

TOXICITY FROM LOCAL ANAESTHETIC DRUGS

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Introduction

Toxic side effects of local anaesthetic drugs occur when excessive blood levels occur. This is usually due to:

- Accidental rapid intravenous injection.
- Rapid absorption, such as from a very vascular site ie mucous membranes. Intercostal nerve blocks will give a higher blood level than subcutaneous infiltration, whereas plexus blocks are associated with the slowest rates of absorption and therefore give the lowest blood levels.
- Absolute overdose if the dose used is excessive.

Reducing the risk of toxicity

- Decide on the **concentration** of the local anaesthetic that is required for the block to be performed. Calculate the **total volume** of drug that is allowed according to the table below.
- Use the least toxic drug available.
- Use lower doses in frail patients or at the extremes of ages.
- Always inject the drug slowly (slower than 10ml / minute) and aspirate regularly looking for blood to indicate an accidental intravenous injection.
- Injection of a test dose of 2-3ml of local anaesthetic containing adrenaline will often (but not always) cause a significant tachycardia if accidental intravenous injection occurs.

- Most nerve blocks are more dependent on **volume** of drug injected than the **total dose**. Therefore if more volume is needed it is better dilute the local anaesthetic with 0.9% saline than to add more local anaesthetic and increase the dose unnecessarily.
- Add adrenaline (epinephrine) to **reduce the speed of absorption**. The addition of adrenaline will reduce the maximum blood concentration by about 50%. Usually adrenaline is added in a concentration of 1:200,000, with a maximum dose of 200 micrograms. This is made up by taking an ampoule of adrenaline with a concentration of 1:1,000 = 1mg/ml = 0.1mg%. From this you take 0.1ml (zero point one millilitres) and add it to each 20ml of the local anaesthetic. **The addition of adrenaline will make no difference to the toxicity of the local anaesthetic if it is injected intravenously.**
- Make sure that the patient is monitored closely by the anaesthetist or a trained nurse during the administration of the local anaesthetic and the following surgery.

Signs and Symptoms of Local Anaesthetic Toxicity

The systemic toxic effects due to local anaesthetic overdose primarily involve the central nervous and cardiovascular systems. In general the Central Nervous System (CNS) is more sensitive to local anaesthetics than the Cardiovascular System (CVS). Therefore CNS manifestations tend to occur earlier. Brain excitatory effects occur before the depressant effects.

Drug	Maximum dose for infiltration	*Maximum dose for plexus anaesthesia
Lignocaine	4mg/kg	5mg/kg
Lignocaine with adrenaline	7mg/kg	7mg/kg
Bupivacaine	2mg/kg	2mg/kg
Bupivacaine with adrenaline	3mg/kg	3mg/kg
Prilocaine	6mg/kg	7mg/kg
Prilocaine with adrenaline / octapressin	8mg/kg	8mg/kg

* when performing intercostal blocks, reduce the dose for infiltration by 25%

CNS signs & symptoms

Early or mild toxicity: light-headedness, dizziness, tinnitus, circumoral numbness, abnormal taste, **confusion** and drowsiness. Patients often will not volunteer information about these symptoms unless asked. **Throughout the injection talk to the patient asking them how they feel. Any suggestion of confusion should alert you to the possibility of toxicity and you should stop any further injection.**

Severe toxicity: tonic-clonic convulsion leading to progressive loss of consciousness, coma, respiratory depression, and respiratory arrest.

Depending on the drug and the speed of the rise in blood level the patient may go from awake to convulsing within a very short time.

CVS signs & symptoms

Early or mild toxicity: tachycardia and rise in blood pressure. This will usually only occur if there is adrenaline in the local anaesthetic. If no adrenaline is added then bradycardia with hypotension will occur.

Severe toxicity: Usually about 4 - 7 times the convulsant dose needs to be injected before cardiovascular collapse occurs. Collapse is due to the depressant effect of the local anaesthetic acting directly on the myocardium. Bupivacaine is considered to be more cardiotoxic than lignocaine. Severe and intractable arrhythmias can occur with accidental iv injection.

The acute toxicity of local anaesthetics is due to the speed of rise of blood concentration. Therefore a rapid injection of a small volume may cause toxicity.

Essential Precautions

- **Always** secure intravenous access before injection of any dose that may cause toxic effects.
- **Always** have adequate resuscitation equipment and drugs available **before** starting to inject.

