Co-analgesics and adjuvant medication in opioid treated cancer pain

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Introduction

Although opioids continue to be the mainstay approach for the management of moderate or severe pain in patients with serious illness, the outcome of opioid therapy is not uniformly favourable and clinicians must know a range of alternative analgesic strategies. The appropriate use of co-analgesics is one of the strategies to the neuropathic, skeletal related and visceral component of the pain. *Co-analgesics* are administered to those patients whose pain has not completely responded to optimal analgesic therapy according to the WHO 3-step ladder. The existence of large inter-individual and intra-individual variability in the response to co-analgesics suggests that sequential therapeutic trials are often advocated to identify the most effective drug for each individual patient. The useful analgesic dose of opioids is, due to the absence of a ceiling effect, mainly limited by the appearance of adverse effects. The effective treatment of the opioid-induced adverse effects with *adjuvant medication*, is secondly of paramount importance in the successful opioid treatment of pain.

Co-analgesics

Co-analgesics do not belong to the class of analgesics, but have some intrinsic analgesic effect in well specified circumstances. They can be used alone or in combination with analgesics, in the latter case they can have some analgesic sparing effect, sometimes resulting in fewer adverse effects from the analgesics. Co-analgesics mostly do not provide complete analgesia, but just realise a recognisable decrease in the pain score; patients should be informed about this to make their compliance more likely.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) are classified in the WHO step 1 class of analgesics, but are frequently not used in daily clinical practice. Therefore is it useful to remember this important class of drugs with analgesic, anti-inflammatory and antipyretic effects and to use them properly in cancer pain. These drugs have a potent inhibitory effect on prostaglandin synthesis and this makes them a useful adjunct in the management of pain involving inflammatory processes [1]. They have a central nervous system action site in the brain or the spinal cord [2].

As in all chronic pain situations, these drugs should also be administered regularly around the clock and not on demand. The dose ranges are limited and exceeding the recommended upper dose will not enhance analgesia. NSAIDs have a ceiling effect to their analgesic efficacy; their use as sole agents in the management of pain should therefore be restricted to mild or moderate pain because severe pain is often above their ceiling dose for analgesic efficacy. For this reason NSAIDs are mainly part of a combined modality approach to management of severe pain in combination with analgesics from the WHO step 3 analgesic ladder. They are very useful in the treatment of painful bone metastases and inflammatory processes. Some neuropathic pain can also be treated with NSAIDs by their action at the NMDA receptor.

Many NSAIDs are available and they differ in dosing, interval to be given and cost, and to some extent in their analgesic ceiling and safety. The ideal NSAID does not exist and there is no significant difference in efficacy between NSAIDs. Individual preferences, activity levels and short- or long-acting drugs are important determinants to choose between the different available preparations.

The gastrointestinal side effects of these drugs are well known but there is also some influence on haemostasis (loss of platelet aggregation) and renal impairment in patients with reduced effective circulating volume. Hypersensitivity or allergic reactions occur rarely but may be severe and life threatening.

The selective COX-2 inhibitors have shown to have fewer gastrointestinal and renal side effects, but in long-term use they are associated with a slight increase in cardiovascular morbidity. For this reason the use

of these COX-2 inhibitors since 2004 is questioned more and more. This relative contraindication in good prognostic patients is less valid in the advanced cancer and palliative patients with mostly short survival (one year or less). It is not proven in clinical trials that these COX-2 inhibitors, compared to the other non-selective COX inhibitors, are more effective in the treatment of cancer pain and the degree to which the use of these drugs improves outcomes remains speculative in the medically ill patients.

Ibuprofen, up to a dose of 1600 mg/d, has been associated with the lowest risk of gastro-intestinal haemorrhage; aspirin, indomethacin, naproxen and sundilac were associated with intermediate risk, and ketoprofen and piroxicam had the highest risk [3]. Regular monitoring for common adverse effects is usually advised during long-term NSAID therapy: control of faecal blood loss, control of renal and hepatic function.

