentanyl, alfentanil, remifentanil), thebaine (buprenorphine), benzomorphon (pentazocine) and diphenylheptanes (methadone). Specific clinical requirements are met by the different chemical and physical properties of these agents. Particularly important are metabolism, bioavailability, protein binding, lipid solubility and as discussed above the varying affinity to different receptor subtypes [2].

The mechanism of the opioid effect is the inhibition of neuronal action potentials at not only nociceptive, but also specific sensoric, somatomotoric and autonomic neurons [3]. Opioid receptors are all G-protein coupled receptors . The (- and (-receptors open potassium ion channels causing hyper-polarization and decreased neuronal firing. At the nerve terminal the action potential plateau will shorten and so reduce calcium ion influx and neurotransmitter release. At nociceptive neurons this means mainly the inhibition of substance P and glutamine release [25]. This explains the functional antagonism of Calcium demonstrated by a reduced opioid effect at (-receptors. In contrast (-receptor close calcium channels.

As mentioned above, opioids also suppress mono- and polysynaptic reflexes by decreasing the evoked excitatory postsynaptic potential. This is reached by the reduction of the glutamin-induced influx of sodium [27]. Furthermore opioids lead to a reduction of presynaptic excitatory signals of A?- and C-fibers coming from skin and skeletal muscle. In contrast the excitatory input from Aß-fibers is enhanced [10]. These effects are founded on a change in transmembranal sodium and potassium flux [7].

The distinctive pain-relieving character which differentiate the opioids from the antiphlogistic analgetic substances is their apparent psychotropic component. Three main modes of opioid actions are underlining this:

Intrathecal, and to a lesser extent systemic, -adrenergic-agonists are able to augment the spinal and supraspinal analgesia produced by opioids [26]. Additionally (2 agonists exert a central sedative effect and reduce anxiety. These properties have been used in a number of clinical situations – in anaesthetic premedication to promote sedation, during induction and intubation for hemodynamic stability and to reduce anaesthetic requirements (MAC reduction of anaesthetic agents). The (2 agonists have also been shown to reverse platelet aggregation and suppress the normal increase in postoperative fibrinogen levels, and may therefore reduce the incidence of postoperative thrombosis.

The most popular mixed (1+2 agonist clonidine activates mainly presynaptic (2 adrenoceptors and exerts a depressant effect on both spontaneous sympathetic outflow and afferent A-delta and C fibre mediated somatosympathetic reflexes and nociceptive afferents. Epidural clonidine (0,1-1mg) produces dose dependent analgesia for about 5 hours without sensory or motor block, however high doses can cause significant hypotension and sedation. Therefore clonidine is useful as a single agent in only a minority of patients and combinations with local anesthetics and opioids are usually used for analgesia. Combinations of opioids with (2 agonists have been employed in chronic pain situations especially epidurally and intrathecal, e.g. in the management of cancer pain, sympathetic dystrophy and neuropathic pain.

III. EFFECTS AND ADVERSE EFFECTS OF OPIOIDS

RESPIRATORY DEPRESSION

Already in subanalgetic concentrations opioids can cause respiratory depression. This central effect is founded on the decreased sensitivity of the respiratory centers in pons and medulla oblongata to carbon dioxide. Dose-related respiratory depression is mediated mainly via µ2-receptors [10].

Additionally the application of opioids leads to a reduction

of cilary movement and thus to accumulation of secretion in the tracheobronchial tree. Therefore, especially if the lungs are ventilated and the opiate requirements are high, e.g. intraoperative or on the ICU, sufficient humidification of the fresh gas flow and other auxiliary measures to improve the bronchial clearance are beneficial.

After the injection of a sufficient amount of an opioid you can observe the development of apnoea in a usual characteristic course :

Due to the opioid induced respiratory depression a hypercapnic cerebral vasodilatation can lead to a rise in the intracranial pressure. In endangered individuals (e.g. patients with an intracranial hematoma or edema) this rise in ICP can be partially compensated by adequate ventilation.

