The anaesthetist’s role in acute sickle cell crisis

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Over the past 30 years, there has been a significant increase in the life expectancy of patients suffering from sickle cell disease (SCD). In the early 1970s the median life expectancy was only 14.3 yr, whereas in the 1990s this has risen to 42 yr for men and 48 yr for women.22 51 Nevertheless, there is a definite need to improve further the management of the acute complications of SCD, as these continue to cause significant morbidity and mortality. Furthermore, many patients are dissatisfied with their management during hospital admission.26 We believe that the acute clinical problems of SCD, including pain, acute chest syndrome, thrombo-embolic disease and overwhelming infection, need expert management by a multidisciplinary team. Pain is by far the most common indication for hospital admission in these patients.13 15 3 The primary requirement of the patient is therefore adequate pain relief. As a result of recent developments in the administration of analgesia, acute pain teams and, in particular, anaesthetists have become involved in the management of these patients with complex medical problems. In addition, the anaesthetist may be involved in the treatment of patients with sickle cell crisis perioperatively and in the intensive care unit.

Pathophysiology of sickle cell disease

Sickle cell disease (SCD) is a complex clinical entity characterized by an inherited, chronic haemolytic anaemia that is punctuated by a variable number of acute, painful vaso-occlusive episodes. The fundamental defect is the presence of a mutant haemoglobin (HbS) within the red cells of affected individuals; the defect is the consequence of a single-point mutation within the β-globin gene. This mutation results in a valine substitution for glutamic acid at position, six of the β-globin molecule. The result is that, when the haemoglobin tetramer undergoes conformational change following deoxygenation, the hydrophobic valine residue is translocated to an external position on the globin molecule. In that position it interacts with other hydrophobic elements within neighbouring globin chains to form insoluble globin polymers. Polymerization of HbS after deoxygenation is the fundamental molecular event that underlies the protean clinical manifestations of SCD.

Vaso-occlusion

Vaso-occlusion is the single most important pathological process that results in most of the acute complications of SCD.26 Haemoglobin polymerization is the initial step in this process and significantly increases whole-blood viscosity. However, polymerized HbS rapidly reverts to normal once the haemoglobin molecule is re-oxygenated and the formation of irreversibly sickled cells (ISCs) is required for vaso-occlusion to occur. ISCs are formed as a consequence of irreversible oxidative damage to the cell membrane after repeated cycles of red cells sickling and unsickling. The oxidative damage occurs because Hbs, in addition to having a propensity for polymerization, is an unstable haemoglobin and when exposed to oxidant stress elaborates a range of oxygen radicals. These highly reactive molecular species damage a wide variety of cytoplasmic, cytoskeletal and membrane proteins. The resultant ISCs have poor deformability and are prone to cellular dehydration; they are therefore removed prematurely from the circulation by the reticuloendothelial system. The altered membrane of sickled cells results in abnormal erythrocyte adhesion to endothelial cells and it is this process that initiates vascular occlusion.30 The extent of sickle cell adhesion to endothelium in vitro is directly correlated with the clinical severity of vaso-occlusive phenomena in individual patients.33 Once microvascular occlusion has occurred, the resultant hypoxia causes further sickling and the start of a vicious cycle that results in tissue infarction, the release of inflammatory cytokines and pain. The pathophysiology of the microvascular occlusion that occurs in SCD is discussed in more detail later.

Genotypes and phenotypes in SCD

SCD most commonly occurs in individuals who have the SS genotype, although patients heterozygous for Hbs and β-thalassaemia (Hbs/Bthal) or Hbs and haemoglobin C (HbsC) display a similar clinical phenotype. Sickle cell disease is increasingly prevalent in the UK, particularly in urban areas, and there are around 2000 patients in London alone. It is interesting that such a harmful mutation has not been eradicated from the gene pool by negative selection.
Managing pain during acute sickle cell crisis

selection pressure; the explanation appears to be that heterozygotes have a survival advantage over normals when infected by the malarial parasite *Plasmodium falciparum*. However, individuals with SCD itself are exquisitely vulnerable to overwhelming malarial infection.