Corticosteroids

These are important in symptom control in malignant diseases with a variety of indications. Headache secondary to intracranial hypertension, caused by brain tumours and brain metastases, is more effectively treated with dexamethasone (4–24 mg/day p.o. or i.v.) or methylprednisolone (16–28 mg/day p.o., i.v. or i.m.) than with analgesics. Liver capsule distension pain by a primary liver tumour or metastatic hepatomegalia is also a classical indication for corticosteroids. They are also successfully used when there is pain caused by extensive tissue destruction and invasion, especially when pain is the result of nerve compression or destruction. Corticosteroids are sometimes of benefit in painful gastrointestinal subobstruction, in pruritus caused by hyperbilirubinemia and in excessive sweating in some malignant conditions. Other forms of symptom control by corticosteroids are: a continuous low dose of steroids (dexamethasone 4 mg/day or methylprednisolone 16–32 mg/day), which can improve dyspnoea, loss of appetite and the general feeling of wellbeing. When single agent anti-emetics are not enough, the addition of corticosteroids in moderate doses is frequently highly effective at stopping nausea and vomiting.

The administration of high doses of corticosteroids (>6 mg dexamethasone or >32 mg methylprednisolone) may be divided over the day, but the last dose should not be given after 6 p.m. as this may result in insomnia. Moon face, buffalo hump (Cushing) and fluid retention are classical adverse effects of long-term use of doses of $\geqslant$8 mg/day dexamethasone, 24 mg/day methylprednisolone or more. Candida infections and gastro-intestinal side effects are common in long time treatments. Although they can cause all these side effects, corticosteroids, in most situations, do not have a valid substitute. The combination of corticosteroids and NSAIDs should be avoided in cancer patients because of the high incidence of gastric erosion and sometimes severe gastric bleeding.

Neuropathic pain

The most common target of co-analgesics in cancer patients is neuropathic pain that is not responding to opioids. In this case, different drug classes can be used.

Antidepressants

Antidepressants show some analgesic efficacy in chronic neuropathic pain. The doses required to produce analgesia are generally lower and the analgesic effect quicker (typical onset within 1 week, but sometimes already within 1 day), compared to the antidepressant effects. The positive mood effect of these agents is not required for analgesic efficacy.

There is an extensive body of evidence-based data supporting the analgesic efficacy of tricyclic antidepressants [4], while there are few controlled trials of the selective serotonine reuptake inhibitors (SSRIs) and there are very few comparative trials of antidepressants where amitryptiline tends to be the standard by which other antidepressants are compared. This class of antidepressants, unlike benzodiazepines, are often more suitable as a sedative for the restless, depressed, insomniac patient with malignant disease. The tricyclic antidepressants have a central analgesic effect in neurogenic pain, especially when the pain is of a burning dysaesthetic nature.

The new selective serotonine re-uptake inhibitors (SSRIs) have fewer side effects than the tricyclic antidepressants but also have a mixed analgesic effect. There is some evidence to support the analgesic effects of some of these drugs, such as paroxetine hydrochloride [5], maprotiline hydrochloride [6] and bupropion hydrochloride [7]. The SSRIs are generally used as second-line agents because the data supporting their efficacy in neuropathic pain are not as strong as those regarding the tricyclic antidepressants.

The antidepressants can relieve both continuous and paroxysmal neuropathic pains, but extensive clinical experience supports greater utility in continuous pain. Therefore, it is common in clinical practice to consider the antidepressants for continuous pain and to use the anticonvulsants for paroxysmal neuropathic pain.

The antidepressants are initiated at low doses (10–25 mg at night) and the dose is increased every few days by adding the starting dose each time. The analgesic effects in general occur within 4 to 7 days (rarely already after the first day) after achieving an effective daily dose, which is around 50–150 mg/d for amitriptiline hydrochloride. Doses should be increased if pain relief is not reached while adverse effects are still tolerable, or if pain is complicated by depression. If there is no pain relief within a week after starting, the drug has to be stopped and replaced by other drugs.

Both the antidepressive and analgesic effect can vary individually. This means that failure of one co-analgesic does not automatically predict failure of another drug, even if the second one is in the same class. Patients that fail to respond to one drug should be considered for another antidepressant trial.

Monitoring the cardiac rhythm electrocardiographically is advocated at higher doses because the atrioventricular conduction maybe affected. Tricyclic antidepressants have to be stopped if side effects occur, such as somnolence and dry mouth. However, these drugs should never be stopped abruptly after a treatment of more than 10 days, but should be gradually tapered in dose to reduce any withdrawal phenomenon such as insomnia or mood changes.