Naloxone, being a pure opioid antagonist and having a high affinity for (-receptors, reverses the respiratory depression and analgesia of opioids and precipitates withdrawal in opioid addicts. It may also block the actions of endogenous opioids. Incremental titration of the intravenous dose is preferable to minimize the reversal of the analgesic effects of the given opioid agonists. Naloxone acts for about 30 minutes and so further doses or an infusion may be necessary to avoid the return of the respiratory depressant effects of agonists that outlasts the effects of naloxone.

With the application of opioid antagonists you may find unpleasant side effects in about 40% of treated patients. Predominantly nausea, vomiting, vertigo, burning headaches and the feeling of a sore throat after extubation are observed. The sore throat can easily be treated with a topical local anaesthetic and the incidence of the other side effects can be reduced to about 20% by slow and titrated application of the antagonist .

The sudden onset of pain may lead to circulatory and autonomic changes as tachycardia, hypertension, arrhythmias and if the worst comes to the worst hypertensive crisis and arterial or capillary rupture. Many of these reported effects have occurred in postoperative patients with known pre-existing cardiac abnormalities given small doses of naloxone (100-400mcg). It is essential that naloxone is used with great caution in patients with underlying pain, as it is thought that the sudden reversal of analgesia produces an outpouring of catecholamines, which in turn leads to the adverse effects on the cardiovascular system

With intrathecal and epidural administration of opioids the main disadvantage, apart from those always associated with these routes, is the possibility of respiratory depression. This has been reported up to 24 hours after the use of epidural morphine in postoperative patients, when it is called late respiratory depression. On the other hand early respiratory depression that can follow intraspinal opioids is sometimes very sudden, and may not be preceded by a progressive fall in respiratory rate or level of consciousness [24].

Risk factors for respiratory depression include:

ANTI-TUSSIVE EFFECT

In analgetic doses opioids suppress the cough reflex and luckily there is not a direct relation between the amount of respiratory depression and the suppression of the cough reflex, which seems to be founded on the blockade of the very opioid sensitive cough center in the medulla. Codeine, the most popular opioid for this indication, is a natural opioid and one of the principal alkaloids of opium. Codeine has 20% the potency of morphine due to a low affinity for opioid receptors, but about 10% of the given amount is metabolized to morphine, which contributes to its analgesic effect.

SEDATIVE AND HYPNOTIC EFFECTS

These effects are particularly important with the use of mixed agonists/antagonists. Morphine exerts anxiolytic and sedative effects in the therapeutic range. And there is also a drop in cognitive and coordinative performance in this range. Single opioid doses are demonstrated to suppress the REM phases during sleep in former addicts. Very high doses of morphine and methadone ellict convulsion which are controlled with naloxone, while they are not always controlled with conventional antiepileptic drugs, suggesting myoclonic events which are not accompanied by cortical seizure equivalents.

MUSCLE RIGIDITY

Opioid induced muscle rigidity involving thoracic and abdominal muscles can interfere with ventilation. It also often involves the muscles of the extremities and the jaw, and therefore can complicate the handling of the patient in a critical situation (e.g. maintaining a difficult airway). These problems are most commonly associated with induction of anesthesia using high dose opioids. It may involve inhibition of dopamine release and GABA pathways in the striatum and substantia nigra. Especially (-receptors, present in very high concentrations in striatum and overlying cortex, are thought to be involved in a number of processes, including analgesia, mood, reward, modulation of neuronal

excitability, and alterations in neurotransmitter release [8]. At the moment (-receptor agonists with antagonism at (-receptors are investigated regarding their effectivity in the management of neurological symptoms of nigro-striatal origin including parkinsonism. In contrast opioids with agonism at and high affinity for the (-receptors and therefore good analgetic potency often do reduce dopaminergic neurotransmission immediately, while agonists/antagonists and other weak opioids do not cause any muscular rigidity. Antagonists have been shown to reverse the muscle rigidity ellicted by powerful (-receptor agonists. It was observed that fentanyl application at induction of anesthesia in doses between 0.08-0.2 mg causes clinical apparent muscle rigidity in 8% of patients and that this effect was aggravated by simultaneous ventilation with nitrous oxide / oxygen mixture. A symptomatic prophylaxis can be achieved by premedication with benzodiazepines. The application of a small amount of a non-depolarising muscle relaxant before induction with potent opioids is able to mask the peripheral symptoms. If the muscle rigidity is so strong that it cause problems with the handling of the patient the application of naloxone or a fast acting muscle relaxant can help (e.g. to achieve airway control again).

