Pain Management

39

John Currie

Introduction

It is one of the "Rights of the Child" not to have to endure pain [1, 2]. In the past there was little knowledge or understanding of pain in children [3]. Many of us were taught that babies do not feel pain. Minor operations such as circumcision were often performed on neonates with no analgesia. We now know this to be a cruel misconception and in fact neonates have an enhanced, more global response to pain. Sensitization of the nervous system by trauma at such an early age can lead to different pain behavior in later life [4]. This global response in neonates is due in part to the poor hyalinization of nerves at this early stage of life, and also to the inability to localize pain until the brain develops a proper body image in the first few months of life.

This better understanding of pediatric pain has led to a revolution in pain management for acute and peri-operative pain in children. Most children's hospitals now have a well established "pain team" who ensure protocols are followed and that pain is adequately assessed and treated. It is from this initiative that the problem of chronic pain in children came to be recognized. These principles have been applied to chronic pain due to terminal disease.

Pain is an adaptive mechanism. Pain is a sensation and a reaction to that sensation. It helps us to avoid noxious stimuli in our environment and protect any injury while healing takes place. Pain is incorporated in our body image, localized and then changes our behavior. Our body image and pain behavior develop throughout childhood. For instance, a child under 5 years of age may describe any pain as "tummy ache" [5]. The pain may be somatic, visceral, or both, each type of pain having a different effect on the child. Somatic pain is easier to incorporate into the body image; a cut or broken arm can be seen. It is part of the body, outside of "self." Visceral pain, on the other hand, is more difficult to visualize. It is mediated mainly by C fiber pathways with anatomical connections into the limbic system. This is more frightening and has a greater emotional response. It is also harder to localize. We do not have a well-developed internal body image. A good example of this is appendicitis, which presents as a central abdominal pain until our nervous system works it all out.

Pain may be useful and protective, and this is easier to tolerate, and usually time limited. Chronic pain can be thought of as "useless" pain. This can lead to more suffering. Suffering is a global concept, associated with negative feeling, and impairs quality of life. This type of pain needs a different approach and this is what is provided by pain clinics in their pain management programs.

If the pain is associated with neoplasia then these negative feelings are enhanced. Any worsening of the pain will be interpreted by the patient and their family as progression of the disease. The final stage is palliative care. Here pain and symptom management is the goal, realizing that a cure is impossible and the outcome hopeless. This situation is obviously very psychologically demanding on staff as well as devastating for the family. The more closely staff are involved with the care of these children then the more difficult this situation will be. Nurses in particular will be in need of psychological support when caring for a dying child.

A palliative care team is extremely valuable for providing objective advice regarding difficult decisions and support to the primary care team. This team should meet regularly in an environment conducive to open discussion, rather than on the ward itself. In our own institution the team consists of our lead oncologist, pain management consultant, liaison psychiatrist, pediatrician, surgeon, and the nurses who coordinate care in the child's home as well as during ward admissions. We find that this approach works well. It is also useful to maintain close contact with the hospital ethics committee for help with end of life decisions and "do not resuscitate" orders.

Pain from childhood tumors is chronic "useless" pain which may develop as the disease progresses to become terminal pain needing palliative care. There may be acute

J. Currie
Retired
e-mail: John.Currie@ggc.scot.nhs.uk

R. Carachi, J.L. Grosfeld (eds.), *The Surgery of Childhood Tumors*, DOI 10.1007/978-3-662-48590-3_39

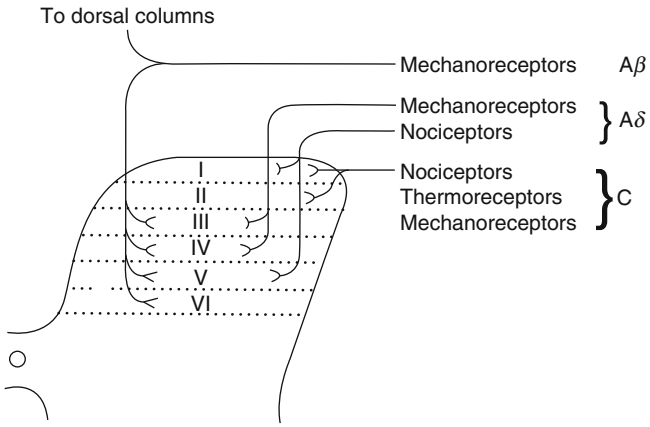

Fig. 39.1 Integration of sensory input in the dorsal horn of the spinal cord

events related to the progression of the disease, such as fractures related to bone metastases, pleuritic pain due to infection, or pain due to lymphoedema, for example.

What do we mean by "chronic pain?" The most widely accepted definition is that of Bonica [6]. He defined chronic pain as:

> Pain which persists a month beyond the usual course of an acute disease or reasonable time for an injury to heal or is associated with a chronological pathological process which causes continuous pain or pain which recurs at intervals for months or years.

In palliative care the ongoing disease process leads to a chronic pain picture which is progressive. The last few years have seen a considerable development in our understanding of pain mechanisms [7]. Laboratory and clinical studies have demonstrated increased spontaneous activity involving both mechanosensitivity and chemosensitivity in damaged peripheral nerves [8]. The consequent increased neural activity effects changes in both the dorsal root ganglion and the dorsal horn of the spinal cord (Fig. 39.1). This is a well-known phenomenon of dorsal horn windup. Abolition of spontaneous activity from damaged nociceptors or nerves may allow remodeling of the dorsal horn, and other areas of the central nervous system, resulting in prolonged pain relief.

This is an example of how the nervous system adapts to a chronic stimulus. The nervous system "learns" and tends to facilitate chronic stimulation. This has led to the concept of the plasticity of the nervous system which is now well established [9–11]. Understanding of the way in which the nervous system adapts to chronic pain inputs has lead to a range of techniques and specific drug treatments for the control of chronic pain [12].

This "learning" takes place throughout the nervous system all the way through to how the body image is mapped into higher centers and hence to consciousness [13] (Fig. 39.2).

Thus the pain may become "neuropathic" (from the Greek "neuro," meaning nerves, and "pathy," meaning abnormality). This is pain either originating from abnormal firing of nerve cells, or abnormal propagation of sensory input so that non-noxious sensations are perceived as painful. This type of pain relies on different transmitters within the nervous system, notably the n-methyl d-aspartate (NMDA), gamma amino butyric acid (GABA), and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) systems [14–16]. Neuropathic pain does not usually respond to conventional analgesic regimes and is opiate resistant.