Tricyclic antidepressants are probably more effective at relieving neuropathic pain than newer antidepressants, but have more adverse effects [8]. The adverse effects of the tricyclic antidepressants, like sedation, anticholinergic effects and postural hypotension, are usually mild when used in low dose for neuropathic pain, but nevertheless may be troublesome in individual palliative patients.

Anticonvulsants

Anticonvulsants can be started as primary treatment and given in combination with other analgesics. The paroxysmal or lancinating neuropathic pain (described as ' shooting' and the patient may liken it to electric shocks), is a good indication for treatment with anticonvulsants. The pain relieving potency of the old anticonvulsants diphantoïne, carbamazepine or valproic acid is well known. In the last two decades gabapentin is the upcoming first-line treatment for paroxysmal or lancinating neuropathic pain, although conflicting data have been published. In one study, gabapentin was effective in 20/22 patients with neuropathic pain, incompletely controlled with opioids and including burning and lancinating pain, and allodynia [9], while in another study less than half of the patients responded to gabapentin [10]. Finally, gabapentin may not be as effective as carbamazepine but causes less troublesome adverse effects [11].

The dose and the initial titration are the same as for anticonvulsant therapy, although there are no data relating to blood levels and analgesic activity. The classic drug for use in lancinating pain is carbamazepine starting at 100 mg, 8-hourly and increased to 200 mg, 8-hourly; if necessary it can be progressively increased further to a maximum of 600 mg, 8-hourly. The dose is increased stepwise until sufficient analgesic response or toxicity occurs. Serum levels can be checked and the drug should be stopped if there is no analgesic response when the levels are in the therapeutic range for anticonvulsant therapy. There is considerable lack of cross-resistance between the drugs, and treatment with a second anticonvulsant is sometimes successful. The anticonvulsants can be used in conjunction with the antidepressants and may be prescribed concurrently with opioid analgesics if necessary.

Topical therapies

Topical therapies are evolving in clinical trials and anecdotal experience is continuously expanding but, as yet, there are no evidence-based accepted treatments. Local anaesthetics have been used empirically for all types of neuropathic pain. These applications can sometimes play a role in the treatment of pain by injury to skin or subcutaneous tissues. Topical anaesthesia can be reached with a Eutectic Mixture of Local Anaesthetics (EMLA), high concentrations of lidocaine and local anaesthetic creams or gels. If a simple application is not effective, an effort should be made to apply these formulations under an occlusive dressing.

Patients with neuropathic pain from peripheral nerve injury can be treated with topical capsaicin, a compound that depletes peptides in small primary afferent neurons, including those that mediate nociceptive transmission like substance P. A therapeutic trial of high concentration formulation (0.075%) is advocated for 3 to 4 applications daily for 3–4 weeks. Some patients experience burning, this may disappear over time or remit with the use of an oral analgesic, cutaneous application of lidocaine 5% ointment, or use of the lower concentration formulation of capsaicin (0.05%) [12]. There are favourable anecdotal reports of topical opioids for pain associated with a variety of lesions. The effectiveness of this approach remains to be confirmed [13]. There are also case reports of the successful use of mexilitine, an oral local anaesthetic-type drug, in patients with cancer-related neuropathic pain [14]. Particular attention has

to be given during these treatments to patients with ischaemic heart disease or cardiac arrhythmias.

N-methyl-D-aspartate-receptor antagonists
NMDA receptors in the spinal cord are activated by continuous stimuli in nociceptive afferents, leading to sensitisation of the dorsal horn cells and causing perpetuation of the sensation of pain and reduced opioid sensitivity [15]. This mechanism can underlie opioid tolerance and the relative opioid insensitivity of neuropathic pain. The NMDA-receptor antagonists, including ketamine, dextromethorphan and methadone, inhibit this process. Low magnesium levels predispose to NMDA activity, and administration of intravenous magnesium has been reported to relieve refractory neuropathic pain [16]. NMDA receptor antagonists are indicated for the treatment of refractory neuropathic pain and other severe pain when opioid tolerance is of concern. Ketamine in subanaesthetic doses has been shown to improve the effect of opioids in relieving refractory neuropathic pain or other opioid insensitive pain in patients with cancer. It can be given orally, intravenously, intrathecally or as a burst therapy subcutaneously. Ketamine can reduce pain score and decreases the morphine requirements [17]. Dextromethorphan also has an NMDA receptor activity but is reported ineffective in cancer patients [18].