CARDIOVASCULAR EFFECTS

In the usual dosage opioids produce little effect on the cardiovascular system. In the supine position blood pressure and cardiac output remain constant. With the exception of pentazocine and meperidene, which is called pethedine in Europe, a dose dependent bradycardia occurs with all opioids to a different degree. The bradycardia, especially occurring with the first time application of potent opioids (e.g. fentanyl), is related to the stimulation of vagus nuclei in the medulla. Hypotension, which occurs mainly if opioids are combined with benzodiazepines, is founded on a peripheral vasodilatation which is the result of a decreased sympathetic drive.

Meperidine, a synthetic opioid which was developed in Germany during World War II because of the termination of opium poppy supply, has anticholinergic effects because of its structural similarity to atropine and therefore may cause tachycardia in high doses. With the application of pentazocine heart rate and also blood pressure may rise because of a rise in plasma catecholamine concentration or through the activation of (-receptors producing tachycardia not only by itself, but also hallucinations and dysphoria which can boost the cardiovascular symptoms. Therefore meperidine and pentazocine should not be used in patients with cardiovascular risk factors, because they may induce an increase in myocardial oxygen demand [$_4$].

Nalbuphine, a (-receptor agonist which is used for premedication and for the treatment of moderate to severe pain in cardiovascular instable patients, has no (-receptor mediated effects and is an antagonist at (-receptors. It has therefore little effect on the heart rate, mean arterial pressure, systemic or pulmonary vascular resistance in the opioid naive patient. Unfortunately it is also ineffective in obtunding the cardiovascular response to laryngoscopy and intubation, but it can be used effectively in the management of postoperative shivering, especially as an alternative to meperidine in the cardiovascular risk patient.

Particular caution should be applied in the situation of intravascular volume deficit. Because of venous pooling with peripheral vasodilatation and the reduced sympathetic tone with inhibition of the baroceptor reflex, a sudden cardiovascular collapse can develop after the application of opioids in this setting.

Cardiovascular effects of opioids are of advantage, if:

Because these effects usually improve the balance between myocardial oxygen consumption and coronary oxygen delivery, some opioids (esp. morphine and were allowed diamorphine) are used in the management of myocardial infarction and pulmonary edema.

Figure 3

Opioid	Blood pressure	heart rate	PAD
Morphine	↓	↓ / -	↓ / 0
Buprenorphine	↓	↓ / -	-
Pentazocine	(↑)	(↑)	↑
Nalbuphine	-	↓	-
Meperidine	(↓)	↓ / - / ↑	-
Piritramid	(↓)	-	-
Fentanyl	↓	↓	-

CARDIOVASCULAR EFFECTS OF OPIOIDS GASTROINTESTINAL EFFECTS

Most opioids cause :

Morphine inhibits gastric secretion and reduces the activity of most of the smooth muscle of the stomach except the pyloric muscle, therefore delaying gastric emptying. In the colon a spastic contraction of the circular muscles and the

sphincter muscles is observed, leading again to a delayed passage and a thickening of the faeces resulting in constipation. Morphin-induced spasms of the sphincter of Oddi may lead to bilious colic which sometimes can be managed by anticholinergic drugs or nitrates. Antagonists like naloxone usually reverse morphin-3 and lipase may be caused by bile reflux into the pancreatic duct due to increased billiary tract pressure. Meperidine may then be the opioid of choice because its atropine like effect counteracts the opioid effect on smooth muscle, but there aren't any good clinical studies to support this.

Most opioids also cause increased tone or spasms of the smooth muscles in ureter, bladder and uterus. The increased tone of the detrusor muscle and the bladder sphincter may lead to the sensation of urinary urgency without the ability to pass water. These side effects especially occur if the patient is suffering from prostatic hyperplasia. Again naloxone is able to reverse the spasms and reduce the tonus of the muscles.