Management of Pain in the Child with Advanced Malignancy

The effects of a tumor are complex and debilitating. As the tumor grows it may compress local tissues or nerves causing pain. Compression of nerves is a classic way in which neuropathic pain in produced. Indeed, compression by ligature is the most common way of producing an experimental neuropathic pain model. The tumor may also infiltrate into a nerve bundle or plexus causing pain. Infiltration into bone will initially cause painful pressure on the periosteum and may progress to cause pathological fractures. The same is true of bone metastases. Tumors also produce secretions which can act locally or systemically. Locally acting secretions include kallikreins [17, 18] and bradykinin [19, 20], which cause pain in nerve endings adjacent to the tumor. Recent research has focused on the purine pain pathway, mediated by adenosine triphosphate [21–23]. This is particularly interesting with relation to pain caused by tumors due to the very high levels of adenosine triphosphate in cancer cells. Systemically cancers produce substances that alter metabolism and the immune response. This leads to systemic pain, which is not well understood. Pain can also result from recumbence and pressure on thinned and weakened tissues.

Successful management of pain and other symptoms of pediatric tumors demands a team approach. Nurse pain specialists will liaise with the ward teams on a day-to-day basis, and in particular with the home support nurses. This latter group is key to managing pain at home. Most children are

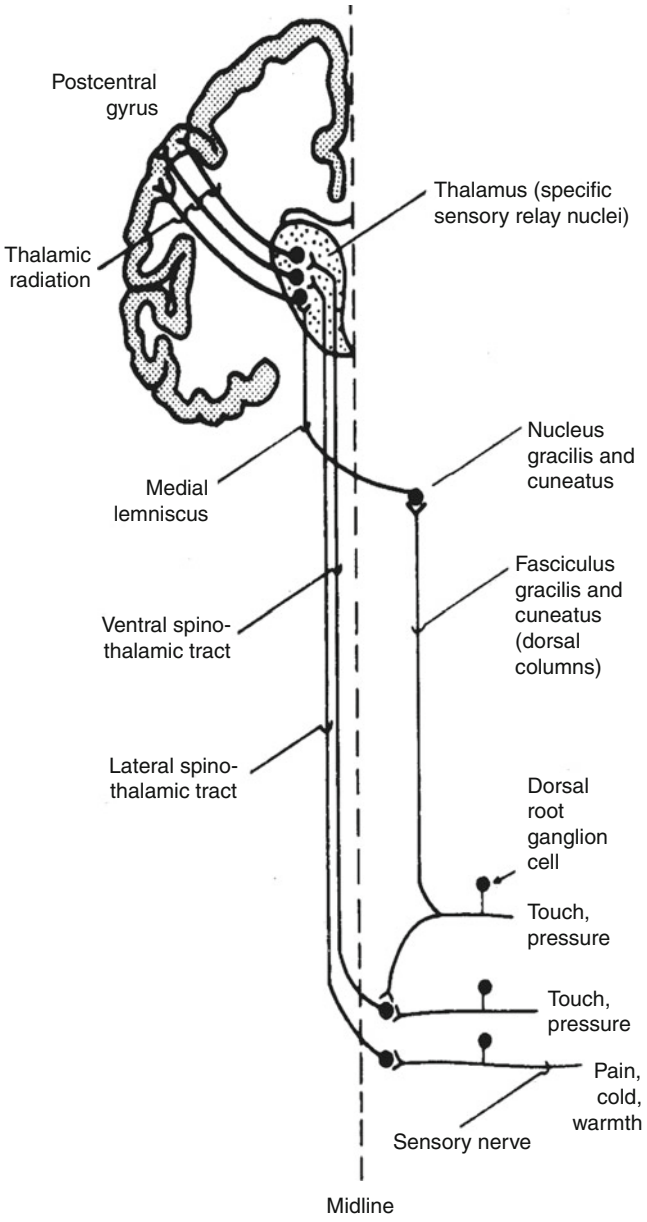

Fig. 39.2 Mapping of the body image through the thalamus to the post central gyrus. The post central gyrus is the area of the sensory cortex where the body is mapped as the homunculus (little man)

better nursed at home with their families where possible. This is particularly true at the end stages of life. The ideal is for the child to die comfortably at home. Other members of the team will include a psychologist and perhaps also a psychiatrist to try to help with the inevitable depression and anxiety. Where a family has a strong religious faith then close involvement with their church and hospital chaplain, etc., is extremely helpful. The physiotherapists can help with stiffness and pain due to recumbence as well as breathing exercises and helping to clear secretions. Any acute exacerbations of pain can be assessed with the help of the diagnostic imaging department to diagnose fractures, effusions, etc.

When assessing a patient with pain due to malignancy, adequate enquiry to obtain information is essential. We use a detailed questionnaire that the child fills in with the help of the family. This can identify the different types of pain the child has, as well as how it changes during each day. A pain diary can help with how the pain is responding to treatment or progressing.

The first step is to try to gain control and break the cycle of pain. Patient-controlled methods are preferably as they give some control to the child. They have something they can do. This can also help allay the fear that the pain may crescendo and become completely uncontrollable. Children often fear what the pain may be like rather than deal with what it is. Anyone who has performed a venipuncture on a child will know this well! A transcutaneous nerve stimulation device is extremely useful and is often our first line of approach. For visceral pain we have found a TSE (Transcutaneous Spinal Electro-analgesia) machine extremely useful. This is coupled with explanation and reassuring the patient and family, i.e., explanation as to why the child has pain, due to the mechanisms we have described, and reassurance that pain does not necessarily mean progression of the disease.

Sometimes more of an intervention event is necessary to break the cycle of pain. This may be a local anesthetic injection or an infusion of medication. It is important to get control of the pain in order to gain the confidence of the child and family.

Then a systematic approach is followed, developing a plan to deal with the pain. This is where the team approach is essential to monitor progress and avoid over treatment. Careful enquiry must be made as to the effect of the pain on the child's sleep pattern. If the child is kept awake or woken by pain, the whole family will be woken and lose sleep. This has a detrimental effect on everyone's mood and ability to cope. Pain relief must be first directed to give the child a good night's sleep. Melatonin is extremely useful for re-establishing normal sleep patterns. After that, pain control at rest is the goal, followed by pain control for whatever activity the child may be capable of. Pain control during all activity may not be possible, but some degree of mobility can usually be achieved, even if only from bed to chair.

