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Pain management in older people

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Summary

At times providing pain relief in elderly patients can prove troublesome. Their tolerance and perception of pain can differ from that of younger patients, while the incidence of pain is above that found in those of less advanced years.

Conventional approaches to providing pain relief can be successful, but the tolerance to the side-effects of those drugs used to provide pain relief can be less. Furthermore, polypharmacy can have implications for the range of analgesic drugs that can be considered. Fortunately there are an increasing range of medicinal products with reduced potential for side-effects that can be considered when treating older patients with pain.

Keywords: pain, neuropathic pain, opioids, anti-depressants, anti-epileptics, older people, ageing.

Introduction

One of the fundamental precepts of medical practice is the relief of suffering. When that suffering is associated with pain then undoubtedly our ability to successfully intervene has increased over the recent past. However, we are not yet at the position where we could realistically claim that pain is an entirely treatable symptom or that the pharmacological modalities available for such treatment are devoid of significant side-effects.

When the issue of pain relief in patients of advanced age is considered, then the problems that those providing treatment are faced with are increased. While many elderly patients seem more stoical in their acceptance of pain, the possible causes of pain increase with ageing. Degenerative diseases and neoplasia are more frequent, as is the pain that accompanies them. Decrease in cerebral function may reduce the patient's ability to report the presence of pain, while social isolation and difficulties accessing health services may reduce the opportunities to access treatment. Even where the pain symptom is communicated effectively and the patient is able to access treatment, then accompanying disease states and their treatments may reduce the range of analgesic medication that can safely be prescribed.

What then do the patient and their physician do when 'conventional' analgesics are ineffective or are contraindicated? Does the patient just have to put up with their pain? Fortunately the answer may be 'no'. There are a number of pharmacological preparations, some not usually thought of as analgesics but for which a significant evidence base exists, which can provide further options for pain relief and which have an acceptable side-effect profile. Therefore the aim of this review is to examine those factors that influence the incidence of pain in older people, how their neural processes for dealing with noxious insults differ, how existing analgesics can be used with effect, and lastly what other options for pain relief exist when the more commonly used options are inappropriate.

Neural changes in older people

Ageing deeply influences morphological and functional features of the nervous system. In the peripheral nervous system there is a loss of myelinated and unmyelinated fibres in older people, with the decrease in myelin being at least partially attributable to a decrease in expression of the major myelin proteins. Axonal atrophy is also more commonly observed.[1] Nerve conduction and endoneural blood flow are reduced as age advances and, as nerve regeneration is less commonly observed, there may be a reduction in peripheral nerve function.[1] Even when regeneration of damaged neurones occurs, these regenerated fibres have a smaller number of terminal and collateral synapses.

Spinal cord immunochemical studies reveal an increase in mRNA content of the neuropeptide tyrosine and galanin mRNA in dorsal root ganglia (DRG) neurones of aged rats. In these animals there are decreased cellular contents of calcitonin

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gene-related peptide (CRGP) and substance P (SP) compared with younger animals, while the levels of somatostatin are similar. The labelling intensity for encoding high-affinity tyrosine receptors (TrkA, TrkB and TrkC) are decreased in the DRG neurones of aged rats.[2]

In addition, there is progressive loss of serotinergic and noradrenergic neurones in the superficial lamina of the spinal dorsal horn,[3,4] and since serotonin and norepinephrine play important roles in the descending inhibitory control pathways, such loss may upset the natural endogenous pain-suppressing mechanisms. At supraspinal levels, there is reduced neurotransmitter content and expression,[5] decreased metabolic turnover, and a loss of neurons and dendritic connections throughout the cerebral cortex, midbrain and brainstem.[6]

Even at the molecular and enzyme level, changes are seen with ageing. For example, the G-protein signalling proteins act as modulators of G-protein-coupled receptors, which have a function in opioid signalling. In rats, one such protein, RGS9, is found in increased levels in the caudate-putamen, nucleus accumbens, olfactory tubercle, periaqueductal grey and grey matter of the spinal cord in aged animals, compared with young animals. In contrast, it is found at decreased levels in the thalamic nuclei and locus coeruleus in older animals.[7]

It would therefore seem not unreasonable to assume that if there are neural differences between young and the old that there may also be differences in pain perception and modulation.