Treatment of Toxicity

If a patient you are attending shows any signs or symptoms of toxicity during injection of local anaesthetic **stop the injection and assess the patient.**

Treatment is based on the A B C D of Basic Life Support

Call for help while treating the patient

A. Ensure an adequate **airway**, give **oxygen** in high concentration if available.

B. Ensure that the patient is **breathing** adequately. Ventilate the patient with a self inflating bag if there is inadequate spontaneous respiration. Intubation may be required if the patient is unconscious and unable to maintain an airway.

C. Treat **circulatory failure** with intravenous fluids and vasopressors such as ephedrine (10mg boluses) if hypotension occurs. Adrenaline may be used cautiously intravenously in boluses of 0.5 - 1ml of 1:10,000 (1mg in 10ml) if ephedrine is either not available or not effective in correcting the hypotension. Treat arrhythmias.

Start chest compressions if cardiac arrest occurs.

D. Drugs to stop fitting such as Diazepam 0.2-0.4mg/kg intravenously slowly over 5 minutes repeated after 10 minutes if required, or 2.5mg - 10 mg rectally. Thiopentone 1-4 mg/kg intravenously may also be used in theatre.

Observe the patient closely after any reaction.

Treatment of local anaesthetic toxicity is likely to have a good outcome if toxicity is recognised and basic resuscitation is started early. Monitor patients closely when using local anaesthetics. If a reaction occurs:

- Prevent hypoxia which will cause brain damage and make fitting or arrhythmias more difficult to control.
- Ensure that hypotension and arrhythmias are treated early.
- Ensure that fits are adequately treated.
- Most reactions are short-lived if the above advice is followed.

Case History

A 20 year old mother who had just delivered a baby started to fit and then developed a cardiac arrest whilst a midwife was injecting lignocaine prior to suturing her episiotomy. Prompt resuscitation with airway, intubation and ventilation, chest compressions, intravenous fluid and adrenaline saved her life. When the ampoule of lignocaine was checked it was found that the midwife had used 10mls of 10% lignocaine for infiltration (1000mg), more than 5 times the maximum permitted dose for infiltration.

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PAIN IN SICKLE CELL DISEASE

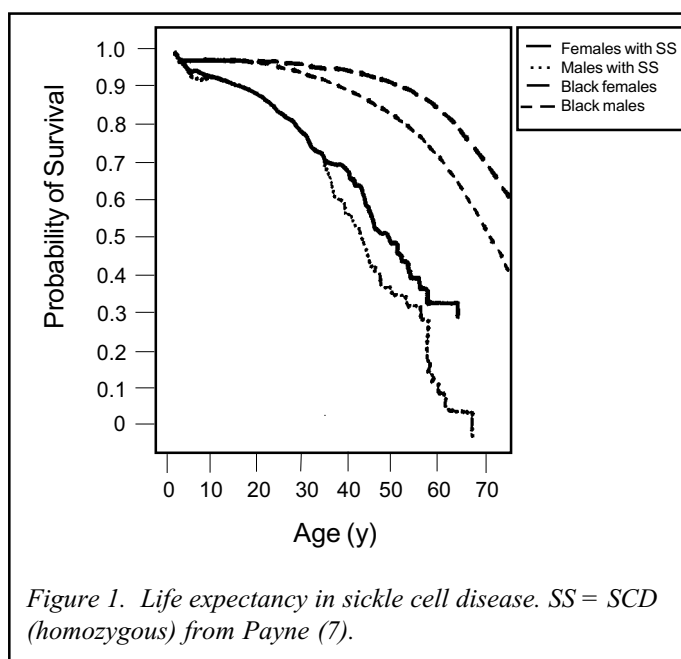
Pain in sickle cell disease (SCD) presents unique challenges for patients, families, and health care professionals. Pain is the most frequent problem experienced by people with SCD. It has profound effects upon comfort and function in work, school, play and social relationships(1). The frequency and severity of painful episodes are highly variable among patients. Some patients have pain daily but others only occasionally (1,2). Painful episodes may start in the first year of life and continue thereafter. The episodes last from hours to weeks followed by a return to baseline. Onset and resolution can be sudden or gradual. Dehydration, infection, stress, fatigue, menses, and cold (including air conditioning and swimming in cold water) can precipitate painful episodes (3). However, the majority of painful episodes have no clear precipitant. Patients experience a wide variety of symptoms spanning acute and chronic pain and assessment and management must be suitable for both. Because pain and SCD itself are lifelong problems that have profound effects upon the quality of life, understanding of individual development and adopting a biopsychosocial approach are crucial(4). The experience of pain varies with each developmental phase(5,6) as should assessment and treatment.