Medical Treatment

There is still a place for conventional analgesia regimes. Many children will respond and not progress to the more intractable pain picture. Care must be taken to give adequate analgesic doses of these drugs and to make full use of the synergism between different drug groups. A good example

of this is to combine paracetamol with nonsteroidal anti-inflammatory drugs (NSAIDs).

This represents the first stage of the World Health Organization analgesic ladder (Fig. 39.3). Most units would progress from this first stage to stage three, strong opiates. This bypasses stage two, weak opiates. Stage two is unlikely to control the pain for long, and the side effects of the weak opiates are out of proportion with their efficacy in controlling pain.

Morphine is the standard opiate used and will initially be given intravenously to determine the required dose. This can then be converted to oral morphine given as a long-lasting (continuous) preparation twice daily. Breakthrough pain can be controlled by oral morphine given as the standard preparation. As long as oral intake is possible this is the ideal regime as is effective in most cases. Diamorphine can be used if morphine becomes ineffective, as it is a more powerful analgesic with the added benefit of a more profound anxiolytic action. It is extremely soluble making it the ideal agent for subcutaneous administration usually as an infusion. Fentanyl patches allow opiate absorption without a cannula. Patches are available in different strengths allowing titration of the dose. Each patch will give a steady dose of opiate through the skin for 72 h. Oral morphine can be used for breakthrough effect.

Nerve blocking techniques are useful, and may be peripheral or central. Laboratory and clinical studies have demonstrated increased spontaneous activity involving both mechanosensitivity and chemosensitivity in damaged peripheral nerves. The consequent increased neural activity effects changes in both the dorsal root ganglion and the dorsal horn of the spinal cord [8]. Abolition of spontaneous activity from damaged nociceptors or nerves may allow remodeling of the dorsal horn, and other areas of the central nervous system, resulting in prolonged pain relief. Local anesthetic administered by subcutaneous infiltration or directly to specific nerves can produce long-lasting pain relief for a variety of chronic painful conditions [10, 12]. Pain relief will often last for months [17]. Intrapleural blocks can be very useful for upper abdominal pain as well as pain in the thorax. A catheter can be used and an infusion given. This can be a very useful "event" to gain control of pain that has become intractable.

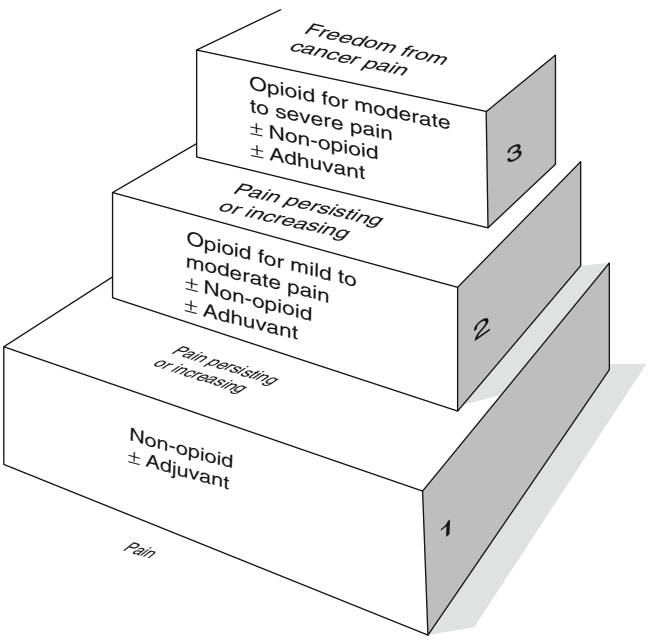

Fig. 39.3 WHO "Pain Ladder"

Many treatments despite involving short-term modification of the neural pathways nevertheless have long-term effects, for example, injecting local anesthetic drugs. We are manipulating the plasticity of the nervous system. I like to think of this as rebooting the system so that the normal program can run. In this computer age children relate well to this analogy.

Some pain may be mediated by the sympathetic nervous system and be helped by sympathetic blockade [24]. A good example is coeliac plexus block for pain mediated by upper abdominal tumors, particularly those affecting the pancreas. We have, in our unit, a particular interest in coeliac plexus block for upper abdominal pain [25, 26] (Figs. 39.4, 39.5, 39.6, and 39.7).

Stellate ganglion block can be very effective in controlling pain mediated by the sympathetic nervous system in the upper quadrants. A block using local anesthetic such as levobupivacaine gives long-term relief and seldom needs to be repeated (Fig. 39.8).

In chronic pain epidural block is often a technique of last resort. The catheter can be tunneled to allow for long-term use. There are difficulties involved in managing a patient with a long-term epidural catheter, but these can be overcome with careful monitoring. These epidural infusions can be successfully managed at home. There are more drug preparations now available for administration by the epidural or caudal route as well as techniques for modification of neuronal function at this level [27, 28]. Catheters can also be placed intrathecally and this is an extremely effective method of achieving pain control [29]. The high risk of infection limits its usefulness [30]. Reservoirs of medication can be implanted under the skin, but this technique is limited by cost not just of the system itself but also in terms of resources to manage it effectively. The most common drugs used in these central blocks are local anesthetics such as levobupivacaine and opiates such as morphine or diamorphine. Adjuvant drugs such as clonidine can enhance the effect of local anesthetic.

The position of the tip of the epidural catheter can be confirmed by radiography or ultrasound to ensure accurate delivery of the medication (Fig. 39.9).