Effect of age on results from animal pain models

Some insight into the effect of age on pain perception can be gained from examination of the results of animal pain testing. When nociception is tested in mice using an electrical current, it seems that there are age-related changes in nociception that are curvilinear with the graphical representation of electrical thresholds needed to induce a vocal response being of a U-shaped pattern.[8] That said, not all testing methods definitively show age-related changes, with some being more definitive than others.[9,10]

Among those examinations that do reveal age-related changes are those involving substance P (SP). It is known that SP levels in the spinal cord of very old rats are less than the levels in young rats. After injury to a peripheral nerve, immunoreactivity to the SP receptor (NK1, neurokinin 1 receptor), increases in the spinal cord ipsilateral to the injury and increases correlated to the development of thermal hyperalgesia. After peripheral nerve injury, aged rats develop thermal hyperalgesia and tactile allodynia more slowly than young rats, and the thermal hyperalgesia correlates with increases in the number of NK1 receptors with these receptors becoming apparent more slowly.[11]

Another animal nociceptive test is that of rat paw incision with measurement of mechanical sensitivity with von Frey filaments and thermal responses assessed with radiant heat. Young and old animals respond in a similar fashion to the thermal stimulus. However, younger animals appear to recover more quickly from the mechanical allodynia produced by paw incision when compared with the older animals.[12] This suggests that modulation of A fibre-mediated sensitization differs in young and old rats.

In the formalin test, where formalin application to a paw produces a chronic inflammation characterized by a biphasic response demonstrable both by behavioural and electrophysiological testing, maximum response is seen in middle-aged, as opposed to young or old animals.[13] An antinociceptive effect in this test is seen when animals are forced to exercise. When mice of varying ages are examined in this variant of the formalin test, the degree of exercise-induced analgesia is maximal in young animals, and minimal in the aged animals.[14] This exercise-induced analgesia is not blocked by opioid antagonists, but is blocked by N-methy-D-aspartate receptor antagonists.[14]

When we look at isolated neuronal function, studies on spinal cord nociceptive neurons show that spontaneous firing rates are higher and the responses to thermal stimulation are greater in aged compared with adult rats.[15] Furthermore, the size of the receptive field area of wide dynamic range neurons are larger and that of low-threshold neurons smaller in aged compared with adult rats.[15] The increased nociceptive neuronal activity in aged rats correlates with the finding that the paw withdrawal latency is significantly shorter in aged compared with adult rats following heat stimulation of the paw.[12] This, along with the loss of serotinergic and noradrenergic fibres in the spinal dorsal horn of aged rats,[13–15] may contribute to the apparent

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diminution of descending inhibitory control of nociceptive processing in older animals.

The effect of drugs may differ in older people as well. We are currently seeing an increasing use of opioids, and in particular strong opioids, in the management of chronic pain. Analgesic tolerance is a potential complication of such opioid use. In rat models tolerance is easy to demonstrate. Wand and colleagues (2005) examined rats aged 3 weeks, and 3, 6 and 12 months. Morphine was injected twice daily and the time until analgesic tolerance measured (which they defined as a 75% reduction in morphine-induced analgesia compared with day 1). Tolerance was apparent on the 4th, 10th, 14th and 22nd days of morphine treatment, respectively. Plasma morphine levels and that of its metabolites did not correlate with the differences in tolerance development.[16]

One other factor that impinges on pain perception is the hormonal status of the patient. We have seen in animal models that advancing age does have a noticeable effect. However, particularly in the female, age brings about hormonal changes as well so that, for example, response to opioid analgesics is similar in males to gonadectomized and reproductively senescent females but differs from that of reproductively active females.[17]

Effect of age on human experimental pain

Perhaps the most clinically relevant issues are those of pain threshold and pain tolerance. Gibson (2003) reports that over 50 studies have examined age differences in the sensitivity to experimentally induced pain and that the majority of these studies focus on pain threshold. Twenty-one studies report an increase in pain threshold with advancing age, three a decrease and seventeen no change. When all results are examined meta-analytically, the effect size is 0.74 ($P < 0.0005$), indicating that there is definite evidence of an increase in pain threshold with advancing age.[18] If pain tolerance is considered, the ten studies examining the effect of age on pain tolerance show a definite age-related decrease in the willingness to endure very strong pain. The decrease in pain tolerance effect size is estimated at –0.45 ($P < 0.001$) across these studies.[18]

Threshold and tolerance are not the only phenomena that are relevant when pain is considered. For example, Zheng and colleagues studied the effect of age on the response to capsaicin-induced hyperalgesia. Older adults took longer to report first pain while age had no effect on the magnitude of pain reported, flare size or heat hyperalgesia. This heat hyperalgesia lessened rapidly in all age groups. However, punctate hyperalgesia and mechanical pain thresholds remained at higher levels for considerably longer in elderly as opposed to younger adults.[19]

