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Review

Predictive Factors and Opioid Responsiveness in Cancer Pain

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The management of cancer pain not readily responsive to morphine is often problematic. Several factors can interfere with an appropriate analgesic opioid response in the course of the illness, including the progression of the disease and tolerance, the appearance of intractable side-effects, type and temporal pattern of pain, morphine metabolites, pharmacokinetic and pharmacodynamic factors, as well as individual factors. Different methodologies capable of accurately predicting or monitoring opioid response have been proposed in an attempt to allow researchers to 'speak a common language'. Tolerance is a component of the concept of opioid responsiveness. However, the assessment of analgesic tolerance in cancer patients is constrained by numerous difficulties because of the changes in the noxious stimuli with increasing activity in nociceptive pathways. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

ALTHOUGH CANCER pain can be relieved in 80–90% of patients with the analgesic ladder proposed by the WHO, some cancer pain syndromes are resistant to treatment. The management of cancer pain not readily responsive to morphine is often problematic. Unacceptable side-effects with minimal analgesia result in increased suffering for cancer patients. The 'difficult pain' due to poor responsiveness to morphine has recently been debated in the literature and several different terms, such as paradoxical pain, insensitivity, unresponsiveness, resistance, have been used to confound the situation [1]. Opioid responsiveness can be defined by the degree of analgesia achieved during dose escalation to either intolerable side-effects or the occurrence of an adequate analgesia. Several factors can interfere with an appropriate analgesic opioid response in the course of the illness, including the progression of the disease and tolerance, the appearance of intractable side-effects, the type and temporal pattern of pain, morphine metabolites, pharmacokinetic and pharmacodynamic factors, and individual factors [2–5].

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PROGNOSTIC FACTORS

Tolerance

Tolerance is a component of the concept of opioid responsiveness. Analgesic tolerance is pharmacologically defined as a reduced potency of the analgesic effects of opioids following its repeated administration or the need for a higher dose to maintain the same effect, thus causing a shift to the right of the dose response. Increases in morphine doses during chronic treatment are related to particular events resulting in an increase in pain [6], although it should be considered that there is no clear relationship between the progression of disease and the associated pain syndrome, since some primary tumours or metastasis may not produce pain whilst small lesions may produce severe pain [7].

The development of tolerance to adverse effects is favourable, as this condition represents an enlargement of the therapeutic window which may facilitate successful dose titration [8]. This observation is often neglected and has been the reason generally reported to avoid early use of opioids. However, patients who are clinically given opioids for cancer pain may remain on a stable dosage for a long period, after achieving adequate analgesia [9]. In some circumstances, morphine doses can be decreased or stopped if pain is relieved by another treatment or the source of the pain is abruptly eliminated. Therefore, tolerance to either analgesic and non-analgesic effects commonly occur, although other factors may operate that allow the patient to tolerate higher doses of opioids.

A high baseline opioid requirement may be determined by a prior opioid exposure. Large increments are required to observe further analgesic effects during dose titration. Misinterpretation of poor analgesic response can be attributed to a low-dose increment, as tolerance does not in itself reduce opioid responsiveness [5]. However, with high dosages, there is a risk of metabolite accumulation and the occurrence of adverse effects.

Neuropathic mechanisms may influence the development of tolerance. Patients with long-term pain or neuropathic pain, although not previously exposed to opioids, may develop tolerance to opioids and their syndrome might result in less response to opioid administration and require higher doses. Relatively high opioid doses and the need for a rapid increase in opioid dose predict a poor outcome in pain relief [3]. Rapid tolerance and opioid-related side-effects are often associated with neuropathic cancer pain syndromes [10].