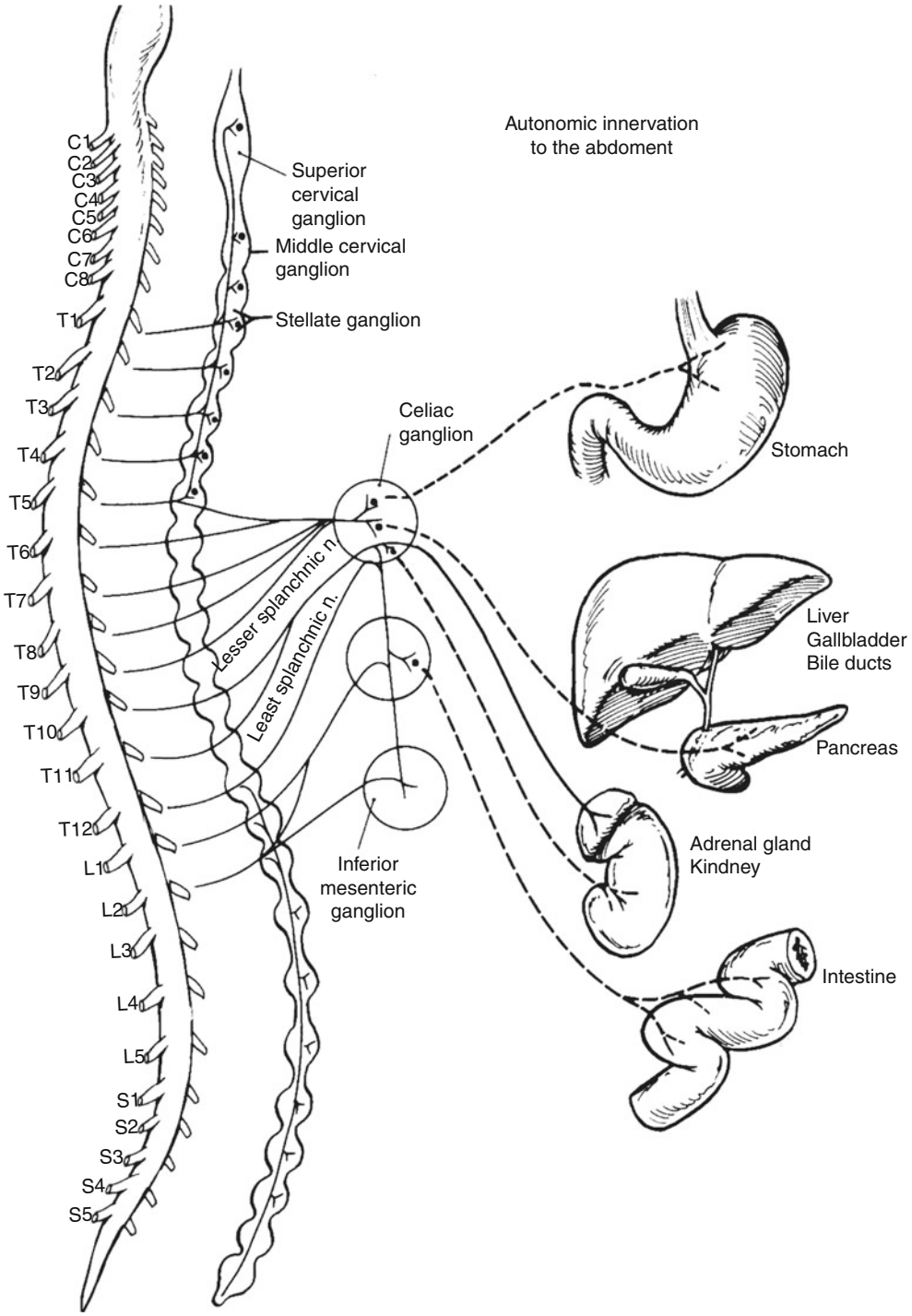

Fig. 39.4 The autonomic innervation of abdominal viscera

Other more invasive techniques may include nerve destruction, but this is seldom employed in children. An exception is ablation of the coeliac plexus after successful block with local anesthetic. A single localized lesion may be the major source of pain, for example, collapse of a vertebra due to tumor infiltration causing pain by nerve compression. This may be treated by injecting polymethyl methacrylate into the vertebra, which hardens and supports the damaged spine. Although obviously rarely used this is an extremely effective technique for controlling this type of very localized pain. We have ourselves used this successfully in a case of vertebral collapse due to hemo-lymphangioma.

The use of other techniques such as acupuncture and aromatherapy can be very effective [27]. Careful patient

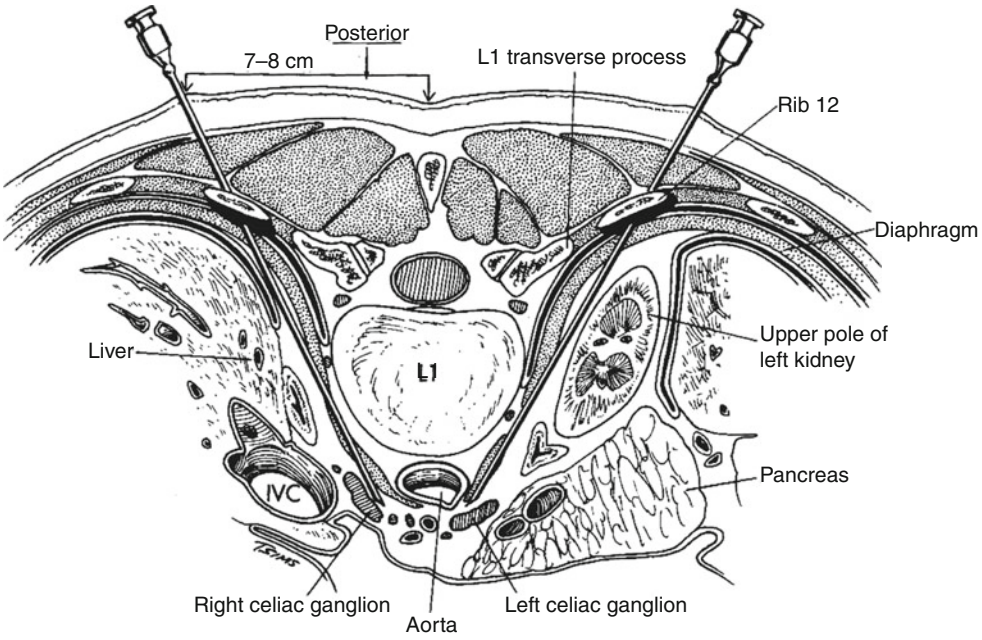

Fig. 39.5 Showing the positioning of the two needles for coeliac plexus (ganglion) block