Alpha-2 adrenergic agonists
Epidural clonidine has shown effectiveness for some patients with refractory pain, particularly with neuropathic pain [19]. Treatment begins at very low dose, which is followed by gradual dose escalation until analgesia occurs or treatment–limiting toxicity (sedation and hypotension) supervenes.

GABA agonist
Baclofen is effective in the treatment of trigeminal neuralgia and may be of benefit for patients with the lancinating type of neuropathic pain, but there are no trials specific for cancer patients. There is a wide range of effective oral doses, starting at 5 mg b.i.d. up to 150 mg/day.

Neuroleptics
Pimozide has shown some activity in trigeminal neuralgia, but the side effect profile will limit its applications. It is not frequently used in terminal oncological patients but, favourable anecdotal experience suggests that a trial may be considered for patients with any type of neuropathic pain. The dose ranges from 30 to 300 mg/day. Gradual uptitration reduces the risk for adverse effects, while tapering the dose will prevent serious withdrawal effects after long-term (>1 week) use.

Benzodiazepines
Clonazepam is sometimes used to treat paroxysmal neuropathic pain. Alprazolam may also have some analgesic effects. Many cancer patients suffer from some degree of anxiety and/or muscle spasms, phenomena that can intensify the pain sensation but respond well to benzodiazepines. Therefore, it seems reasonable to try benzodiazepines if anxiety and/or muscle spasms are present in patients with neuropathic pain.

Bone pain

Bisphosphonates
It is well known that severe pain is experienced by 60–80% of patients with metastatic bone disease. Skeletal metastases are associated with pathological fractures, spinal cord compression and hypercalcaemia. Therefore, prevention of bone pain and bone-related events are an attractive alternate option. Bisphosphonates are effective for prevention and treatment of skeletal-related complications from metastatic bone disease and are an important addition to other strategies for the treatment of bone pain. Bisphosphonates are the first-line approach, based on the abundance of supportive evidence, the benefit to non-painful skeletal co-morbidities and convenience for the patient. The cost is relatively high, but the cost–benefit may be favourable due to their effectiveness in reducing skeletal co-morbidities [20,21]. While the trials of clodronate, pamidronate and zoledronic acid showed some pain relief activity, the results were sometimes inconsistent between trials [22–24]. Pain relief of clodronate was the least pronounced in clinical practice. The effect of zoledronic acid on pain seems to be similar to pamidronate [25]. Zoledronic acid and ibandronate are third generation bisphophonates. Zoledronic acid is only available intravenously, while ibandronate can be injected intravenously or taken orally. This is the first parenteral and oral bisphosphonate and is therefore, an appealing bisphosphonate because it is more convenient for patients by avoiding hospital visits.

Intravenous ibandronate (6 mg i.v. every 3 to 4 weeks as the standard schedule), in a randomised placebo-controlled trial in breast cancer patients with bone metastases, produced better pain relief ($p < 0.001$), better global quality of life ($p = 0.005$) and better physical, emotional and social functioning ($p \leqslant 0.05$) than placebo [26]. Ibandronate at 6 mg i.v.

every 4 weeks significantly improved ($p < 0.05$) nausea and vomiting, dyspnoea, insomnia, appetite loss and constipation compared to placebo [27]. Significant improvements in the symptoms of fatigue and pain were observed after 6 mg ibandronate i.v. every 3 to 4 weeks for up to 96 weeks. Ibandronate is the only bisphophonate to demonstrate marked reductions in bone pain that are prolonged and sustained below baseline levels over 2 years of treatment [26]. There was also significant improvement in quality of life. It is an effective and well-tolerated palliative treatment in patients with bone metastases due to breast cancer [27].

Oral ibandronate (50 mg/d) reduced mean pain score significantly ($p = 0.019$) compared to placebo in a randomised placebo-controlled trial in advanced breast cancer patients. Patients in the ibandronate group used fewer analgesics than patients on placebo ($p = 0.019$). The global assessment of quality of life deteriorated more in the placebo group than the ibandronate group ($p = 0.032$). The individual functioning scales, physical and role functioning scores were significantly better in the ibandronate group than in the placebo group ($p \leqslant 0.05$) [28].