The clinical phenotype of SCD is characterized by repeated vaso-occlusive events that can result in acute pain crisis, acute chest syndrome, priapism, stroke, skin ulceration and, in children, splenic sequestration. Autoinfarction of the spleen results in functional hyposplenism that is usually manifest by the age of 7 yr. This, together with a variety of other defects in opsonization, phagocytic function and cell-mediated immunity, results in a greatly increased risk of systemic bacterial infection and infections at unusual sites, such as osteomyelitis and splenic abscesses. Patients also suffer from a chronic haemolytic anaemia that results in poor growth, reduced fertility and gallstones. Erythropoiesis, while attempting to compensate for the rapid haemolysis, operates at near maximal levels; this renders the patient highly vulnerable to any further insult, such as folate deficiency, or Parvovirus infection, which causes pure red cell aplasia. In communities with inadequate parental education and poor availability of medical care, the major causes of early death in patients with SCD are overwhelming bacterial infection, splenic sequestration and, in tropical areas, malaria.

**Clinical features**

The two major acute complications of SCD that are likely to involve the anaesthetist are the acute pain crisis and the acute chest syndrome.

**The acute pain crisis**

Acute pain in SCD is thought to be caused by vascular occlusion and, in the case of bone pain, the consequent release of inflammatory mediators that results in raised intramedullary pressure and stimulation of nociceptors. Pain is the commonest manifestation of SCD after the age of 2 yr and painful episodes are most frequent from 20–40 yr of age. Large studies of the epidemiology and clinical presentations of pain crisis have highlighted several important points. The average rate of painful episodes is 0.8 per patient-year in sickle cell anaemia; however, 1% of these patients have more than six episodes per year, whereas some experience none. Medical staff working in the acute health-care sector are likely to see only a few severely affected patients and may well develop misconceptions about the natural history of SCD. The extreme variability in severity of the clinical phenotype is largely unexplained. However, several important risk factors for recurrent painful episodes have been identified. SS or S/αThal patients (αThal indicates absence of α globin chain synthesis from the affected gene) tend to have more pain than those with the genotype S/βThal (βThal indicates reduced β globin chain synthesis from the affected gene) or SC, although many individuals with ‘milder’ genotypes experience more pain episodes than individuals with ‘severe’ genotypes. Patients with raised levels of haemoglobin F (ααγγ), which inhibits the polymerization of HbS, have fewer painful episodes. Paradoxically, patients with lower haemoglobin levels have less pain. This is likely to be the result of lower whole blood viscosity associated with a lower haematocrit. This observation also explains why patients with coexistent α-thalassaemia trait, which results in a higher haematocrit, do not have a more benign clinical phenotype. Patients with more than three pain episodes per year are at a significantly increased risk of early death. Among patients with repeated painful episodes, a few develop a chronic pain syndrome that results in restricted activity, fear of further pain and a high risk of depression.

The ability to predict which individuals affected by sickle cell disease will go on to manifest a severe clinical phenotype would be of great clinical benefit. If such individuals could be identified in early life, they could be offered bone marrow transplantation in childhood, when this procedure is best tolerated.

Numerous precipitating factors have been identified for acute pain crises. Pain is more likely to start at night, perhaps because of nocturnal desaturation or relative dehydration. Other potential precipitants...
are exposure to cold, dehydration, alcohol intake, stress, menstruation and intercurrent infections. However, 57% of episodes have no identifiable precipitant. The lumbar spine, femur, knee, sternum and abdomen are the most commonly affected sites. It is uncommon for pain to affect only one area and usually two or three sites are involved. An intriguing observation is the high frequency of symmetrical, bilateral bony pain. This observation has prompted the hypothesis that marrow ischaemia might result from a centrally mediated reflex that shunts blood flow away from the medullary cavity.