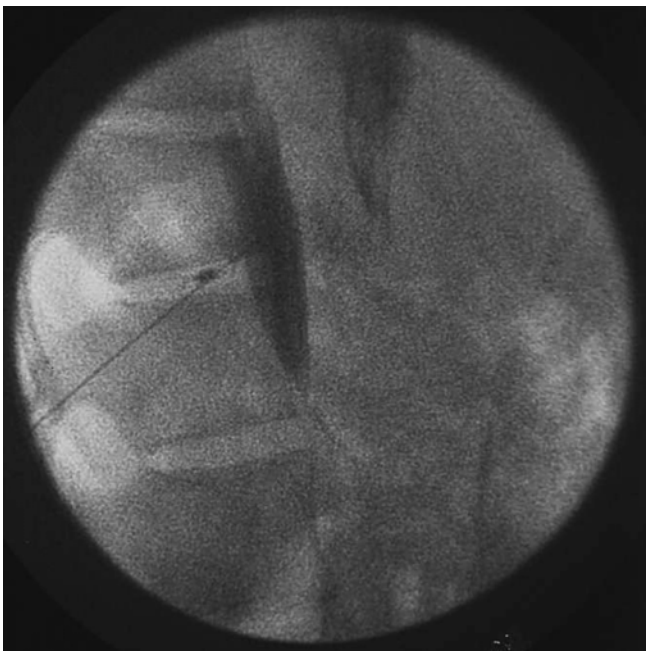

Fig. 39.6 Lateral radiograph showing dye around the aorta at the level of the coeliac ganglion

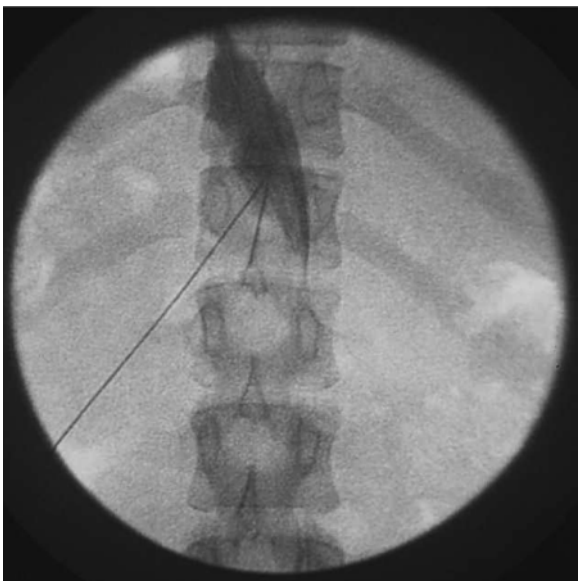

Fig. 39.7 Antero-posterior radiograph showing dye in the midline at T12

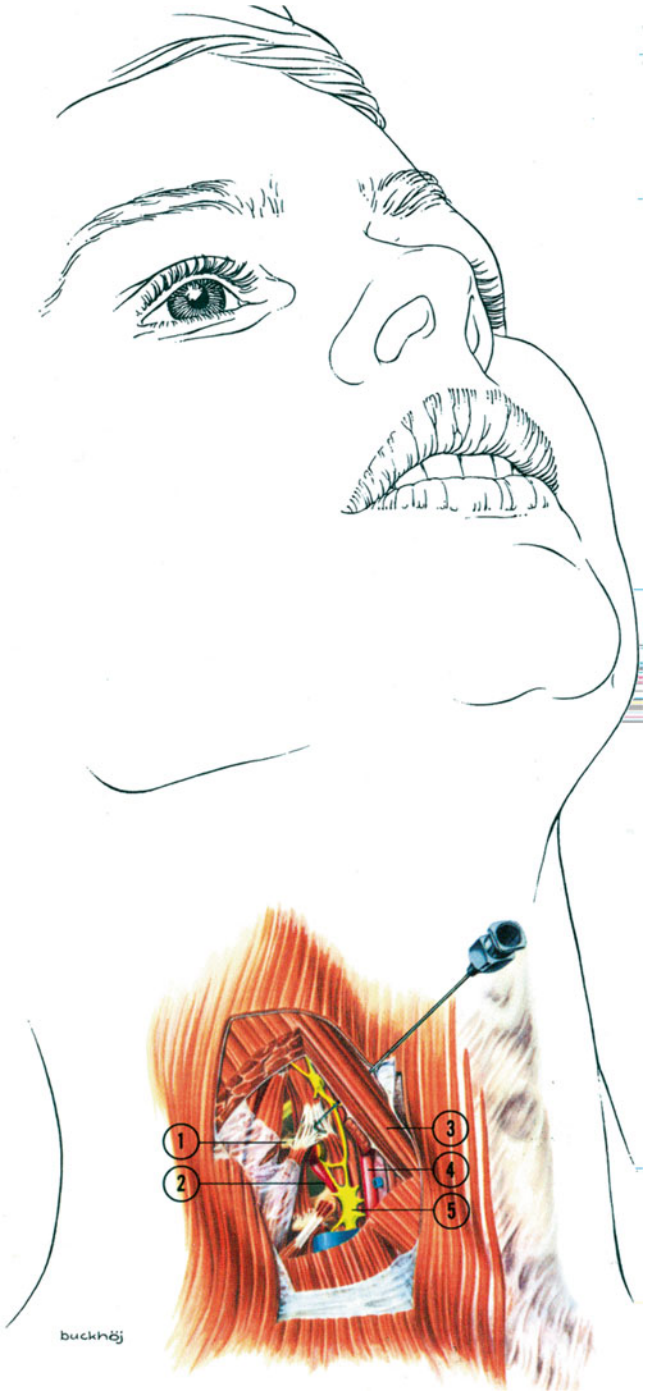

Fig. 39.8 Stellate Ganglion Block, showing the position of the ganglion in the neck and enlarged to show position of the needle adjacent to the ganglion. (*1*) Transverse process of C6, (*2*) Vertebral artery, (*3*) Sternocleidomastoid muscle, (*4*) Common carotid artery, (*5*) Stellate ganglion

selection is important, particularly for acupuncture. Aromatherapy has the major advantage of allowing parental involvement. Modern treatment regimes can lead to excessive "medicalization" of the child. The ability to be involved in care is very valuable to parents.