Pain mechanisms

Neuropathic cancer pain is an irreversible and variable syndrome, which can follow injury to the peripheral or central nervous system. Once established, neuropathic pain and spinal hyperexcitability are independent of afferent input. Subcategories of neuropathic pain, especially in a clinical situation, should be considered according to the diversity of the underlying pathophysiology. The variability in the response of patients to opioids has been attributed to characteristics inherent in the pain syndrome. Neuropathic pain has been described as not responsive to opioids at usually effective doses [11] and considered to be a negative predictive prognostic factor in cancer pain [3]. Although neuropathic mechanism may reduce opioid responsiveness, pain can still be responsive to analgesic treatment and does not result in an inherent resistance to opioids [5, 12]. Neuropathic pain has been described as a syndrome of decreased responsiveness to systemic opioids requiring higher doses of opioids to achieve acceptable analgesia, which is often accompanied by greater toxicity. On these grounds, a specific approach according to the pain mechanism would not be useful, as opioids should not be withheld on the assumption that the mechanism precludes a favourable response [13]. Neuropathic pain has been as well controlled as bone pain at rest [2]. Patients with neuropathic pain do not show a particular disadvantage compared to those exhibiting nociceptive pain [4], unless associated with neurological impairment [1]. Moreover, early onset nerve trunk pain, due to inflammation or active damage of the free unmyelinated nerve ending in the perineurium of the nerve root or plexus [14], may be more likely to respond to opioids.

Temporal factors and breakthrough pain

A significant variation in the circadian distribution of extra doses of opioids in patients with cancer pain, with a lower consumption between 02.00 and 10.00 h, has been reported [15]. Mobile patients or patients who have incidental pain, being more likely to have pain during the day, were excluded. Increased mobility during the day, due to nursing procedures, decreased perception of pain at night, or a circadian variation in the pharmacokinetics of opioids or in the sensitivity of opioid receptors, may explain this observation [15].

In the presence of significant incident pain, the titration of opioid dosage is very difficult. The prevalence and the characteristics of breakthrough pain have been evaluated in a survey of cancer pain patients. Sixty-three per cent of patients who were receiving stable doses of opioids and had controlled baseline pain described one or more episodes [16]. Most terminally ill patients with incident pain found that it was a major limiting factor to activity [17]. Freedom of pain was particularly difficult to achieve in patients with bone metastasis and incident pain [2]. Incident pain reduced the possibility of pain control, although this negative influence was counterbalanced by the possible individual response to analgesics administered sequentially during a 1-week period [4]. The difficulty with incident pain is not a lack of response to systemic opioids, but rather that the doses required to control the incidental pain produce unacceptable side-effects when the patient is at rest. Pain control is usually excellent if the patient remains immobile or refrains from performing the pain-causing manoeuvre [3]. Some breakthrough pains are related to a baseline opioid dose. When exacerbations of pain occur predictably prior to the next scheduled dose of opioid, pain can be managed by increasing the basal dose or decreasing the interval between dosing [18]. Incident pain is best managed by supplementing the basal regimen with analgesics with a rapid onset of action and short duration as the rescue, or in anticipation of the activity identified to provoke pain. Between 5 and 10% of the total daily opioid intake administered as needed is generally suggested [16]. However, this may still result in severe sedation during pain-free intervals [18]. Anti-inflammatory drugs may be a useful option [19]. Moreover, many of the pains may remit spontaneously after a short time.

Drug selective effects

Strategies for selection of opioid drugs and their route of administration determine improvements in opioid responsiveness. Sequential trials of different opioids have been suggested clinically by the large intra-individual differences in response to various opioids. Many patients can experience an improvement in the balance between adequate analgesia and adverse effects when an opioid is replaced by another. Forty-four per cent of patients required trials of two or more opioids due to dose-limiting toxic side-effects [20].

Efficacy of opioid agents

Characterisation of various opioids into high-efficacy and low-efficacy agents has been suggested. To generate a given effect it is necessary to occupy a number of receptors out of the total population, so-called fractional receptor occupancy. The number of receptors to be occupied is inversely proportional to the intrinsic activity. The amount of the remaining unoccupied receptors depends on this property. The larger the receptor reserve, the greater the intrinsic efficacy.

The greater shift in morphine dose response, relative to sufentanil, when the stimulus intensity rises, supports the receptor occupancy theory [21, 22]. Any receptor agonist, including morphine, may become a partial agonist when the stimulus intensity surpasses the receptor reserve, explaining the loss of efficacy with increasing doses on the one hand and the possibility of excitatory side-effects, according to the extra opioid receptor neurotoxic effects of itself or its metabolites on the other hand.

Although the individualised receptor inheritance, in terms of receptor heterogeneity, number, co-localisation and interactions, to pain stimulation and opioid exposure may render the interpretation of these data in cancer pain difficult, a

switch to an alternative opioid in patients with inadequate analgesia and unmanageable side-effects may result in a dramatically improved opioid responsiveness [23].