Opioid induced histamine liberation and pruritus

Allergic reactions to opioids are rare. In the first line meperidine and morphine are known as histamine liberators. A lesser histamine liberating potentialia ascribed to fentanyl, alfentanil and sulfentanil. Whether a prophylaxis with antihistamines should be established before opioid classification depends on the individual risk for each patient. Moderate to high risks patients according to Lorenz [$_{12}$] are:

Opioid induced histamine release from mast cells resulting in urticaria, pruritus , bronchospasm and hypotension doesn't usually demonstrate a typical anaphylactic reaction cascade but nevertheless can in severe cases ellict the clinical picture of an anaphylactic shock. This response is therefore an anaphylactoid reaction, which can be induced by a number of drugs which act on mast cells directly and not via IgE.

Opioid induced pruritus can either be caused peripherally by histamine liberation or centrally. the mechanism of centrally ellicted pruritus is poorly understood. It has previously been linked with the pain pathway and it has been suggested that pain and pruritus are transmitted by the same population of sensory neurons [$_{13}$]. The opioid induced central pruritus can be reversed by naloxone and is probably caused by a change in neurotransmitter release in spinal and supraspinal centers [$_{20}$].

TOLERANCE AND DEPENDENCE AFTER REPEATED OPIOID ADMINISTRATION

Opioid addiction has got physiological (sudden absence of the drug produces a withdrawal syndrome) and psychological (the urge to use opioids to achieve euphoria, sedation etc.) components. Dependence is the term referring to physiological response at withdrawal. The property of opioids to produce dependence and addiction is directly proportional to the analgetic potency and depends especially on the receptor kinetics of the individual opioid. The low abuse potential of buprenorphine for example may be founded on the high affinity but low intrinsic activity at (-receptors, therefore causing less euphoria.

In medical practice the indicated treatment with morphine resulted in less than 1% of iatrogenic addiction [$_{14}$], demonstrating that a direct comparison of medical and "recreational" opioid use can't be made. Addiction is so rare when opioids are taken for medical reasons that it should not influence prescribing in all but the most high-risk patients [24].

Decisive for the development of iatrogenic opioid dependence is the route of administration.

PRN opioid medication leads to a higher incidence of opioid dependence than scheduled opioid medication (e.g. with slow release preparations).

A decreased responsiveness to the pharmacological effects of a drug resulting from previous exposure is called tolerance. Except constipation and miosis, most opioid effects exhibit a more or less rapid tolerance development. Surprisingly the tolerance shows selectivity, so that tolerance to one opioid is not necessarily accompanied by tolerance to others, though mechanisms such as down regulation or decoupling of receptors have been suggested as explanations for the phenomenon tolerance. In general it can be stated that adaptive changes of the effector system to the opioid inhibitory effect, in manner of a negative feedback response, are the underlying mechanisms for the development of tolerance (e.g. for the respiratory-depressive or euphoria producing effects).

With dependence and tolerance, withdrawal or antagonism of the drug may lead to the withdrawal syndrome whose symptoms include:

The symptoms are maximal at 2 days and usually last up to 10 days, but some residual symptoms may last for several

weeks. Administration of the previously used opioid usually abolishes the syndrome.

Current addicts need higher opioid doses in pain management. Partial agonists and antagonists should be avoided as they can cause withdrawal symptoms. Former addicts should not be given opioids if at all possible to protect them from relapse into addiction.

NAUSEA AND VOMITING

All over 40% of patients complain about nausea after opioid administration and 15% of patients do vomit because of opioid administration [1]. The emetic effect is based on an increased sensitivity of the vestibular system due to direct stimulation of the trigger zone of chemoreceptors in the area postrema of the medulla. The opioid emesis exhibits tolerance development since repeated doses of the same opioid cause less nausea and vomiting than the first dose. Antidopaminergic, antihistaminergic and antiserotinergic drug regimens for the prevention of opioid nausea are numerous and the efficacy of each regimen depends very much on the individual situation. Other strategies to prevent nausea and vomiting include dietary and psychological measures. Important for the prevention in the postoperative period are the careful handling of the patient who is recovering from anesthesia (i.e. a trolley rally from the theatre to the recovery room may even make the most unsusceptible patient sick). Last but not least regular and adequate gastric emptying and intestinal peristalsis should be achieved, if required with drug intervention as e.g. metoclopramide and laxatives.