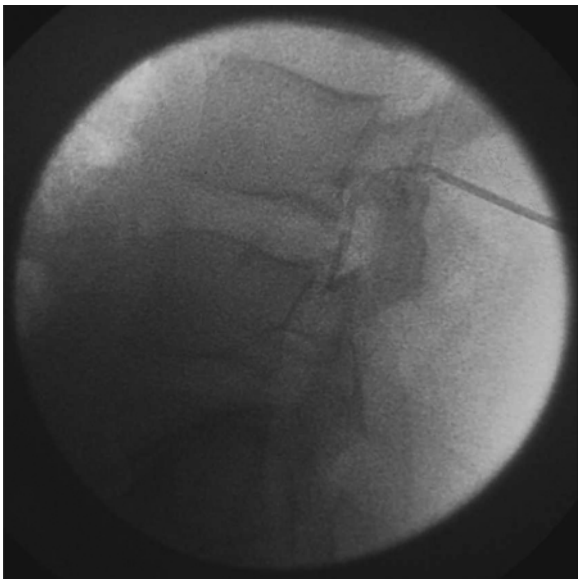

Fig. 39.9 Radiograph of the epidural catheter passing caudad in the epidural space

When the Drugs Don't Work

Most pain related to cancer will be controlled with opiates as the final stage of the analgesic ladder. The palliative team really comes into its own when these standard techniques fail and "the drugs don't work." This is when these more invasive techniques will be employed. Morphine may not control the pain. The pain may be mediated by different pathways particularly if the pain becomes neuropathic. The main pathway in this process is the N-methyl D-aspartate (NMDA) system.

More specific agents are now available for this neuropathic pain and their mechanisms of action are better understood [16, 17]. Our first line treatment for somatic neuropathic pain is gabapentin, lamotrigine being preferred for visceral pain. Ketamine is an excellent NMDA blocker and can be used intravenously or as part of an epidural infusion. Psychological side effects limit its use intrathecally. Methadone is also a very effective NMDA blocking agent, but its usefulness is limited by its narrow therapeutic index and significant side effects.

Other Symptoms

Nausea is a common symptom of cancer pain associated with renal or hepatic dysfunction, chemotherapy, and of course opiates. In children, however, we find that if the dose of opiates is appropriate for the pain then side effects do not present a significant problem. It is only when the dose is escalated in a futile attempt to control pain that has become opiate resistant, that the unwanted effects emerge. Nausea

can be as distressing as the pain itself and should be treated aggressively [36]. The cause should be determined, whether it be due to chemotherapy or metabolic dysfunction. Hypercalcemia, which may occur particularly in metastatic tumors, must always be excluded, as it is a potent cause of vomiting. The antiemetic will be chosen with regard to the cause of vomiting in each particular patient.

Excess secretions can be a major problem in the end stages of palliative care. The child may be too weak to cough and clear normal secretions or infection may lead to increased secretions. This may lead to noisy breathing or indeed choking which is very distressing to relatives and staff caring for the child. Hyoscine usually applied as a patch is very effective in relieving this symptom.

In a pain management program the input of other health care professionals is essential. This is particularly important in palliative care especially at the end of life. Depression and anxiety are features of terminal care in even the youngest of patients. This must be recognized particularly as many of the drugs to help with this can take days to work. A particular feature of palliative care is terminal agitation. The cause of this is multifactorial. Factors include poor metabolism of drugs at the end of life as well as increased anxiety. Nozinan (levomepromazine) is the most effective treatment, and has the added advantage of being an excellent antiemetic.

New drugs on the horizon which may be useful for neuropathic pain are levetiracetam an antiepileptic with a novel mode of action [31], and the AMPA blocking agent Anandamide.

Many of these new techniques and methods have resulted in some ethical dilemmas. For instance, most of the drugs used are not licensed for use in children or are being prescribed for conditions that are "off-license" for that drug.

The Future

There are many promising new developments in the study of chronic pain. We have several new drugs which can be used to modify the method of transmission of chronic pain and research continues in this area. New developments in functional MRI give us a better understanding of the central changes associated with chronic pain and its treatment. Remapping sensory input into consciousness is an exciting possibility [13, 32]. There is also increasing evidence of a genetic basis or predisposition to chronic pain syndromes opening up further avenues of treatment [33–36]. These advances will help us in our understanding of the effects of our therapies on the pain pathways and central pain perception, and may also provide guidence in the choice of appropriate treatment.

The drugs and dosages that we use in our clinic are listed in Table 39.1 [37].

Table 39.1 Drugs and dosages used in author's clinic

Neuropathic pain drugs
These drugs should be titrated slowly up to the effective dose. This will help to avoid unwanted effects. They should not be stopped suddenly, but weaned off gradually. Doses for pain management are generally lower than those used to control epilepsy.
Gabapentin:
>60 kg max dose up to 3600 mg/24 h
<45 kg max dose up to 2400 mg/24 h
<30 kg max dose up to 1200 mg/24 h
<20 kg not recommended
Preparations available: capsules: 100 mg, 300 mg (can be opened & mixed with food, e.g., jam, etc.) Tablets: 600 mg, 800 mg
Amitryptilline: requires ECG before commencement.
>50 kg 25 mg PM – aim for 25 mg BD
<50 kg 10 mg PM – aim for 10 mg BD
<30 kg not recommended
Preparations available: oral solution: 25 mg/ml, 50 mg/5 ml
Tablets: 10 mg, 50 mg
Carbamazepine:
>40 kg 100 mg PM should be effective at this dose
<40 kg not recommended
Preparations available: tablets: 100 mg, 200 mg, 400 mg
Chewtabs (tegretol): 100 mg, 200 mg
Oral solution (tegretol): 100 mg/5 ml
Suppositories (tegretol): 125 mg, 250 mg
Slow release (tegretol retard): 200 mg, 400 mg
Lamotrigine:
>50 kg START 10 mg BD (max 40 mg.BD)
>30 kg START 5 mg BD (Max 25 mg BD)
<30 kg not recommended
Titrate to effect. We start this with child as in-patient as adverse reactions, particularly a rash may be a problem.
Preparations available: tablets: 25 mg, 50 mg, 100 mg, 200 mg
Soluble: 5 mg, 25 mg, 100 mg
Topiramate
>30 kg 2–6 mg/kg per day in two divided doses.
Initiate 25 mg nightly with weekly increments of 1–3 mg/kg withdraw very slowly.
NSAIDs (Non Steroidal Anti Inflammatory Drugs)
Caution if bleeding risk, asthma, atopy, renal dysfunction, GI ulceration/bleeding, on anticoagulants, (avoid if <6 months or weight <10 kg).
Diclofenac:
1 mg/kg up to 8 hourly
Preparations available: tablets: 25 mg, 50 mg
Suppositories: 100 mg
Modified release (diclomax SR): 75 mg
Modified release (voltarol retard): 100 mg
Ibuprofen:
10 mg/kg up to 6 hourly
Preparations available: tablets: 200 mg, 600 mg
Oral suspension: 100 mg/5 ml
Effervescent granules: 600 mg/sachet
Naproxen:
<5 years not recommended
>5 years 10 mg/kg in 2 divided doses
Preparations available: tablets: 250 mg, 500 mg
Oral solution: 125 mg/ml
Suppositories: 500 mg