Opioid metabolites

M6G has been shown to exert a potent agonist effect at mu-receptors, leading to the suggestion that it gives a relevant contribution to the analgesic effect of morphine chronically administered [24]. Alternatively M3G has been shown to antagonise the analgesic effects of morphine when administered either centrally or parenterally, possibly contributing to the development of tolerance [25]. Moreover, M3G has been reported to have excitatory effects and may induce hyperalgesia, respiratory stimulation and behavioural excitation by non-opioid mechanisms via an antiglycinergic effect at the spinal cord level, resulting in a postsynaptic inhibition resulting in hyperalgesia and myoclonus [26].

Controversial results have been reported regarding the relationship between opioid responsiveness and the cerebrospinal fluid (CSF) concentration of M3G and M6G. The ratio of M3G to M6G plus morphine in cerebrospinal fluid during oral administration of morphine has been shown to be significantly higher in patients with uncontrolled pain than in patients with well controlled pain, while no plasma differences have been found in M3G/M6G plus morphine ratio [27]. Hyperalgesia induced by increasing amounts of morphine and its metabolites has been described, sometimes accompanied by myoclonus, although it may be considered an exacerbation of pre-existing pain [28, 29]. In subsequent studies this hypothesis has not been confirmed. In patients with morphine-resistant pain who elected to proceed to intrathecal bupivacaine or percutaneous cordotomy, M3G/M6G ratios have been found to be similar to those of patients with well-controlled pain either in blood and CSF [30]. No relationship between M3G concentration in CSF and pain relief has been detected in patients treated by epidural morphine [31]. The increase of M6G:morphine alone has been shown not to be a determinant of the prevalent opioid-related adverse effects, including myoclonus and cognitive impairment, in a study in which these symptoms were analysed in relation to several factors [32]. The interindividual variations in metabolite production and response to morphine and its metabolites due to different pain mechanisms, make the interpretation of a potential dose-effect relationship difficult.

Although the hypothesis that M3G plays a major role in morphine resistance is weak, it does not exclude the possibility of the occurrence of important toxic effects limiting opioid responsiveness [28, 33]. Changes in production, distribution and metabolism of morphine and its metabolism, due to varying degrees of renal insufficiency may account for the variability of the M:M6G ratio observed [34]. A progressive increase in the concentration of M3G and of M6G in the CSF of patients with renal failure has been found [35]. An accumulation of the metabolite can also occur in patients with normal renal function and mild renal dysfunction does not result in accumulation of morphine metabolites [23]. Moreover, creatinine and BUN may not always reflect renal function adequately in malnourished patients. Antibiotic treatment may facilitate intestinal reabsorption of M6G [36]. Normorphine has been reported to be responsible for some of the neurological side-effects of high-doses of morphine, resembling the neurotoxic properties described for normeperidine [37, 38]. The accumulation of metabolites of hydromorphone may explain the clinically observed recurrence of opioid toxicity when morphine is replaced with hydromorphone in patients with renal insufficiency [39]. If opioid metabolites are involved in the development of dose-limiting toxicity, a change of opioids would allow for clearance of metabolites while maintaining pain control. Taking these clinical observations into account, it has been suggested that the accumulation of toxic metabolites during chronic opioid therapy can lead to severe and untolerable adverse effects, even in patients with apparent normal renal function, limiting the opioid responsiveness.

Route of administration

The route of administration has an important role in determining the M:M3G:M6G ratio in both plasma and CSF. Concentrations of M3G and M6G in relation to morphine have been found to be greater following oral administration than after intravenous administration of morphine [23, 40]. The prevalence of myoclonus among patients receiving oral morphine has been found to be 3-fold higher than those receiving parenteral morphine [32]. These findings have clear clinical implications, particularly during prolonged morphine use or in the presence of renal impairment, when these metabolites may accumulate.

In a prospective randomised comparative study in patients with an involvement of the brachial or lumbar plexus, the epidural route for opioid administration was superior to oral opioids, due to a lower incidence of adverse effects. However, complete pain relief was not achieved in all patients and technical problems arose in the group treated by the epidural route [41]. Patients chronically treated with oral morphine showed all reaction time percentiles significantly longer than controls, whereas the epidural opioid group showed only the involvement of the longest reaction times [42]. However, epidural and subcutaneous administration of morphine were comparable in terms of effectiveness and acceptability. Both treatments provided better pain relief with less adverse effects compared with the previous oral morphine treatment [43].