ENDOCRINE EFFECTS

Opioid induced release of antiduretic hormone, possibly mediated by dopamine receptors in the hypothalamus, may lead to retention of fluid. In contrast thyrotropine and gonadotropine release from the pituitary gland is inhibited. Stress induced release of ACTH is also inhibited and this has an important effect in the acute pain situation and the postoperative period. Basal metabolic rate and temperature also decrease if patients are receiving opioids over a prolonged time though animal data indicate that acute administration of opioids can increase temperature [19].

Morphine induced pain, neuroexcitatory effects of M3G and the serotonin syndrome

In some clinical situations abnormal metabolism of morphine may occur, so that relatively greater quantities of the antagonistic metabolite morphine-3-glucuronide are produced and may reverse the analgesic effect of morphine and morphine-6-glucuronide. Most cases of paradoxical pain have been reported in patients with cancer or receiving multiple drugs, when morphine was used in high doses intravenously or intrathecally.

Allodynia, myoclonus and seizures are neuroexcitatory side effects which have been observed in individual patients receiving large doses of systemic morphine or its structural analogue hydromorphone. These symptoms haven't been observed frequently with the intrathecal administration of morphine, probably because of pharmacodynamic and pharmacokinetic reasons. In several studies it was demonstrated that prolonged oral or subcutaneous administration of morphine to patients with cancer pain increased the cerebrospinal fluid concentration of M3G. The intrathecal concentration was exceeding those of morphine and M6G [22], which next to the factor totally administered and metabolized morphine dose, might be an additional explanation that intrathecal morphine is unlikely to cause neuroexcitatory effects itself and instead may exert protective sedation as expected . Conversion to a structural dissimilar opioid, e.g. transdermal fentanyl or oral methadone as alternatives in chronic pain control, will allow the clearance of the active metabolites from the patients CNS while maintaining analgesia.

New research suggests that opioids may also influence the locomotor activity in some cerebral nuclei via sigma receptors, which are not regarded as opioid receptors. It has been demonstrated that sigma receptor antagonists are able to reverse toxic effects of cocaine in mice, including convulsions, while sigma receptor agonists facilitate them [21].

The serotonin syndrome has been reported with the use of tramadol, either on its own in susceptible patients, or when monoamine oxidase inhibitors or even the relatively safe serotonin reuptake inhibitors have been given concomitantly. Symptoms as facial flushing, tremor, agitation, tachycardia, diaphoresis, atypical chest pain, confusion and psychosis can be observed [15]. The syndrome is caused by the development of a hyperserotoninergic state after initiation or dosage increments of one or more of the offending agents. There is a wide interindividual range of susceptibility to the development of the serotonin syndrome.

It has been demonstrated in a recent multicenter evaluation of tramadol exposure that much of the toxicity in tramadol overdose appeared to be attributable to the monoamine

uptake inhibition rather than its opioid effects [23]. Symptoms like agitation, tachycardia, hypertension and confusion have been pointed out as relative warning signs for the development of a full blown toxic serotonin syndrome. A dose of 500 mg was the lowest dose associated with seizure, tachycardia, hypertension or agitation, while 800 mg was the lowest dose associated with coma and respiratory depression. Naloxone reversed sedation and apnea in only 50% of patients. We think that mechanical ventilation may be more beneficial than reversal of the opioid effect in this setting since the reversal could disinhibit the serotoninergic effect even more.

IV. OPIOIDS IN PRE-EXISTING DISEASE AND SPECIFIC PATIENT CIRCUMSTANCES

NEUROLOGICAL DISEASE

High dose opioids can occasionally cause rigidity, fits and myoclonic movements (see above). Pethidine (meperidine) should be avoided in patients suffering with epilepsy since its metabolite norpethidine is known to trigger epileptic seizures. Current research investigates the implication of opioid receptors in neurological diseases, and the potential of specific agonists and antagonists for the management of neurological symptoms (as e.g. rigidity in basal ganglion disorders).

RENAL DISEASE

Renal impairment reduces excretion of most opioids leading to increased analgesia, sedation and respiratory depression. Again pethidine (meperidine) should be avoided because of the increased accumulation risk of its metabolite norpethidine, whose longer half-life (4-8 fold that of pethidine in healthy patients) is even more prolonged with impaired renal excretory function.