(continued)

Table 39.1 (continued)

Piroxicam:
<15 kg 5 mg stat
16–25 kg 10 mg daily
26–45 kg 15 mg daily
>46 kg 20 mg daily
Preparations available: capsules: 10 mg, 20 mg
Melts (Feldene): 20 mg
Suppositories: 20 mg
Antiemetics should be chosen in relation to the cause of the vomiting.
Ondansetron: is a specific 5HT three serotonin antagonist.
Dose: 0.1 mg/kg (100 μg) 8 hourly
Preparations available: tablets: 4 mg, 8 mg
Oral lyophilisates (zofran melt): 4 mg, 8 mg
Domperidone: does not readily cross the blood–brain barrier, so causes less central effects. It acts at the chemoreceptor trigger zone.
Dose: 200–400 mcg/kg 4–8 hourly
<20 kg not recommended
Preparations available: tablets: 10 mg
Oral solution: 5 mg/5 ml
Suppositories: 30 mg
Hyoscine: topical hyoscine preferred (Scopoderm TTS):
Dose: >35 kg 1 mg patch
Not recommended <10 years
Preparations available: 1 mg/72 h when in contact with skin.
Metoclopramide
500 micrograms/kg/24 h
Oral or IV
Methotrimeprazine
Excellent for intractable nausea/vomiting. Sedative and useful for “terminal agitation” in palliative care.
Initial dose 0.25 mg/kg daily given in 2 or 3 divided doses. This dosage may be increased gradually until an effective level is reached which should not surpass 40 mg/day for a child less than 12 years of age.
Opioids
Minimum monitoring standard for in-patients. Do not mix opioids or routes of administration.
Loading dose
>3 months old 0.1–0.2 mg/kg (100–200 μg/kg).
Switch to oral as soon as possible.
Oral opioids
MST: opioid naïve child: <15 kg expert use only
15–25 kg: 5 mg BD
25–50 kg: 10 mg BD
>50 kg: 15–20 mg BD
Preparations available: tablets: 5 mg, 10 mg, 30 mg, 100 mg
Sachets: 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
Oramorph: opioid naïve child: one-fifth of total MST dose for breakthrough 4/6 hourly. Preparations available: oral solution: 10 mg/5 ml
If more than 3 doses of oromorph per day add to MST dose by adding total dose of drug to MST dose and divide to 2 equal doses.
Always titrate to effect. Doses may be considerably higher in children who are not opiate naïve.
Diamorphine: extremely soluble and so is useful in small volumes for subcutaneous administration. When converting from morphine start with 1/4 to 1/3 of combined oral MST and oromorph dose
Sevredol: as oromorph, one-fifth of total MST dose for breakthrough 4/6 hourly.
Preparations available: oral solution: tablets: 10 mg, 20 mg
Conversion to MST as per oromorph recommendations.
Oxycontin and oxycodone are alternatives to MST and ORAMORPH

Table 39.1 (continued)

Tramadol: >12 years 50 mg 6 hourly
>60 kg 100 mg 6 hourly
Preparations available: capsules: 50 mg
Soluble: 50 mg
Slow release: 100 mg, 150 mg, 200 mg
Effectiveness limited by high incidence of nausea.
Dihydrocodeine: 0.5–1 mg/kg 6 hourly
Preparations available: tablets: 30 mg
Oral solution: 10 mg/5 ml
Slow release: 60 mg
Topical opioids
Fentanyl: opioid naïve child: 25 mcg/h patch
Under 30 kg: half patch
Under 15 kg: quarter patch
Patch should not be cut but placed over nonporous dressing such as
Tegederm to give desired surface area of patch next to the skin.
Preparation available: patch 25 = 25 mcg/h for 72 h
Patch 50 = 50 mcg/h for 72 h
Patch 75 = 75 mcg/h for 72 h
Patch 100 = 100 mcg/h for 72 h
When starting evaluation of the analgesic effect should not be made before the system has been worn for 24 h to allow the gradual increase in plasma-fentanyl concentration. It also may take 17 h or longer for the plasma-fentanyl concentration to decrease by 50 %. Patches should be changed every 72 h.
NMDA (N-methyl-D-aspartic acid) antagonist
These drugs should only be used by specialists for severe intractable pain.
Ketamine:
Binds to specifically to phencyclidine site (PCP site) of the NMDA receptor-gated channel and blocks NMDA receptors. It can be associated with general disturbances of sensory perception.
This is an anesthetic and adequate training before use is essential.
Sublingual: may be used to test efficacy 1 mg/kg diluted in 5 ml water: spit out after 2 min or if feeling dizzy.
Intravenous: start at 15 mg/kg in 24-h period diluted in normal saline to give dose of 2–4 ml/h. May need up to 25 mg/kg/24 h,
Epidurally: epidural agents must be preservative free. Start with bolus of 0.6 mg/kg and then 0.8–1 mg/kg in 24-h period.
Methadone:
Epidurally: as per epidural ketamine doses