The acute pain crisis is accompanied by fever in approximately 50% of cases but only in a few is an infective aetiology confirmed. The occurrence of fever, leucocytosis and an acute-phase response without evidence of microbiological infection has led to the consensus view that the acute pain crises itself initiates an acute inflammatory syndrome. Increasing knowledge about the adhesive mechanisms operating between circulating blood cells and vascular endothelium has allowed the development of a unifying hypothesis that models the acute vaso-occlusive crisis.

Either a concurrent infective episode or an initial minor sickling event results in the elaboration by monocytes and macrophages of the inflammatory cytokines interleukin-1 (IL-1), tumour necrosis factor (TNF) and IL-6. These cytokines cause the upregulation of a variety of cell adhesion molecules (CAMs) on endothelial cells such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selection. The presence of these and other cytokines also leads to neutrophil activation, increased levels of pro-adhesive plasma proteins, such as fibrinogen and von Willebrand factor, and in the activation of the haemostatic system (fig. 1).

Alternatively, viral nucleic acid itself can induce CAM expression by endothelial cells. Whatever the exact mechanism of upregulation, these endothelial CAMs can now mediate the adhesion of circulating cells. Normal mature red cells lack the necessary counter-receptors that bind to these CAMs but young reticulocytes, which are present in increased numbers in sickle cell disease, express CD36 and the integrin molecule VLA-4 and therefore bind to endothelium via VCAM-1 (fig. 2).

It has been clearly established that sickle reticulocytes bind to vascular endothelium using this VLA-4/VCAM-1 adhesive pathway. These cells are therefore retained in the relatively hypoxic environment of the postcapillary venule. Red cell sickling occurs then results in microvascular occlusion and distal ischaemia. Thus the vicious cycle of red cell sickling and vascular occlusion as outlined above is started and reinforced.

Furthermore, endothelial CAMs induced by inflammatory cytokines also bind platelets and neutrophils (via P-selectin, E-selectin and ICAM-1). Microvascular occlusion and resultant hypoxia, in addition to the release of proteolytic enzymes by the neutrophil, result in further endothelial damage (fig. 2). In turn, this is likely to activate the coagulation system, with consequent deposition of fibrin further obstructing blood flow (fig. 3).
Evidence for activation of the coagulation system in SCD exists. There are increased levels of prothrombin fragments 1 and 2 and of fibrinopeptide A in steady SCD.\(^{49}\) Early attempts to reverse this prethrombotic state with oral anticoagulation achieved a reduction of acute painful crises but at the cost of an unacceptably high risk of haemorrhage.\(^{46}\) More recently, it has been realized that low-dose coumarin therapy can normalize this prethrombotic state, although it is uncertain whether this approach can be of benefit in preventing the acute crises of SCD.\(^{72}\)

The acute pain crisis of SCD results from the cumulative effects of HbS polymerization, red cell sickling, sickle cell adhesion to vascular endothelium and fibrin deposition; all of these act together to cause microvascular occlusion.

**PREVENTION OF PAIN CRISIS IN SCD**

Various methods have been tried over the past few years to prevent or reduce recurrent sickle cell crises. Hydroxyurea and other agents have been used in an attempt to increase the production of HbF, inhibiting HbS polymerization.\(^{30,56}\) Induced hyponatraemia has been used to reduce the erythrocyte HbS concentration, but has proved impractical.\(^{57}\) Advice on lifestyle can be useful, such as avoiding excess alcohol consumption; the consequent dehydration can precipitate a pain crisis.

**Pre-operative transfusion**

Surgery is a time of special risk for patients with SCD and in an attempt to reduce complications, including painful crises, it has become standard practice to consider the use of preoperative blood transfusions. In a large retrospective study of surgery in SCD\(^{40}\) there was in general no correlation between the rate of postoperative complications and the HbA level (which is directly proportional to the extent of red cell transfusion). Furthermore, the rate of complications after minor procedures was low in patients who had received no transfusions. A recent prospective study evaluated the relative efficacies of an aggressive perioperative transfusion policy (aimed at reducing the HbS level to below 30%) and a conservative policy (aimed at raising the Hb level to above 10 g dl\(^{-1}\)) in patients with SCD undergoing elective surgery. The frequency of serious complications was similar in both groups but there were twice the number of transfusion-related complications, especially the development of red cell alloantibodies, in the aggressively transfused group.\(^{50}\)