Painful episodes are often termed "crises." Some avoid the term to emphasize that a major goal of treatment is to take the sense of catastrophe out of the crisis. However, replacing a word does not change perceptions. The same is true for the strength, resilience, and vulnerability of each patient, as reflected in coping skills, mood, social life, and function.

Pain—the most frequent problem experienced by people with SCD—profoundly affects comfort and function in work, school, play, and social relationships.

Barriers to Care

Many barriers may impede humane and competent assessment and management of SCD-related pain(4,8). First, most patients with SCD are of African ancestry, but the majority of health care professionals in developed nations are not. Patients and health care professionals often differ in culture and socio-economic standing. Cross-racial and cross-cultural communications can be fraught with difficulty, and there is no reason to assume that the medical arena is immune from the conflicts of society(9). Second, access to health care may be difficult



for many with SCD. For example, non-pharmacologic treatments for chronic pain and chronic illness may be unavailable, unaffordable, or not covered by health insurers. Third, many patients are treated in large tertiary care hospitals where continuity of care is poor and a biomedical orientation overshadows attention to the psychosocial aspects of pain and chronic illness. Fourth, risks of addiction to analgesic medication are overstated frequently(4,10). Fifth, the variability and unpredictability of pain in SCD may make it difficult for the patient to cope and this may lead to the adversarial relationship often observed between patients with SCD and health care professionals.

The term “painful episode” is now used in preference to “crisis”, which suggests catastrophe.

Assessment

Assessment sets the tone for the therapeutic alliance, includes the patient and family in the treatment process, and underlines the respect and concern of the health care professional. It is the foundation of intervention. Assessment during the acute event is brief and focused to guide pharmacotherapy. For a patient with more frequent painful episodes, comprehensive assessment is necessary(11,12). This is best performed when the patient feels well and free of severe pain during an outpatient visit or at discharge from the hospital. Assessment includes physiological, psychological, social, cultural, and spiritual aspects of the pain. It considers not only the patient, but also the family and, where appropriate, the health care system. Assessment of the health care system is often forgotten, but difficult pain problems cannot usually be resolved until this is explored. Such assessment involves a review of the entire network treating the patient, as well as

specific groups and individuals such as nurses, physicians, and social workers. Strengths and problems are identified. Including the health care system in any assessment includes everyone involved in the process of care, beyond just patient and family, and reinforces the mutual responsibility inherent in therapeutic relationships.

The basic principles of pain assessment are universal(11,13). Cognitive and affective states and developmental level must be considered. Frequent reassessment is essential to titrate treatment of pain that rapidly waxes and wanes. The accuracy of the assessment rests on many factors, including past experiences with the health care system(8). Patients do not automatically trust health professionals, especially when they have encountered untrustworthiness. Patients whose pain has been managed inconsistently and inadequately by an ever-changing roster of health care professionals may, for example, always rate their pain as 10 out of 10 or exhibit unusual pain behavior in an attempt to obtain adequate analgesia. Consistent, marked differences between the verbal report and observed behavior warrant further investigation. Factors influencing such discrepancy could include stoicism, past experiences of disbelief and inadequate analgesia, learned coping skills, emotional distress, family dysfunction, or entrenched adversarial relationships with the health care system(12).

Treatment

Medication is the mainstay of treatment for the acute episode but it is only one part of an integrated and individualized treatment plan. Patients and families must be included in the development of any plan. Such inclusion is itself therapeutic, as it reinforces self-efficacy and control(11,12). Consistency is important in treating this unpredictable and inconsistent pain problem, and will serve to reduce anxieties about the type and amount of analgesics to be given.

Medication includes nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol, opioids, adjuvants such as tricyclic antidepressants and invasive approaches such as epidural analgesia. The World Health Organisation ladder for the treatment of mild, moderate, and severe cancer-related pain is applicable to the management of acute episodes of pain associated with SCD(14). NSAIDs or acetaminophen/paracetamol alone are used for mild pain. A mild opioid is added for moderate pain, and strong opioids, sometimes administered by the parenteral route, for severe pain. In general, the types of drugs, route of administration, and schedule (e.g., patient-controlled analgesia) follow recommendations for opioid management of other acute pain problems(11,12,13,15).