Lasch and colleagues (1997) have reported the effect of intra-oesophageal balloon dilation in healthy young and old adults. The volume of air inflated into the balloon before report of pain was measured. This volume was significantly higher in older subjects. Indeed, many of the older subjects failed to report pain even after maximal balloon inflation, in marked contrast to the younger patients.[20] It certainly seems that, using this experimental technique, pain threshold does increase with age. However, this study also reminds us that pain is not always an entirely unhelpful symptom. On many occasions it provides a timely warning of impending problems. For example, if it requires a larger volume within a hollow viscus in an elderly patient before pain is experienced compared with younger subjects, then the discomfort caused by an obstructive lesion in the bowel may take longer to become symptomatic in older patients, with all the consequences for the treatment and prognosis of the causative lesion. It is also clinically apparent that the incidence of silent myocardial ischaemia increases with age. Whether this is due to increased pain threshold in older people, a pain-reducing effect of concomitant medication or the effects of intercurrent illness is debatable, but probably all have some effect. Therefore, while our emphasis is on the management of pain in older people, we should not lose sight of the fact that thought must also be given to the absence of pain in these patients in circumstances where it normally would be present.

Along with advancing age comes an increased incidence of conditions such as Alzheimer's disease. While those with cognitive impairment may have difficulty in communicating the presence of pain, Gibson and colleagues (2001) have shown in a model utilizing a heat pain stimulus and subsequent cerebral event-related potential recordings that the presence of Alzheimer's disease did not have any noticeable effect on these pain-evoked potentials when compared with

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age-matched control subjects.[21] Utilizing a different method of recording evoked potentials, that of auditory-evoked potentials, Harkins (1981) has shown that age has no effect on these potentials but the presence of other sensory impairments, in this case hearing loss, can influence results.[22]

When temporal and spatial summation of pain is considered it seems that temporal summation to a heat pain stimulus, for example, is more pronounced in older people, as when compared with younger subjects spatial summation is not significantly influenced by age.[23] One last pain-related phenomenon to consider is that of diffuse noxious inhibitory control, a measure of endogenous pain inhibition. Edwards and colleagues (2003) have shown that there is an age-related decrement in diffuse noxious inhibitory control.[24] This may well have an influence on the pain modulatory capacity of elderly subjects.

Effect of age on human clinical pain

Clinical observation would suggest that there is an increased incidence of silent myocardial ischaemia in elderly patients and this exemplifies the fact that advancing age has an effect on pain appreciation. Another example would be the atypical presentation of an inflamed appendix where there may be an absence of localized right iliac fossa pain. Differences in the neuroanatomy, physiology and biochemistry of the nociceptive pathways may cause alterations in pain perception, while differences in the pharmacology of drugs in older people may alter expected responses to these drugs. Further compounding these issues is the perception of pain in elderly patients by their physicians. Yunus and colleagues (1988) compared elderly and young patients with fibromyalgia. They found that chronic headaches, anxiety, tension, mental stress and poor sleep were all less common in elderly patients with this condition. However, most importantly, in only 17% of older patients in the study were the features of fibromyalgia recognized initially by their physician prior to rheumatological referral.[25] Many of these patients were exposed to inappropriate corticosteroid treatment in the mistaken belief that they had an inflammatory condition.

The magnitude of the problem of pain in elderly patients is highlighted by figures from Sweden. Here a survey revealed that 73% of those older than 77 years had pain while 68% of those older than 85 years also suffered with pain.[26] The incidence of pain in older people is affected by a range of variables, which include racial and ethnic susceptibility to chronic disease, socioeconomic factors and accessibility to health care.[27]

When one tries to consider individual pain conditions then there is a lack of depth of evidence on which to base conclusions. For example, in the case of low back pain, when consideration is given to evidence in published studies then there is a marked under-representation of studies that include elderly patients and so firm conclusions cannot be reached.[28,29] It is, however, clear that when pain does occur in elderly patients it impacts on the overall quality of life of the individual.[30] Analgesic treatment is therefore desirable remembering that the response of elderly patients to drug therapy may differ from that of younger individuals. It may be that elderly patients require lower dosing of opioid analgesics, have a more rapid response to them and develop analgesic tolerance more slowly than those of less advanced years.[31]