High dose ibandronate (4 mg i.v. over 2 hours on 4 consecutive days) resulted in significantly reduced mean visual analogue scale (VAS)-pain scores within 7 days ($p < 0.001$) and these reductions were maintained over 6 weeks ($p < 0.05$). Also, the quality of life improved on the Edmonton Symptom Assessment System (ESAS) well-being scale by day 7, as well as the functional Edmonton Functional Assessment Tool (EFAT) scores and performances status by day 21 ($p < 0.05$ versus baseline for all measures) [26]. Interestingly, this intensified scheme of ibandronate is effective in opioid-resistant bone pain in patients with skeletal metastases, although in this highly intensified dose regimen there was no evidence of renal toxicity, which is sometimes seen in zoledronic acid [29].

The highest doses of ibandronate and pamidronate were associated with the largest reductions in corrected serum calcium from baseline to day 4, when used for malignant hypercalcaemia [30]. The activity of intravenous ibandronate in reducing metastatic bone disease in breast cancer patients is greater with 6 mg than 2 mg every 4 weeks [31] and an intensified ibandronate treatment with 4 mg $\times$ 4 days reduces pain that was resistant to a daily 400 mg oral morphine equivalent dose of analgesics.

The duration of response in hypercalcaemia of malignancy is significantly longer with ibandronate than pamidronate although the number of patients responding to the two agents was similar [30]. The long-term administration of pamidronate does not lead to a statistically significant reduction in bone pain after 1 to 2 years of treatment [32]. Patients receiving ibandronate 6 mg i.v. every 4 weeks for 2 years experienced highly significant reductions from baseline in bone pain score compared with placebo ($p < 0.001$), which were fully maintained over 2 years of treatment [33].

A reduction in bone pain below baseline to almost the maximum level achieved during the trial period was evident within only 8–12 weeks of treatment initiation with ibandronate 50 mg daily orally. This shows that bisphosphonates are not a good indication for quick pain relief in the very last days of life. They are indicated for relatively stable chronic bone pain in patients with a life expectancy of at least a couple of months to reach the full analgesic potency.

The intensified regimen of ibandronate, 6 mg i.v. over 2 hours on 4 consecutive days, reduces the pain scores significantly at day 7 ($p < 0.001$) and the patients continued to experience significantly reduced pain scores compared with baseline at day 21 ($p < 0.0001$) and day 42 ($p < 0.05$). This intensified ibandronate schedule significantly reduced bone pain from day 7 to 42 in both patients with breast cancer, but also in other tumour types ($p < 0.05$ versus day 0) without an increased use of analgesics over time.

The optimum duration of bisphophonate therapy should still be determined. The American Society of Clinical Oncology (ASCO) guidelines recommend the bisphosphonates therapy from diagnosis of bone metastasis until decline in general performance status [21]. We lack scientific data to conclude if a continuous bisphophonate treatment is necessary and if it is better than a shorter treatment time or intermittent treatment. Prospective randomised trials have to show the optimum time to start treatment, define the best treatment duration and to explore if these drugs have to be given either in continuous or intermittent therapy.

In general, all the different bisphosphonates treatments are subjectively well tolerated. However, increased risk of osteonecrosis of the jaw has been observed in patients treated with pamidronate and zoledronic acid in combination with cancer therapy (irradiation, chemotherapy, corticosteroids, extractions, surgery ...) [34]. This is a severe complication because of the important functional deficit and the irreversibility of the necrosis to any treatment. A real causal relationship between bisphosphonate therapy and osteonecrosis of the jaw has not yet been established. An international expert panel summarises

potential preventive measures prior to the initiation of intravenous bisphosphonate therapy:

- Avoid elective jaw procedures that will require bone to heal.
- Recommend a routine clinical dental exam that may include a panoramic jaw radiograph to detect potential dental and periodontal infections.
- Dental care has to be done preferably before the initiation of bisphosphonate therapy.
- Educate patients regarding the importance of good dental hygiene and symptom reporting.
- Oncologists should perform a brief visual inspection of the oral cavity at baseline and at every follow-up visit.