Although meperidine/pethidine has commonly been used for SCD-related pain, it is no longer recommended because of the risks of seizures and dysphoria(16). However, many adults with SCD have used meperidine/pethidine successfully for years without side effects. A

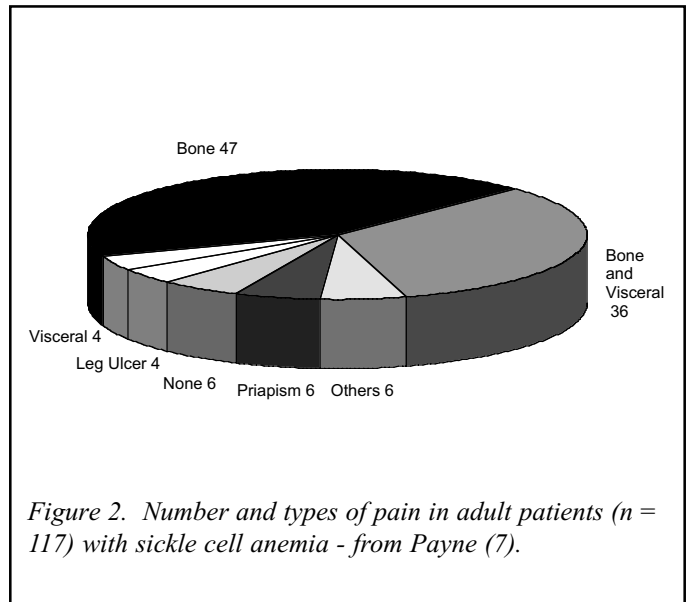
recommendation for abrupt change, especially during an acute painful episode by a physician who is not a primary or trusted caregiver, may evoke resistance and scepticism from the patient. Adherence to guidelines should not supersede concern and respect for the patient's beliefs and past experiences; maintenance of the therapeutic alliance is of prime importance after safety.

We must try to identify high-risk patients early, and provide them with effective, individualized interventions before dysfunction and adversarialism are entrenched.

NSAIDs are often considered benign and preferable to opioids. However, particular risks of NSAID use exist in SCD. Blood loss from occult gastritis, although often unnoticed in other patients, may destabilize precarious haemodynamic compensation in chronic anaemia. Since NSAIDs and acetaminophen/paracetamol are used throughout life, the risk of analgesic nephropathy must be considered, especially in patients who are already at risk of renal failure from SCD(17). Patients and physicians may overuse NSAIDs and acetaminophen/paracetamol in an effort to avoid opioids. This potentially dangerous practice reflects widespread, unfounded fear of opioid addiction.

Average opioid requirements are higher for patients with SCD than for other patients with acute pain(18). Patients often become tolerant with frequent opioid use. Also, it should be emphasised that SCD pain can be exceptionally severe; patients with SCD who have undergone surgery often rate their SCD pain as more severe than postoperative pain(17). Since the degree of opioid tolerance in any single patient is usually unknown, the initial dose must be chosen with concern for both analgesia and safety. After the initial dose, rapid titration to effect is necessary. Severe pain in SCD is an emergency, and patients must be made comfortable as soon as possible. Titration to effect should take only one to two hours, not one to two days.

The majority of painful episodes are managed at home(1). Severe episodes generally require parenteral analgesics. Some patients, however, manage even severe pain with strong oral opioids at home. Parenteral administration is necessary if the patient is vomiting, obstructed, experiencing intractable pain, or otherwise unable to take or benefit from oral agents. Pain management at home has advantages and disadvantages(19). The patient remains in familiar circumstances. Support from the family may facilitate partial continuation and early return to activities of daily living, such as work, school, and social interaction. Without a supportive family at home, safe and effective care is impossible. However, health professionals may overlook the deleterious effects on mood and function of frequent painful episodes inadequately managed at home.



For example, children and adolescents may miss considerable amounts of school, ultimately developing school avoidance, failure, or dropout, without adequate educational intervention by the health care team(1). Also, pain may accompany and mask life-threatening events. Chest pain may herald acute chest syndrome and respiratory failure. Therefore, despite pressure to reduce costs of hospitalization, managing patients at home may potentially be deleterious to comfort and safety.

The use of chronic daily opioids in patients with frequent or daily severe pain is controversial. Many clinicians report improved comfort and function in patients who were formerly debilitated by daily pain(20). Others are concerned about perpetuation of the pain syndrome by symptoms of withdrawal, along with exacerbation or lack of recognition of interacting factors such as depression, anxiety, or intolerable life stresses. Patients for whom daily chronic opioids are considered should undergo in-depth evaluation of physical, psychological, social, and spiritual factors contributing to the pain, and have treatable problems addressed(21). Tricyclic antidepressants may be indicated for treatment of both pain and depression. Clinicians often face the dilemma of treating chronic pain in patients with SCD who could benefit from well-coordinated multidisciplinary interventions that are inaccessible because of economic or geographic barriers. Inequities in the availability of appropriate pharmacologic and non-pharmacologic care raise ethical issues involving allocation of resources, justice, and beneficence.