Morphine is primarily metabolized in the liver and only 10% of the intravenous dose is excreted unchanged in the urine. However 90% of the metabolites are excreted via the urine, and M6G may cause respiratory depression and unwanted sedation, while in contrast M3G may cause neuroexcitatory symptoms and possibly paradoxical pain, depending on the relative concentration of each metabolite at different CNS sites.

Fentanyl, alfentanil and sulfentanil are mainly metabolized in the liver and bilary excretion can usually compensate the lack of renal excretion, while the metabolites themselves don’t seem to cause any clinical problems. Therefore transdermal fentanyl is regarded as relatively safe in the management of chronic pain in patients with renal impairment, as is buphrenorphine whose metabolites are relatively inactive too. Nevertheless, it is important to initiate and maintain the transdermal fentanyl regimen with extreme caution, since patients with renal impairment may get disturbed ventilation and oxygenation for various reasons. A relatively lower strength of the fentanyl patch and sublingual buprenorphine for breakthrough pain may be a rational approach.

RESPIRATORY DISEASE

Logically opioids should be used with caution in severe respiratory disease, especially in patients with respiratory failure type II who are in danger of retaining even more carbon dioxide due to decreased respiratory drive. Nevertheless nebulized morphine or other opioids have been reported to have beneficial effects in the distressing dyspnea in terminal cancer and some respiratory disorders. The inspired nebulized opioids act on peripheral opioid receptors which are located throughout the respiratory tract. In addition to (-, (- and (- receptors `non-conventional` opioid binding sites have been suggested, which might explain the otherwise counterintuitive apparent utility of morphine treatment of dyspnea.

In patients with severe asthma intravenous bolus doses of histamine liberating opioids like morphine are obsolete.

HEPATIC DISEASE

Morphine is metabolized in the liver, therefore in liver impairment lower doses should be used and again a cautious titration against analgesic and sedating effect is indicated. Similar caution is required with all other opioids except remifentanil. Again pethidine should be avoided in any case since accumulation is more likely and patients with liver disease, especially with alcoholic etiology, are more likely to suffer from neuroexcitatory symptoms caused by norpethidine.

Morphine should be used with caution in the presence of advanced hepatic failure as the drug may precipitate encephalopathy.

CARDIAC DISEASE

As reported in the most recent UK confidential inquiry into anaesthetic deaths about 30% of mortality was primarily due to cardiac causes., mainly as a consequence of severe perioperative myocardial ischemia or arrhythmia. High levels of circulating catecholamines associated with perioperative pain and anxiety increase cardiac workload

and may exacerbate the arrhythmogenic potential of some anaesthetic agents and operative procedures. With the above mentioned exceptions opioids therefore play an important beneficial role in the prophylaxis of cardiac problems and some anesthetists advocate an opioid induction for the anesthesia of cardiac high risk patients. But due to the same UK inquiry in which all perioperative deaths in Great Britain are monitored in regular cycles, respiratory problems in the perioperative period are with about 50% the most frequent causes for anaesthetic deaths , and therefore patients which have received protective high dose opioid medication require extensive postoperative observation. Some hospitals might not be able to provide the required monitoring and observation in the recovery room and on the wards.

OPIOIDS AND THE ELDERLY

Old people are sensitive to opioids since clearance and respiratory function are altered. Coexisting neurological disease may make it more difficult to assess sedation and pain control. Pharmacotherapy for coexisting disease may prove difficult because of interactions. Combinations with NSAIDS, though advocated as effective against opioid induced pruritus and reducing the opioid requirements, have to be assessed regarding their capability to reduce renal perfusion and put the patient at an increased risk of bleeding. These risks are higher in the Elderly since renal clearance and perfusion is already diminished, gastrointestinal bleeding may be masked and drug compliance may not be reliable.

OPIOIDS IN CHILDREN AND NEONATES

In neonates the opioid clearance is reduced. There is greater respiratory depression for an equivalent adult dose, as morphine crosses the immature blood-brain barrier more easily. Morphine clearance reaches adult levels in the baby child born at term biz the age of 1 month.