Therefore, in patients about to undergo elective procedures of intermediate or high risk, a relatively conservative transfusion programme aimed at raising the Hb to above 10 g dl\(^{-1}\) can be recommended. For minor procedures, there appears to be little benefit in perioperative transfusion. In contrast, patients who require emergency surgery are often those at greatest risk of postoperative SCD-related complications. The optimal transfusion support for individual patients should be discussed by the surgeon, anaesthetist and haematologist.

**MANAGEMENT OF CRISIS**

The mainstays of management of pain crisis are analgesia and fluid replacement. Oral or intravenous fluids are required to prevent dehydration, which results in a raised haematocrit and increased sickling. Although fever may be a simple consequence of sickling, the presence of fever should prompt a search for an infective focus and cultures of blood, urine and sputum should be taken as indicated.

As there is a high risk of bacterial infection in patients with SCD, most clinicians would recommend the use of broad-spectrum antibiotics in the presence of fever. Functional hyposplenism makes these patients susceptible to streptococcal infection; and the chosen agent (e.g. amoxycillin) must have good activity against *Streptococcus pneumoniae*. Blood transfusion has a place in acute crisis only in the presence of the acute chest syndrome (see below) or stroke, or when a pain crisis is refractory to standard therapy or relapses quickly. In view of the considerable inflammatory element in the acute pain crisis, a trial of high-dose methylprednisolone — two doses of 15 mg kg\(^{-1}\), 24 h apart, has been undertaken. The requirement for opioid analgesia was considerably reduced in the steroid-treated group, and the mean duration of analgesic treatment was reduced from 71.3 to 41.3 h. However, a high rate of rebound attacks was observed and this, in addition to fear of the long-term complications of steroid therapy, has restricted the use of this treatment strategy.\(^{62}\)

Most painful episodes are managed at home by the patients themselves, with oral analgesia and fluids. Episodes of crisis may last from a few minutes to weeks and the severity and location of the pain may vary from time to time or involve the whole body.\(^{60,61}\) Younger children often suffer from limb pain. In contrast, in adolescents, abdominal pain may become the prominent symptom. The few crises that result in hospital attendance often require more intensive analgesia. Accident and emergency staff with limited experience of SCD may underestimate the severity of pain, because no objective criteria accurately quantify it. The result may be unnecessary suffering, inadequate pain control or misinterpretation of the patient’s demands.\(^{12}\) The pain of sickle cell crisis is probably one of the most severe forms of pain. The intensity and description of pain during crisis have been studied and the average pain severity score was 9.5 ± 0.63 on a 10 cm visual analogue scale.\(^{7}\)

The use of large doses of opioids for pain relief has raised concerns about the risk of drug dependence,\(^{43}\) but this has been disputed. In a 1986 survey of 610 patients with sickle cell disease from five institutes in a North London borough, none was known to be addicted, in spite of a local policy of using strong opioids to relieve the pain of crisis.\(^ {14}\) Similarly the use of parenteral opioids is widespread in major sickle cell disease treatment centres in the USA.\(^ {37}\) Clinicians working in tropical countries and those in Britain and the USA seem to diverge markedly in their views on the need for opioids.\(^ {38}\)

It is important to distinguish between tolerance to opioids and addiction. Most patients with sickle cell
crisis requiring prolonged treatment with opioids will develop tolerance, and on discontinuing opioids exhibit some signs of withdrawal. The latter can be minimised by a gradual withdrawal of opioids. Clinicians who are relatively inexperienced in the management of sickle cell crisis may interpret evidence of tolerance or withdrawal as being indicative of a state of addiction, and understandably this may cause considerable patient distress. But it is vital to realize that many episodes of pain are under-treated. This undertreatment will lead to an increased fear of future episodes and may well contribute to the development of a chronic pain syndrome. The patient’s ability to cope with the present painful situation depends on his or her previous experience of pain relief and the treatment received in hospital, as well as family relationships and social circumstances. The unpredictability and severity of these crises may result in the phenomenon of “learned helplessness” observed in animals. When these animals are exposed to repetitive, unpredictable shocks, their ability to escape shocks in future become severely impaired.