Along with ageing comes an increased incidence of conditions such as Alzheimer's disease. It has been observed that the use of non-steroidal anti-inflammatory drugs is lower in patients with this condition than those of a similar age without it, and the use of anti-inflammatories is not dependent on the stage of the Alzheimer's disease.[32] When patients with Alzheimer's disease and age-matched controls are again considered, those with acute pain consume a similar quantity of pain killers to non-Alzheimer's patients, and it is only in those with chronic pain that consumption is significantly lower.[33] In contrast, patients with vascular dementia seem to suffer more pain than others without cognitive impairment due to this condition.[34] As well as differences in pain experience and analgesic use, cognitive impairment can also lead to a significant under-reporting of pain-related conditions. Indeed Cornali and colleagues (2006) found that 41.4% of patients admitted to a Geriatric Evaluation and Rehabilitation Unit had previously undiagnosed osteoarthritis.[35]

Overall, therefore, as age advances the incidence of pain-causing conditions differs from that of younger patients, impact on quality of life may be greater and a differing response to analgesic intervention may be observed.

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Practical pain treatment in older people

The mainstay of pain treatment across the age spectrum is the individual or combined use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids and paracetamol. It is not realized that these drugs may have a lesser effect on neuropathic pain and so anti-epileptic drugs, anti-depressants and local anaesthetic type drugs are preferentially used in the management of neuropathic pain. However, it would not be particularly unusual for an elderly patient who is in pain to be intolerant of, or have a contraindication to individual drugs in these classes, and so alternatives are needed.

Nociceptive pain

Nociceptive pain is the most frequently encountered type of pain. Trauma is accompanied by pain in the area of trauma, although at times such localized pain is accompanied by a referred pain in the corresponding dermatome to that in which the trauma has occurred. Tenderness is apparent in the area of trauma. The tissue damage may be caused by trauma (e.g. surgical or accidental trauma), degenerative diseases such as osteoarthritis, or by cancer. Paracetamol, opioids and NSAIDs may all provide relief. However, in a significant proportion of patients, NSAIDs may be contraindicated because of history of peptic ulcer or cardiovascular disease.

Where the predominant feature is localized pain and tenderness, then the topical application of lidocaine 5% patches can be rewarded with useful pain relief. These patches, which have a Marketing Authorization for use in post-herpetic neuralgia,[36] contain 750 mg lidocaine of which only about 5% is actually released. Even with multiple uses of patches over prolonged periods of time, systemic levels of lidocaine are low.[37] Topical lidocaine patches have been shown to reduce post-operative pain,[38,39] myofascial pain,[40] low back pain[41] and osteoarthritis,[42] for example. The patches are applied directly over the painful area.

When inflammation accompanies pain, then topical glyceryl trinitrate can be efficacious. The organic nitrates, such as glyceryl trinitrate (GTN) act as nitric oxide (NO) donors and have long been used in the treatment of ischaemic heart disease because of their smooth muscle relaxant and hence vasodilator properties. We now know that nitric oxide is important in the guanylate cyclase system that is implicated in the creation of hyperalgesia after tissue trauma.[43–45] Topical GTN can reduce the pain of infusion-related thrombophlebitis, supraspinatus tendonitis and osteoarthritis to give just three examples.[46–50] It does so by this different mode of action from NSAIDs, and therefore can be used when a NSAID is contraindicated. Its effect is maximal when it is applied close to the wound. The major side-effect is nitrate-associated headache, which may preclude use in some patients.

A further option for pain treatment is the topical application of capsaicin. Those who have experience with the burning discomfort associated with application will know that it can be of an intensity that puts patients off its use. One stratagem for reducing this discomfort is the addition of glyceryl trinitrate ointment to the capsaicin,[51,52] which has the additional advantage of enhancing the analgesic effect of the capsaicin.[53]

We present one last thought about the use of topical analgesics for nociceptive pain. The use of topical NSAIDs continues to be widespread among patients. They perceive that benefit can be apparent and seem to feel that side-effects are less common than when oral NSAIDs are used. As physicians we have been somewhat dismissive of the claims of pain reduction when topical NSAIDs are used. There now seems to be evidence that topical application of NSAIDs can have an effect on N-methyl-D-aspartate receptors,[54] and that such glutamate receptors have an importance peripherally in pain modulation.[55,56] Furthermore, topical NSAIDs can also have an effect on peripheral K^+ channels, which again are implicated in the peripheral processing of pain.[57,58]