With 6 months of age children are no more susceptible to respiratory depression than adults but in children the titration against the pain is even more important. Not only that the psychological coping with pain differs from that of adults because a young child does not understand the temporary limitation of the symptom pain but also because the induced stress response can be more forceful than in adults. These reasons and the underestimated risk of overdosing, because in the most hospital the preparations are orientated at the normal adult dose, underlines that nurses and physicians who are looking after children with opioid requiring pain need special training and supervision by dedicated pediatricians or anesthetists.

V. ROUTES OF OPIOID ADMINISTRATION

ORAL APPLICATION

Oral opioid drugs undergo first pass metabolism. Perioperative gastric stasis and impairment of enteral absorption makes this route unsuitable. Opioids themselves inhibit gastric emptying and oral opioids being absorbed as weak bases in the small intestine therefore slow their own systemic absorption. First-pass metabolism plays an important role for the bioavailability of orally administered opioids. Naloxone for example is almost entirely inactivated through hepatic first-pass metabolism and therefore exhibits no effects after oral administration. With morphine the first-pass metabolism varies greatly between individuals, and this partly accounts for the huge range of morphine doses required by different patients. Fortunately morphine is well absorbed from the gastrointestinal tract, so that instead of a high presystemic metabolism in the liver a interindividual bioavailabilty range from 15-64% has been reported [$_{24}$]. Specific pharmaceutical preparations as (e.g. slow-release or liposomal delivery) may further influence bioavailabilty and systemic efficacy for pain control.

INTRAMUSCULAR APPLICATION

Compared with oral preparations the onset of action is less delayed, but absorption of the drug may also be variable, resulting in variable blood levels and therefore not anticipated risk of respiratory depression or on the other side breakthrough pain. The dose of the intramuscular injected dose therefore should not exceed the calculated intravenous dose. Since the intramuscular application of opioids is mainly performed by nurses and midwives because of traditional or legal reasons (e.g. in the UK a intramuscular pethidine dose of 25-100 mg given by the surgical nurse or midwife is commonly the first line of medical pain management fo surgical and obstetric patients) a critical review seems to be indicated in some countries.

Relative short peak effect, rapid tail-off and the patients discomfort with repeated injections are other drawbacks which makes this route of application obsolete in modern pain management.

SUBCUTANEOUS APPLICATION

Systemic uptake is better than from muscle. With modern preparations plasma levels over time are more predictable and patients discomfort at injection is only mild. Regarding nurse administered opioids this route therefore seems a good

alternative to the intramuscular route. Diamorphine and buprenorphine are the best opioids to use by this route as they can be administered in a small volume.

INTRAVENOUS APPLICATION

Compared to the so far mentioned routes the effect of the intravenous opioid can be better predicted over time. Titration to the patients needs can be achieved very quickly. Nevertheless caution has to be exercised since sudden histamine liberation, true anaphylactic reaction and acute respiratory depression may develop. In some countries only physicians are therefore allowed to administer intravenous opioids.

Bolus injection, continuous infusion and patient-controlled analgesia are the three ways of intravenous opioid application. Especially bolus injection carries the above mentioned risks. With continuous infusion you may rapidly reach a constant plasma concentration of the drug if all variables are taken into account, but the widely variable opioid effect on different individuals makes it both more dangerous and less effective for pain control, especially for episodic pain. Patient-controlled analgesia devices are safer and pain control and therefore patients satisfaction is improved. This is not only because the patients will receive the momentarily required amount of opioid but also the patients prefer to be in charge of their own pain control. The main drawbacks of this method are the cost of the pump and that PCA is not suitable for small children and confused patients.

TRANSDERMAL APPLICATION

Another method of continuous opioid delivery is the application of a fentanyl patch. Transdermal fentanyl is available in four sizes, i.e. 25-50-75-100 mcg/h, containing 2.5-5-7.5-10 mg of fentanyl

respectively.

The advantages of transdermal fentanyl are mainly twofold:

The sustained release provides constant plasma concentration of the drug, unlike intermittent intravenous, intramuscular or oral dosage.

Additionally the ease of administration is very useful in the outpatient control of patient with opioid requiring chronic pain situations.