Physicians greatly overestimate the incidence of addiction in patients with SCD(10,22). This bias results in inadequate dosing, as-needed rather than around-the-clock administration and use of only nonopioid or mixed agonist-antagonist medications for moderate to severe pain. Patients resent being labeled by health care professionals who assume that their request for medication in specific

doses and routes represents addiction rather than the patient's experience and knowledge of what works(23). Having SCD seems neither to increase nor to decrease vulnerability to addiction. Certainly some patients with SCD are addicted. Yet addiction exists in almost every subpopulation in society and our current knowledge is that the incidence in patients with sickle cell disease parallels that of the general population, and may be less than the incidence in health care professionals.

Clinicians have employed epidural analgesia for painful episodes but this practice is controversial(24). This approach can be effective in the short run, and in some cases, such as acute chest syndrome, may be life-saving by providing adequate analgesia without hypoventilation. However, before recommending any intervention the chronicity of the pain must be considered. The goal is not just to manage current pain, but also to enhance future pain management and improve coping with the pain and illness. The potential benefits and drawbacks must be weighed against a lifetime of pain. Problems experienced with long term use may include deleterious side effects such as epidural adhesions at the treatment site. In addition, high-technology approaches can be onerous and frightening for patients and families, so that even as pain itself is reduced during the episode, overall quality of life might suffer. The author recommends epidural analgesia only for particularly severe episodes refractory to the patient's ordinary treatment.

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Psychological and spiritual approaches and modalities are presumed useful in SCD related pain, as for other acute and chronic pain syndromes. A *sine qua non* is continuity and predictability of care within a trusting relationship. Without this, individual approaches applied in a random manner may be ineffective. Endorsement and support of the primary care physician for cognitive, behavioral, and psychological approaches are essential. Otherwise the patient often resists, fearing (sometimes accurately) dismissal, labeling of the pain as "not real" and of himself or herself as "mentally ill" or undesirable, or substitution of these approaches for adequate medication.

In SCD, although genetic and physiologic factors determine disease severity, psychosocial factors and coping skills interact with pathophysiology to determine the severity of pain and its impact on the individual and the family(25). Certain coping skills correlate with reduced impact of the pain and the illness. However, these are associations and not a mathematical model. As pain becomes more severe and frequent, the greater its impact on the individual, and the harder it will be for that individual to use effective coping skills.

Advancing knowledge [alone] will not benefit the majority of patients without concurrent changes in beliefs and attitudes.

Physical approaches include but are not limited to TENS, heat, positioning, and splints for a painful extremity. Cold exacerbates vaso-occlusion and worsens pain so in general should not be used.

Future Directions

Research on SCD-related pain is sparse, but undertreatment of pain in patients with SCD is not due to lack of knowledge. Instead, barriers to implementing available knowledge in clinical practice are the major reason for this shortfall(4,8,10,22) As has been found for the treatment of cancer pain, advancing knowledge through research, while clearly desirable, does not benefit the majority of patients without concurrent changes in beliefs and attitudes(26).

Current health care systems inadequately address the needs of patients with SCD-related pain. Many painful episodes cannot and (at least initially) should not be managed at home, but the environment of acute care usually is not conducive to timely and adequate analgesia. Although emergency departments are the gateway to care for patients with SCD-related pain who cannot manage at home, most provide neither consistent care nor adequate broadly-based assessment and follow up. Some hospitals have established short-stay or day-treatment facilities where patients with SCD receive parenteral analgesia early in the course of the painful episode(27). This approach provides immediate, accessible treatment that may shorten the duration and severity of the episode and obviate the need for acute care hospitalization.

Some patients function well in life despite frequent and intense painful episodes. Others do not. Patients whose functioning is impaired often display psychosocial dysfunction by adolescence. Signs of high-risk status include increasing numbers of hospitalizations for pain, increasing school absences, school failure, increased use of analgesics, family discord and dysfunction, and mood changes(4). An adversarial relationship with health care professionals often develops and intervention is necessary before this becomes entrenched and function is reduced. We must try to identify high-risk patients early, and provide them with individualized, multi-faceted interventions. Waiting to do so until adulthood may doom all attempts to failure.

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