There are also guidelines defined to manage the patients with osteonecrosis of the jaw:

- A non-surgical approach may prevent further osseous injury.
- Intermittent or continuous antibiotics may be beneficial to prevent secondary soft tissue infections, osteomyelitis and pain.
  - (*) Penicillin V/K 500 mg or amoxicilline 500 mg 4 times a day for induction and 2 times a day for maintenance.
  - (*) Patients allergic to penicillin are treated with Clindamycine 150 tot 300 mg QID, Vibramycine 100 mg once daily, Erythromycine ethylsuccinate 400 mg 3 times daily.
  - (*) Antifungals when required: Nystatin oral suspension 5 to 15 ml QID or 100.0000 IU/ML, Mycelex troches (clotrimazol 10 mg) × 5/day, Fluconazole 200 mg initially, then 100 mg q.d. or itraconazole or ketoconazole
  - (*) Antivirals that can be used are Acyclovir 400 mg. b.i.d. or Valacyclovir hydrochloride 500 mg to 2 g BID
- Dentures can be worn but should be adjusted to minimize soft tissue trauma and should be removed at night.
- All patients should be monitored every 3 months.
- Cessation or interruption of bisphosphonates therapy may be considered in severe cases. However, the cessation of bisphosphonates therapy appears to have no effect on established osteonecrosis.
- Hyperbaric oxygen has not been shown to be effective and is therefore, not recommended.
- Osseointegrated dental implants are contraindicated and may result in further osteonecrosis.

Third generation bisphosphonates are much safer for renal function even after relatively rapid administration (4 mg/day repeated for 4 consecutive days) [35]. Ibandronate can be injected over 15 minutes as for zoledronic acid, but without requirement of renal function monitoring, while this has to be done in zoledronic acid treated patients. The simple dosing regimen of oral ibandronate makes at-home treatment possible with less hospital visits and as a consequence lesser health care costs. In the high dose intensity ibandronate regimen had 38% of the patients had biochemical hypocalcaemia at day 7 and 36% of the patients had asymptomatic hypophosphataemia but none of these patients required a specific therapy. The hypocalcaemia was followed by a spontaneous, but significant increase in parathormone concentrations at day 7, which did not persist on day 21.

Quality of life

As well as apparent efficacy advantages over pamidronate, zoledronic acid is already more convenient, with a rapid 15-minute infusion instead of a 3-hour pamidronate infusion. However, significant demands on hospital resources are still necessary and this has an impact on patients' quality of life.

Intravenous ibandronate, given by short infusion time or even by oral intake, improved the quality of life as assessed by the well-being score on the ESAS compared to baseline as early as day 7 ($p < 0.05$), which was maintained for the duration of the study ($p < 0.05$) [29]. Ibandronate also provided benefit for functional status (EFAT scores) at all time points compared with baseline values, with statistical significance reached at day 21 ($p < 0.05$). The mean performance status scores on the ECOG scale significantly improved at day 21 as well as on day 42 ($p < 0.05$).

Economics

The significantly shorter infusion time of zoledronic acid and ibandronate has the potential to provide a more convenient administration regimen that minimizes the length of hospital visits and ensures greater efficiency in the use of healthcare resources [30]. Ibandronate can even be taken orally and avoids 4-weekly hospital visits, which make it the most convenient, but also the cheapest bisphosphonates treatment without lessening efficacy.

Conclusion

Third generation bisphosphonates zoledronic acid and ibandronate are very effective in relieving chronic metastatic bone pain. Prospective randomised trials comparing the effects of i.v. and oral ibandronate on bone pain versus the other bisphosphonates (and not only against placebo) are warranted to assess fully this palliative efficacy, not only on bone pain, but also

for subjective wellbeing and physical and social independent functioning. Studies show that ibandronate, given in an intensified scheme, has analgesic activity in patients with severe opioid resistant, bone pain from breast cancer and a variety of other tumour types.

Guidelines on the use of bisphosphonates from ASCO, recommend initiating the use of bisphosphonates at the first detection of bone metastases but, there is no scientific data when treatment can safely be interrupted or stopped. This is also the subject of further clinical research.

The anti-inflammatory activity of corticosteroids may help to control pain when there is extensive tissue destruction and invasion. This is especially true for pain resulting from nerve compression or bone destruction.