References

1. Southall DP, et al. The Child-Friendly Healthcare Initiative (CFHI): healthcare provision in accordance with the UN Convention on the Rights of the Child. Pediatrics. 2000;106(5):1054–64.
2. http://www.childfriendlyhealthcare.org/publications/pediatrics.htm.
3. Bonica JJ. Evolution and current status of pain programs. J Pain Symptom Manage. 1990;5(6):368–74 (review).
4. Taddio A, Katz J. The effects of early pain experience in neonates on pain responses in infancy and childhood. Paediatr Drugs. 2005;7(4):245–57 (review).
5. Franck LS, Greenberg CS, Stevens B. Pain assessment in infants and children. In: Yaster M, editor. The pediatric clinics of North America. Philadelphia: Lippincott; 2000. p. 487–512.
6. Bonica JJ. The management of pain, vol. 1. 2nd ed. Pennsylvania: Lea and Febiger; 1990.
7. Fitzgerald M, Howard RF. The neurobiologic basis of pediatric pain. In: Schecter NL, Berde CB, Yaster M, editors. Pain in infants, children and adolescents. 2nd ed. Philadelphia: Lippincott; 2003. p. 19–42.
8. Hu P, McLachlan EM. Long-term changes in the distribution of galanin in dorsal root ganglia after sciatic or spinal nerve transection in rats. Neuroscience. 2001;103(4):1059–71.
9. Bago M, Dean C. Sympathoinhibition from ventrolateral periaqueductal gray mediated by 5-HT(1A) receptors in the RVLM. Am J Physiol Regul Integr Comp Physiol. 2001;280(4):R976–84.
10. Holmberg K, Shi TJ, Albers KM, Davis BM, Hokfelt T. Effect of peripheral nerve lesion and lumbar sympathectomy on peptide regulation in dorsal root ganglia in the NGF-overexpressing mouse. Exp Neurol. 2001;167(2):290–303.
11. Scislo TJ, Kitchen AM, Augustyniak RA, O'Leary DS. Differential patterns of sympathetic responses to selective stimulation of nucleus tractus solitarius purinergic receptor subtypes. Clin Exp Pharmacol Physiol. 2001;28(1–2):120–4 (review).
12. Chabal C. Membrane stabilizing agents and experimental neuromas. In: Fields HL, Liebeskind JC, editors. Pharmacological approaches to the treatment of chronic pain: new concepts and critical issues, Progress in pain research and management, vol. 1. Seattle: IASP Press; 1994. p. 205–10.

13. Halligan PW, Zeman A, Berger A. Phantoms in the brain. Question the assumption that the adult brain is "hard wired.". BMJ. 1999; 319(7210):587–8.
14. Centre for Synaptic Plasticity. http://www.bris.ac.uk/Depts/Synaptic/info/glutamate.html.
15. Dev KK, Henley JM. The regulation of AMPA receptor-binding sites. Mol Neurobiol. 1998;17(1–3):33–58.
16. Parpura V, Basarsky TA, Liu F, Jeftinija K, Jeftinija S, Haydon PG. Glutamate-mediated astrocyte-neuron signalling. Nature. 1994;369(6483):707–8.
17. Dendorfer A, Wolfrum S, Dominiak P. Pharmacology and cardiovascular implications of the kinin-kallikrein system. Jpn J Pharmacol. 1999;79:403–26.
18. Skidgel RA, Alhenc-Gelas F, Campbell WB. Relation of cardiovascular signaling by kinins and products of similar converting enzyme systems; prologue: kinins and related systems. New life for old discoveries. Am J Physiol Heart Circ Physiol. 2003;284: H1886–91.
19. Dendorfer A, Wolfrum S, Wagemann M, Qadri F, Dominiak P. Pathways of bradykinin degradation in blood and plasma of normotensive and hypertensive rats. Am J Physiol Heart Circ Physiol. 2001;280:H2182–8.
20. Kuoppala A, Lindstedt KA, Saarinen J, Kovanen PT, Kokkonen JO. Inactivation of bradykinin by angiotensin-converting enzyme and by carboxypeptidase N in human plasma. Am J Physiol Heart Circ Physiol. 2000;278(4):H1069–74.
21. Kozlowska M, Smolenski RT, Makarewicz W, Hoffmann C, Jastorff B, Swierczynski J. ATP depletion, purine riboside triphosphate accumulation and rat thymocyte death induced by purine riboside. Toxicol Lett. 1999;104(3):171–81.
22. Kondo M, Yamaoka T, Honda S, et al. The rate of cell growth is regulated by purine biosynthesis via ATP production and G1 to S phase transition 1. J Biochem. 2000;128(1):57–64.
23. Yegutkin GG, Samburski SS, Jalkanen S. Soluble purine-converting enzymes circulate in human blood and regulate extracellular ATP level via counteracting pyrophosphatase and phosphotransfer reactions. FASEB J. 2003;17(10):1328–30. Epub 2003 May 20.
24. Schurmann M, Gradl G, Wizgal I, Tutic M, Moser C, Azad S, Beyer A. Clinical and physiologic evaluation of stellate ganglion blockade for complex regional pain syndrome type I. Clin J Pain. 2001; 17(1):94–100.
25. Cleary AG, Sills JA, Davidson JE, Cohen AM. Reflex sympathetic dystrophy. Rheumatology (Oxford). 2001;40(5):590–1.
26. Ceballos A, Cabezudo L, Bovaira M, Fenollosa P, Moro B. Spinal cord stimulation: a possible therapeutic alternative for chronic mesenteric ischaemia. Pain. 2000;87(1):99–101.
27. McCleane G. Pharmacological strategies in relieving neuropathic pain. Expert Opin Pharmacother. 2004;5(6):1299–312.
28. Manning DC. New and emerging pharmacological targets for neuropathic pain. Curr Pain Headache Rep. 2004;8(3):192–8.
29. Cousins MJ, Mather LE. Intrathecal and extradural administration of opioids. Anesthesiology. 1984;61:276–310.
30. Chaney MA. Side effects of intrathecal and extradural opiates. Can J Anaesth. 1995;42:891–903.
31. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci. 2004;101(26):9861–6.
32. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganisation in complex regional pain syndrome. Neurology. 2003;61(12):1707–15.
33. Buskila D, Neumann L, Press J. Genetic factors in neuromuscular pain. CNS Spectr. 2005;10(4):281–4.
34. Finegold AA, Mannes AJ, Iadarola MJ. A paracrine paradigm for in vivo gene therapy in the central nervous system: treatment of chronic pain. Hum Gene Ther. 1999;10(7):1251–7.
35. Kaye P. Pocket book of symptom control. Northampton: EPL Publications; 1994. p. 72.
36. Smith O. Pain-killer genes. Science. 1999;284(5420):1634.
37. Currie JM. Management of chronic pain in children. Arch Dis Child. 2006;91:111–4.