AN INVISIBLE CHRONIC ILLNESS

In common with other chronic pain syndromes, there appears to be considerable variation in the coping abilities of patients with sickle cell disease. Among children, frequent hospital admissions with painful crises, separation from the family and feelings of ‘being different’ seem to be significant problems. Cohesive family relationships as well as sympathetic staff at school and hospital all seem to improve coping mechanisms. For adolescents, anxieties about delayed physical maturity combined with interruption of normal teenage activities can result in feelings of isolation. These factors, together with fears of a potential early death or of academic failure, are among the main reasons for the psychological instability in this group of patients. The lack of visible stigmata associated with SCD may prompt mistrust and suspicion on the part of care providers and family members, resulting in a loss of self-esteem, and suspicion on the part of care providers and family members, resulting in a loss of self-esteem, and in the formation of a state of addiction, and understandably this may cause considerable patient distress. But it is vital to realize that many episodes of pain are under-treated. This undertreatment will lead to an increased fear of future episodes and may well contribute to the development of a chronic pain syndrome. The patient’s ability to cope with the present painful situation depends on his or her previous experience of pain relief and the treatment received in hospital, as well as family relationships and social circumstances. The unpredictability and severity of these crises may result in the phenomenon of “learned helplessness” observed in animals. When these animals are exposed to repetitive, unpredictable shocks, their ability to escape shocks in future become severely impaired.

MODES OF ANALGESIA IN SCD

The choice of analgesic drugs includes nonsteroidal anti-inflammatory agents (NSAIDs), which are particularly helpful for bone pain, and a variety of opioid analgesics (see below). In certain situations, the use of local anaesthetics and extradural anaesthesia can be considered. Analgesics ranging in potency from paracetamol to strong opioids can be administered orally during a crisis without the need for an intravenous cannula. However, the onset of such analgesia is then not immediate and the efficacy depends upon the rate of absorption and bioavailability. Absorption may also be influenced by the presence of nausea and vomiting.

Transdermal administration

Transdermal fentanyl patches are effective in postoperative pain. These patches are easy to administer and contain multiday dosage, but stable plasma levels may not be reached for 12 h after application. The main disadvantages of the patches are that analgesia is slow in onset and difficult to titrate against response, and that a residual depot is left after removal of the patch. We have used fentanyl patches successfully in a few patients in the later stages of admission for acute sickle cell crisis and have discharged the patients home with them.

Intramuscular administration

The intramuscular route offers simplicity with a relatively rapid onset of analgesia after injection. This mode of delivery may be useful for initial analgesia when the patient arrives in hospital before the establishment of venous access, which can itself be problematic. However, repeated intramuscular injections are painful and may result in myofibrosis, myositis and the formation of abscesses. In addition, pain relief may be inadequate because the rate of absorption is unpredictable. The peak concentration of pethidine may vary two-fold and time to reach peak concentration may vary three-fold with repeated intramuscular injections in the same patient. Subcutaneous infusions are simple and effective but the unpredictable rate of absorption from the site results in a variable quality of analgesia.

Intravenous administration

Venous access is almost always required for hydration and for the administration of antibiotics. Early involvement of anaesthetists from the acute pain team may lessen the problems encountered when attempting to secure i.v. access. Analgesia by continuous i.v. infusion is safe and effective. Doses required may be higher than those used for the routine management of postoperative pain. A protocol described for children recommended a loading dose of pethidine 1.0 mg kg\(^{-1}\) followed by an infusion of 0.5 mg kg\(^{-1}\) h\(^{-1}\) although some patients required doses up to 1.5 g kg\(^{-1}\) h\(^{-1}\). When this protocol was used in a series of 98 patients, none exhibited signs of dependency or withdrawal when the infusion was discontinued. Severity of pain may fluctuate with time and continuous infusions may provide inadequate pain relief or a risk of overdosage. This is illustrated in a case report of a boy aged 15 yr, in whom the uncontrolled administration of morphine, without proper monitoring and in the presence of decreasing pain, led to respiratory depression, acidosis, increased sickling, and ultimately cardiopulmonary arrest.