The disadvantages of transdermal fentanyl are :

Especially during the conversion from oral morphine to transdermal fentanyl respiratory depression is more likely. Mean pain intensity usually decreases after the conversion from oral morphine to transdermal fentanyl with a conversion ratio of 100:1 which might be a factor for the higher incidence of respiratory depression; although breakthrough pain, requiring immediate-release morphine as a rescue medication was higher with transdermal fentanyl than with equipotent slow release oral morphine preparations. Constipation, effecting the chronic pain patients wellbeing and sometimes severe enough to cause significant abdominal pain, seems to be an important adverse effect in both regimen groups. The number of patients complaining about problematic bowel movements was only reduced to a small extent after conversion to transdermal fentanyl, though in recent studies, the number of patients requiring laxatives to overcome constipation was reduced significantly by switch to a fentanyl regimen [$_{18}$].

Transdermal fentanyl must not be used in acute pain. The decline in serum drug levels after removal of the patch is considerably slower than after intravenous use and if the pain decreases acutely respiratory depression may develop.

Reduction or termination of transdermal fentanyl treatment (esp. high strength i.e. 75-100 mcg/h) should only be stepwise since withdrawal symptoms in the long term management with fentanyl patches are more likely than in the acute pain setting. Sometimes the adhesive substance of the patch can cause an allergic skin reaction. This may also develop during therapy and a conversion to another form of application is then indicated.

A transdermal delivery system for buprenorphine will soon be available in some countries and its main indication will be chronic cancer pain , stable opioid sensitive pain due to skeletal changes (including osteogenic rheumatic pain) and chronic visceral pain. The advantages of the buprenorphine transdermal delivery system are a very low incidence of constipation (5.3%), the lack of respiratory depression in comparison to transdermal fentanyl and very little requirement of medication for breakthrough pain. The drug of choice for breakthrough pain during treatment with buprenorphine patches is logically buprenorphine in the sublingual preparation.

SUBLINGUAL AND BUCCAL APPLICATION

Another new approach to administering fentanyl is via the transmucosal route. This route has the advantage over the oral route of avoiding the first pass hepatic metabolism. In

some countries the preparation is available as 200-400mcg lozengers and the recommended dose is 5-15 mcg/kg. Good analgesia occurs within 20-30 minutes and lasts 4-6 hours. Again for the above mentioned reasons respiratory depression is much less common than with the transdermal route. Buccal morphine has also been tried, but because it is so poorly lipid soluble, transmucosal absorption is not very effective.

NEUROAXIAL APPLICATION OF OPIOIDS

The advantages of an intrathecal over systemic application of opioids are the good analgesic effect and the long duration of analgesia achieved with a relatively small dose. If used cautiously, mainly because of better pain control with reduced systemic adverse effects, a better respiratory function and early mobilization of the patient are beneficial consequences. Caution must be exercised, as varying opioids or drug combinations are not licensed for intrathecal or epidural use in many countries.

Opioid drugs attach themselves to specific receptors in the spinal cord after intrathecal or epidural administration. Since the dura mater is not a lipid membrane, the rate of diffusion from epidural into intrathecal space is inversely proportional to molecular size, and high lipophilicity actually increases the uptake into epidural fat and blood vessels. Therefore fentanyl for example, which is about 500 times more lipid-soluble than morphine, is taken up rapidly into the systemic circulation. Fortunately, due to its lower molecular size, fentanyl will also pass the dura mater more rapidly than morphine.

Once the drug has reached the intrathecal space (whether through diffusion or direct application), onset and duration of the effects depend on the lipophilicity of the opioid. Morphine has a slow onset of action since it is a poorly lipid-soluble opioid, but also the cerebrospinal fluid concentration stays therefore higher for a longer time giving prolonged wide segmental analgesia. The risk of delayed respiratory depression is therefore also increased since morphine may reach the respiratory center in the medulla via the intrathecal route. In contrast, with the lipophilic fentanyl onset is rapid and duration of effectiveness is usually limited to 2 hours.

Epidural and intrathecal opioids cause preferably central side effects as nausea, vomiting, sedation, respiratory depression and centrally mediated pruritus since intrathecal rostral spread of the opioids may occur. Logically the side effects mediated by the lower and more accessible supraspinal centers (i.e. medullary centers as e.g. area postrema) are prominent. The pruritus commonly occurs in the head and neck region, or if the opioid is used as an adjunct to a neuroaxial local anaesthetic block sometimes just above the limit of the sensory block caused by the local anaesthetic agent.

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