Pain from liver capsule distension and intracranial hypertension are excellent indications to use the corticosteroids. 12–24 mg of dexamethasone is a reasonable daily dose. The last dose each day may not be given after 18:00 hrs. If useful pain control is achieved, the dose can be reduced after a week, and a maintenance dose established. Dexamethasone and methylprednisolone can be given orally or parenterally, dexamethasone (Aacidexam®) can also be given by subcutaneous injection or infusion. Long-term use of these drugs will result in a moon face or buffalo hump as a side effect of the corticosteroids treatment.

Calcitonine-salmon has some beneficial effect in reflex sympathetic dystrophy [36] or acute phantom pain [37]. This analgesic effect on neuropathic pain and this favourable side effect profile justifies a trial with 200 IU/day in refractory neuropathic pain in cancer patients.

Visceral pain

Malignant bowel obstruction can cause important abdominal pain where corticosteroids, anticholinergic drugs and somatostatine analogues (activated in this sequence) are the treatment of choice.

Corticosteroids are used in dose-ranges of 8–60 mg dexamethasone or its equivalents, starting with a loading dose followed by a maintenance treatment.

If intestinal colicky pain persists, *hyoscine butylbromide* can be given at 10–20 mg 6-hourly s.c. or i.v., as a bolus or as a continuous subcutaneous or intravenous infusion.

Somastatine-analogue, octreotide in a dosage of 300–1800 μg/d in subcutaneous or intravenous infusion is effective in the treatment for nausea, vomiting and diarrhoea associated with painful malignant bowel obstruction. The dose is titrated progressively from 300 μg/day as a starting dose with additions of 300 μg/day until effective levels are reached. Chronic nasogastric or percutaneous drainage by catheters and subsequent hospital stay can be minimised frequently by optimal use of this drug [38].

Anti-emetics are generally required, but metoclopramide and domperidon should be stopped as they stimulate the upper gut to act against the obstruction at a lower level. Cyclizine at 50 mg 8-hourly (s.c. or rectal) is the first choice anti-emetic in this situation. If this is ineffective, haloperidol can be added in a dose of 5 mg at night.

Adjuvant drugs

Adjuvant drugs have no intrinsic or indirect analgesic effect. They are used to counteract the side effects of analgesic drugs. The common side effects of opioids are: constipation, sedation and nausea. Narcosis is not a side effect but a complication, mostly due to inadequate use of opioid doses. More rarely reported side effects are: confusion, myoclonus, miosis, delayed gastric emptying, dry mouth, biliary colic, suppression of cough reflex, postural hypotension, urinary urgency or retention, flushing, sweating and pruritus.

Laxatives

All patients taking opioids regularly will develop constipation. There is some tolerance for nausea and somnolence to opioids, but there has never been a reported tolerance for constipation to opioids. Opioids cause constipation by decreased gastric, biliary, pancreatic and intestinal secretions, and a decrease in the propulsive motility of stomach and intestine, resulting in delayed passage of increasingly viscous stool. A prophylactic laxative regimen must *always* be instituted at the same time the opioid is started and maintained for the duration of opioid therapy. Patients with a normal daily fluid intake have to receive a prescription of an osmotic laxative for 10–30 g/day (e.g. lactitol, lactulose) that has to be taken orally 1 to 3 times a day. When this is not effective, the osmotic laxatives have to be combined or replaced by contact laxatives in the evening; in general these agents may cause more painful colics. When this treatment is still ineffective after two days, an enema needs to be added as a last resort. A small sorbitol enema (100 ml) or a glycerine suppository is advocated if there is rectal faecal impaction. If the rectum is empty a larger amount of fluid (up to 1 litre) is administered in an enema water–soap solution or acetylcysteine 200 mg in about 500 ml of water. Other

possible enemas are glycerine or gastrografine® in water solution.

Patients with an impaired gastro-intestinal motility, secondary to opioids, and nausea may benefit from an oral or parenteral given prokinetic anti-emetic drug (e.g. metoclopramide or domperidom).