Patient-controlled analgesia

Patient-controlled analgesia (PCA) is widely used for pain relief after surgery and may well be superior to more traditional methods of pain relief; however, its place in the management of sickle cell crisis has yet to be fully established. Nevertheless, in sickle cell crisis,
PCA has been reported to improve the adequacy of pain relief when the latter is suboptimal because of insufficient dosage or delay in administration. It can also match the individual variability of analgesic demand and enables the patient to administer his or her own analgesia. A prospective controlled trial of morphine PCA in patients with SCD, using bolus mode only, showed that PCA was as effective as an aggressive fixed schedule of intermittent, nurse-administered i.v. injections of morphine. Among the advantages of PCA identified by nurses in this study were convenience and increased involvement of patients with their own care. The disadvantages included a long set-up time. Of these patients, 80% described the PCA analgesic regimen as good to excellent.

One difficulty with fixed dosing when compared with PCA is the enormous variability of opioid pharmacokinetics. A recent study of morphine use in children with sickle cell disease found morphine clearances ranging from 6.2 to 59 ml min⁻¹ kg⁻¹. In another series of 46 children and adolescents receiving morphine, nalbuphine or hydromorphone PCA, 30% had problems. Eleven patients disliked the technique, one patient required naloxone and one tampered with the machine. To reduce the need for extra venepuncture, the main i.v. infusion line can be used for the PCA if an anti-reflux valve is used.

All patients should be monitored with a pain chart. In our unit, pain scores achieved with PCA were less satisfactory in patients with acute sickle cell crisis compared with those recovering from surgery. With a five-point pain score, 95% of observations in postoperative patients were below 3, whereas only 26% of those in patients with acute sickle cell crisis had a pain score of less than 3. Many patients with sickle cell crisis felt comfortable enough to request discontinuation of their PCA, while still recording their pain as severe. Most patients with sickle cell crisis require both a background infusion and demand dosing during the initial acute episode. The background infusion is tailored with improving pain scores before discontinuing the demand dosing, but the presence of a background infusion may reduce the safety of this technique. Tolerance to the effect of opioids can develop rapidly and it is not uncommon for patients to require very large doses at some period during their admission. With large doses, problems such as pruritus, dysphoria, hallucinations and respiratory depression can be troublesome, with many patients requiring antipruritic and antiemetic agents.

**Slow-release oral opioids**

An alternative strategy is to manage the pain of sickle cell disease in the same way as one would manage pain associated with cancer. Thus, rather than offering strong analgesia only during admissions for severe crisis, one may prescribe regular slow-release morphine to outpatients with the addition of a small amount of standard morphine for breakthrough pain. The authors who tried this approach claimed a dramatic reduction in hospital admissions. However, a subsequent report suggested that this observation might be the result of patients attending alternative institutions for their care. It is well known that patients with sickle cell disease will transfer to another institution if a new or unpopular analgesic regimen is introduced, particularly the substitution of other opioids for pethidine.

**Extradural analgesia**

Extradural analgesia has been used in the management of acute sickle cell crisis. Recent evidence suggests that it might be superior in sickle cell patients with localized pain who are unresponsive to high-dose systemic opioids, nonsteroidal drugs or adjunctive measures. Continuous local anaesthetic infusions and a combination of local anaesthetic with fentanyl seem to be effective with minimal opioid-related side-effects. Inadvertent dural puncture and hypotension following a higher block may be a concern.