Moreover, continuous pain originating from deep somatic tissues can be equally extensively well controlled by both oral and spinal opioids, while somatic pain from mucocutaneous ulcers and from fractures, from intestinal distension, as well as neuropathic pain, respond poorly to spinal opioids, suggesting a lack of improved analgesic activity by spinal morphine [44].

Predisposition to side-effects

Upward dose titration is often difficult due to the development of adverse effects. Pharmacokinetic factors or pharmacodynamic factors may favour the occurrence of adverse effects, due to a higher than anticipated plasma concentration or exaggerated responses at low plasma opioid concentration.

Gender and age can influence opioid responsiveness. Women report severe levels of pain, more frequent pain and pain of longer duration than men [45]. Females have been reported to present a high prevalence of nausea and vomiting, thus limiting opioid dose escalation. The presence of these side-effects may limit dose escalation and the achievement of adequate analgesia, as the opioid escalation index was lower and intervals without changing therapy were longer in the presence of higher VAS and frequency of intestinal symptoms in women rather than in men [1]. Metabolic and cerebral derangement, commonly present in older patients, may

facilitate the occurrence of undesiderable effects. There are significant associations between increasing age, elevated bilirubin or LDH levels and the occurrence of cognitive impairment [32]. Concurrent administration of other neurotropic drugs may also increase the risk of side-effects. However, aggressive management of opioid-related symptoms may allow further escalation of the dose [5]. A poor response to opioids has been shown during cognitive failure episodes. Specific treatment for agitation should be more appropriate in these circumstances. Delirium may be an important and frequently unrecognised factor associated with crescendo pain, and opioids can contribute to exacerbate delirium. An appropriate assessment may abort the pattern of crescendo pain with the use of a therapeutic trial of neuroleptic drugs, switching to an alternative drug or a different route of opioid administration [46]. Confusion has been associated with an increased OEI and neuropathic pain. The response of these patients may be less than that observed in patients with nociceptive pain, because the neurological impairment is more likely when a quick escalation is required [1].

Psychological factors

Cancer pain is a complex experience, as it involves personality, learning and situational components [47]. Although difficult to assess, psychological status plays an important role in the experience of cancer pain. The degree of psychological distress has been reported as the major negative prognostic factor. Addictive personalities were considered at risk of poor prognosis for pain control [3].

Cultural variables can affect the perception of pain and its expression [48]. Patient misinformation may be a source of inadequate dosage. Pain severity has been shown to correlate with patient's belief that their pain was due to cancer [49]. The clinical implications are obvious for cancer patients who not only ignore the cause of the pain but also their diagnosis and prognosis. Patients' or physicians' fears of risks of using opioids may still induce an artificial opioid resistance resulting in an inadequate pain relief.

Other factors

Different aetiologies may account for rapid opioid escalation. Occult local infection has been proved to be the cause of worsening pain and escalating opioid requirement [50, 51]. This clinical feature should be aggressively pursued as a potentially reversible cause of intractable pain. Antibiotic therapy and drainage of the abscess has resulted in markedly improved pain control, decreased analgesic requirements and improved quality of life in a patient with metastatic breast cancer [52].

CONCLUSION

Opioid responsiveness is not a phenomenon dependent on the pathophysiology of the pain, but rather a complex phenomenon related to several individual factors. Pain mechanisms, tolerance, progression of disease, the presence of metabolites during chronic therapy with opioids, the route of administration are all factors influencing this delicate individual balance in cancer patients with pain. Opioid responsiveness should be defined by the degree of analgesia achieved during an appropriate dose escalation to either intolerable side-effects or the occurrence of an acceptable analgesia. Therefore, it depends on an individual continuum of responses determined by the balance between analgesia and side-effects, that might be influenced by a large number of patient- and drug-related, as well as pain-related, factors [5]. The anticipatory classification of opioid-resistant pain in cancer is inappropriate as an appropriate dose escalation can identify patients with neuropathic pain who will achieve adequate relief. Pain which is relatively less sensitive to opioids should be better considered as opioid-poorly responsive. This term has to be considered retrospectively after appropriate trials of opioids and routes of opioid administration. Attention should be paid to the underlying psychological condition.

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