Neuropathic pain

The analgesic response to 'conventional' analgesics such as paracetamol, mild opioids and NSAIDs in patients with neuropathic pain can be disappointing. Most will now know that as a consequence we utilize, for example, anti-depressants, anti-epileptic drugs and strong opioids when managing neuropathic pain. However, use of these drugs often results in unacceptable side-effects. For example, oral tricyclic anti-depressants (TCAs) can cause cognitive impairment, weight gain, urinary retention and eye problems. Strong

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opioids also can bring unwanted side-effects. For example, on initiation of strong opioid therapy, effects on cognition may be observed. In a study of 124,655 patients in Denmark, it was found that opioids were being taken by 8.0% of subjects who had sustained a fracture, whereas only 3.2% of 373,962 control subjects not taking opioids sustained fractures. The odds ratio for sustaining a fracture were 1.47 with morphine, 2.23 with fentanyl, 1.39 with methadone, 1.36 with oxycodone, 1.54 with tramadol, 1.16 with codeine and 0.86 with buprenorphine.[59]

Therefore, when an anti-neuropathic pain agent is chosen, its potential for producing side-effects should be a major determining factor in deciding about its use in an elderly patient. It could be argued that since oral tricyclic anti-depressants have a high propensity to cause side-effects then a selective serotonin norepinephrine reuptake inhibitor, such as duloxetine, should be chosen. Duloxetine has been found to be efficacious in the treatment of painful neuropathy,[60] and has also been found to be helpful in treating fibromyalgia pain.[61] Duloxetine has other indications as well, which include the treatment of major depressive disorder and urinary stress incontinence.

Fortunately tricyclic anti-depressants also achieve an analgesic effect by virtue of a peripheral mode of action (as well as the better-known central effect). This has been well demonstrated in animal pain models[62–68] and now replicated in human clinical studies.[69–72] Topical application of TCAs can therefore be used where neuropathic pain is localized and has the advantage of localized pain relief with a reduced risk of side-effects usually encountered when the drug is administered systemically.

Topical lidocaine patches and capsaicin can also be used when treating neuropathic pain in an elderly patient,[73–75] with the potential for enhancing the pain relief associated with capsaicin application when glyceryl trinitrate is co-applied, as mentioned above.

Several other low-risk pharmacological strategies exist for neuropathic pain treatment, which makes them of particular value when considering older patients. The first of these is a dietary supplement, L-carnitine, often sold in health food shops to aid weight loss and reduce depression. It has now been shown to reduce neuropathic pain associated with diabetes[76,77] and that following cancer and HIV chemotherapy.[78–82] It may also reduce the pain associated with fibromyalgia. It achieves its effect by virtue of its effect on glutamate receptors in the spinal cord.[83,84]

The other is the use of oral, intramuscular or intravenous $5HT_3$ antagonists, conventionally used in the management of post-operative and chemotherapy-induced nausea and vomiting. These $5HT_3$ antagonists, such as ondansetron, granisetron and tropisetreon specifically block neurokinin-1 expressing neurons in the superficial lamina of the spinal dorsal horn and interfere with the transmission of noxious impulses from the periphery to the central nervous system.[85–87] They have been shown to be useful in the reduction of the pain associated with fibromyalgia[88–90] and with neuropathic pain,[91] and because of their low risk of producing serious adverse events are commendable for use in elderly patients with neuropathic pain. They may also help reduce visceral pain.[92]

So there are a number of pharmacological entities that can be of particular value when treating pain in elderly patients. That said, in no group of patients is monitoring of therapy more important than in elderly patients. There is no place for keeping these patients on medications for their pain when they have no or little effect. The only place for such treatment is when the prescribed agent produces an improvement in the quality of life of the patient. Furthermore, the dangers of polypharmacy are greater than in younger subjects. Elderly patients are more likely to be taking medications for other health problems and so the danger of drug-induced side-effects or complications are increased with a decreased ability for the patient to cope with these complications.

Conclusion

The neurobiology of pain differs between young and older patients, as does the incidence, tolerance and perception of pain. Treatment may more frequently be requested and yet the patient's tolerance of prescribed medication may be reduced. While a number of low-risk pharmacological options exist for pain treatment in elderly patients, the most important principle of treatment is the close monitoring of effect and side-effects produced by prescribed medication and awareness not only

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of the incident pain being treated, but also of the overall general health of the patient as a whole.

Conflicts of interest

There are no conflicts of interest in relation to the preparation of this manuscript.

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