**PHARMACOLOGICAL AGENTS FOR SICKLE CELL CRISIS**

**Opioid analgesics**

Opioid analgesics agents bind to specific opioid receptors — μ, κ and σ — and block slow transmission of pain. Efficacy of analgesia and unwanted side-effects are determined by the relative affinity of these agents for the individual receptors. Pethidine seems to be the opioid chosen most often by sickle cell patients. Familiarity, degree of predictability and belief that pethidine produces a rapid onset of analgesia with less "hangover", make pethidine the first choice for many patients with sickle cell crisis. In comparison of pethidine with morphine in children, subjective side-effects including lethargy, abdominal distension, constipation, pruritus and wheezing were less common with pethidine, although dizziness was more common. The main disadvantage of pethidine is attributable to its metabolite, norpethidine. Norpethidine significantly stimulates the central nervous system and daily doses of pethidine in excess of 25 mg kg⁻¹ are associated with blood levels of norpethidine high enough to precipitate convulsions. In a survey of 21 major centres treating sickle cell disease in the USA, nine reported problems with pethidine-associated convulsions. The recognized risk factors for norpethidine-related convulsions are renal failure, high pethidine dosage and co-administration of hepatic enzyme inducers.

Pethidine has also been shown in dogs to impair cardiac performance by reducing myocardial contractility when doses exceed 2 mg kg⁻¹. For these reasons it is widely accepted by physicians looking after patients with acute sickle cell crisis that pethidine should be avoided whenever possible. However, this may prove unacceptable to a few patients with sickle cell crisis who may insist on the drug. It is advisable not to use pethidine as a first-choice analgesic for new patients or those unfamiliar with pethidine, but reserve it for those patients who experience unacceptable side-effects, such as pruritus, with other strong analgesics.

Morphine is often used as the opioid of choice for initial treatment, when a strong analgesic is required. Excessive sedation is a recognized problem, in addition to other opioid-related side-effects such as itching, respiratory depression, nausea and vomiting. In
the presence of renal impairment, morphine-6-glucuronide, which is an active metabolite of morphine, may accumulate and cause respiratory depression. However, one study was unable to identify any opioid-sparing activity using ketorolac in the emergency room. The antiplatelet activity of these compounds may also be beneficial in patients with renal failure and mild hepatic dysfunction. It is relatively nonsedative and can be used in patients with renal failure and mild hepatic dysfunction.

Fentanyl administered by PCA is the analgesic mode of choice in our unit.

**Nonopioid agents**

Aspirin and other NSAIDs can be of use in bony crisis, to alleviate mild to moderate pain and as an adjunct to opioids in a severe crisis. However, one study was unable to identify any opioid-sparing activity using ketorolac in the emergency room. The antiplatelet activity of these compounds may also be beneficial in patients who are susceptible to venous thrombosis. However, in view of the renal impairment associated with NSAIDs, care must be taken with their use.

**Adjuvant drugs**

Patients with SCD may develop features of a chronic pain syndrome. Some psychotropic drugs, particularly tricyclic antidepressants such as amitriptyline, possess analgesic properties that may be useful in the management of SCD. These agents inhibit the reuptake of noradrenaline and 5-hydroxytryptamine, which are released by descending systems of supraspinal origin, thus modulating the nociceptive input into the spinal cord. Benzodiazepines are of value in relieving muscle spasm, anxiety and insomnia.

**NON PHARMACOLOGICAL METHODS OF PAIN CONTROL**

Non pharmacological methods of pain control are used to alleviate stress, to increase the individual’s ability to cope with acute and chronic pain, and to improve the patient’s sense of well-being. Although these methods have not been extensively tested in sickle cell disease, some modalities such as diversion techniques, self-motivation, massage and mechanical stimulation are beneficial in some patients. The main value of stimulation techniques may be in the treatment of localized pain. Cognitive-behavioural methods modulate the affective response to pain by acting at the level of the cerebral cortex, limbic system and reticular formation.

Self-hypnosis, bio-feedback, relaxation and cognitive methods have been used successfully in reducing pain symptoms, hospital admissions and the use of opioids during painful episodes. Recently, acupuncture has been found to be effective in treating a few patients with sickle cell crisis when conventional therapies have failed.