Drugs for sedation or somnolence

Some, mostly mild, sedation is possible in the onset of strong opioid treatment during the first 24 to 48 hours. Patients and families should be warned of this side effect and should be informed that it will disappear spontaneously in the next few days. It is important for caregivers to encourage patients to continue their opioid medication through this period. More susceptible to this adverse effect are elderly or frail patients, patients with renal impairment, patients with other causes of central nervous system depression, opioid-naïve patients or patients during opioid maintenance therapy, when pain has been acutely relieved by an interventional procedure or the start of specific treatment for neuropathic pain. Opioid induced sedation must always be differentiated from the predictable deep sleep that follows pain relief in sleep-deprived patients.

If sedation persists without renal impairment or other correctable causes, opioid rotation has to be done or a treatment with methylphenidate [39] or donepezilhydrochloride (an oral acetylcholinesterase inhibitor) [40] may be tried.

Methylphenidate

Methylphenidate (Rilatine®) has no independent analgesic action but is effective in reducing opioid induced sedation in a dose of 5–10 mg in the morning and 5 mg at noon. The pain score is lowered, there is less need for extra doses of analgesics, the activity increased and drowsiness is decreased [39].

Donepezil

Donepezil (Aricept®) is also effective in opioid-related sedation in a dose of 5 mg/day [40].

Anti-emetics

Nausea occurs frequently at the onset of an opioid therapy, while vomiting is exceptional. The nausea is normally mild and will disappear in a few days. Patients should be informed of these adverse effects and should be instructed not to lower the effective opioid dose but to take an adequate dose of anti-emetics. They should receive, together with the receipt of the opioids, always a receipt for anti-emetics as well as for laxatives, so that they can take it on an as needed basis. Different anti-emetics (alizapride, domperidon, metoclopramide, $5HT_3$-antagonisten), are considered equally effective by most physicians and randomised controlled trials do not show any difference between ondansetron, metoclopramide and placebo in the control of opioid induced emesis [41]. Patients with nausea and vomiting due to intracranial hypertension do better with corticosteroids (e.g. methylprednisolone 32–64 mg/day or dexamethasone 5–10 mg orally or s.c.) than with anti-emetics. Patients who suffer from some opioid induced confusion or delirium can have some benefit by treatment with haloperidol (0.5–1 mg × 3/day).

Narcosis

Narcosis can happen only in exceptional cases with accidental or intended large overdoses. There is then, not only narcosis, but also extreme miosis and respiratory depression even to a rate of <8 respirations per minute. Immediate s.c., i.m. or i.v. administration of 0.1 mg naloxon (Narcan®) should be given every 2–3 minutes until the adverse effects disappear. Since the half-life of opioids ranges from about 4 hours to more than 24 hours (respectively for short-acting morphine and slow-release forms) and the half life of naloxon is only 1 hour, the adverse effects (narcosis and respiratory depression) can recur within an hour and treatment with naloxon has to be repeated as frequent as necessary, while the patient is closely monitored for at least 24 hours after discontinuation of the high-dose opioids.

The myth of opioid-induced respiratory depression is one of the major reasons for undertreatment of cancer pain in terminally ill patients. Patients with cancer pain normally do not develop respiratory depression if opioids are used according to internationally accepted and published guidelines for the following reasons: pain is the best physiological antagonist to the respiratory depressant effect op opioids; cancer patients are treated consecutively with weak and strong opioids and are rarely opioid naïve when strong opioids are started; patients use oral medication or slow-release opioids, which have no risk of high peak serum concentrations, and the dose is slowly titrated proportionally to the increased intensity of the cancer pain.

However, patients who are at risk of respiratory depression for other reasons (e.g. chronic obstructive lung diseases, pulmonary infections in frail or cachectic patients) the addition of opioids can result in a reduced response to rising carbon dioxide levels,

especially when these opioids are associated with benzodiazepines in benzodiazepine-naïve patients. The respiration depends then only on hypoxic drive and therefore oxygen treatment has to be avoided in these patients.

Myoclonus

Benzodiazepines

Many cancer patients experience some degree of anxiety and/or muscle spasms. Alprazolam and clonazepam can be given, if these co-morbidities exist, to relief these symptoms and may result indirectly in better pain control. Midazolam is another benzodiazepine that can be given p.o., i.v., i.m. and also s.c. in bolus or in continuous infusion. These different administration routes make this drug appealing for the different phases of terminal cancer patients.

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