**The acute chest syndrome**

The acute chest syndrome (ACS) is one of the most serious complications of SCD, with a mortality approaching 10%. Its pathogenesis is not clearly understood. Bacterial pneumonia, pulmonary thromboembolism and infarcted marrow embolism can all cause acute respiratory compromise. Many cases have no recognizable infective or embolic causation. Progressive pulmonary fibrosis has been detected in children with multiple episodes of acute chest crisis. Typically, such cases present with an acute pain crisis, often affecting the lower chest wall. Patients quickly develop fever, cough, chest signs, radiological changes — usually affecting the bases of the lungs — and oxygen desaturation on air. The radiological changes may be delayed. A substantial number of these patients have rib infarcts and it is thought that the resulting splinting of the lower chest wall with basal hypoventilation results in rapidly progressive intrapulmonary vaso-occlusion, hypoxaemia, increasing pulmonary problems and ACS.

Evidence for this model is the reduced development of pulmonary complications with the use of prophylactic incentive spirometry. There are concerns that narcotic analogues, with their associated respiratory suppression, may contribute to the acute chest syndrome, although adequate analgesia is probably essential to prevent atelectasis.

The acute chest syndrome should be treated as a medical emergency and adequate oxygenation ensured by increased inspired oxygen concentrations; continuous positive airway pressure (CPAP) to

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**Table 1 Guidelines for pain relief in sickle cell crisis (Royal London Hospital)**

| Preferred mode of analgesia is patient-controlled analgesia (PCA) using i.v. fentanyl |
| Intermittent analgesia by i.m. injection may be the patient’s preferred option. Suitable regimens for an adult would be: |
| Morphine 7.5–15 mg, every 2–4 h |
| Diamorphine 2.5–5.0 mg, every 2–4 h |
| Cyclizine 50 mg, every 6–8 h for anti-emesis |
| Dosage may be adjusted according to: |
| 1. Previous drug regimen |
| 2. Severity of pain |
| 3. Size of the patient |

NSAIDs should be prescribed, unless contraindicated in a particular patient

Monitor pain management. Start pain chart when giving initial analgesia.
maintain ventilation of the lung bases; and, if necessary, mechanical ventilation. The early use of exchange transfusion, with the aim of achieving an HbS% of more than 30% will abort further deterioration and usually reverses respiratory failure within 1–2 days. An alveolar-arterial oxygen gradient of more than 30 mm Hg on air is a predictor of both clinical severity and the need for exchange blood transfusion. The rapidity of the response to exchange transfusion strongly supports the theory that reversible vaso-occlusion, rather than thromboembolism or infection, is the major pathophysiological process in ACS. However, an infective aetiology can never be excluded in an individual case and it is mandatory to treat patients with broad-spectrum antibiotics active against common respiratory bacteria and atypical pathogens.

Conclusion

Most patients with sickle cell disease are managed in the community by their general practitioner in consultation with haematologists and specialist nurses. However, as patients in crisis may arrive outside routine working hours, their first medical contact may be with a relatively inexperienced junior doctor. We recommend therefore that management guidelines are provided for the initial management of patients presenting with the acute complications of SCD (table 1).

Undoubtedly, on arrival at hospital, the primary requirement for patients with sickle cell crisis is adequate analgesia followed by admission to a dedicated unit. This can best be achieved by careful teamwork involving haematologists, ward nurses and members of the acute pain team.

Management of the acute pain crisis should be seen in the context of the overall long-term strategy for the care of patients with SCD, which should include patient education, prophylactic folic acid and penicillin V. Vaccination against the organisms most likely to cause problems in the hyposplenic individual (namely *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b) is appropriate.

Various approaches have been tried, or are under investigation, in an attempt to reduce the frequency of acute painful crises. Regular exchange blood transfusion with appropriate iron chelation, antiinflammatory drugs, agents that prevent sickle cell dehydoration and drugs that increase the haemoglobin F concentration are among such strategies. Combined input from pain specialists, anaesthetists, haematologists, sickle cell nurse specialists and psychologists, together with the formation of self-help groups, will undoubtedly improve the quality of the service provided for these patients.

References


