Miscellaneous Agents

I. Neuroleptic drugs (Beaver et al. 1966; Patt et al. 1994)
   A. Know the indications for using neuroleptic drugs as adjuvant analgesics.
      1. Know that methotrimeprazine is the only neuroleptic with analgesic potential supported by controlled studies.
      2. Know the anecdotal evidence for using neuroleptic drugs in neuropathic pain.
      3. Understand their potential value in treating patients with coexisting symptoms, such as nausea or anxiety.
      4. Be aware of the lack of a theoretical basis for analgesic effects of neuroleptic drugs, and that the evidence for their efficiency is controversial at best.
   B. Be aware of the potential toxicities of the neuroleptic drugs.
      1. Know the potential for long-term, refractory movement disorders (for example, tardive dyskinesia) and consider this risk in the long-term administration of these drugs.
      2. Be aware of the short-term, reversible toxicity, including other movement disorders (e.g., dystonic reactions), sedation, orthostatic hypotension, and the neuroleptic malignant syndrome.
      3. Be aware that combining neuroleptics with tricyclic antidepressants may produce additive toxicity because of overlapping side effects.

II. Antihistamines (Stambaugh and Lance 1983; Rumore and Schlicting 1986)
   A. Be aware of the literature supporting the use of antihistamines, specifically hydroxyzine, orphenadrine, and diphenhydramine, as analgesics.
   B. Recognize the limited role played by these drugs in clinical pain management.
   C. Understand the potential use of certain antihistamines as anxiolytics or antiemetics.

III. Analeptic drugs (Rozans et al. 2002; Bruera et al. 1987)
   A. Be aware of the literature supporting the analgesic potential of analeptic drugs.
   B. Understand the reasons for the limited role played by these drugs in the management of nonmalignant pain (e.g., tolerance on long-term administration, potential for precipitating psychosis, sleep disturbance, and cardiac toxicity).
   C. Understand the potential value of these drugs in the treatment of cancer pain with coexisting opioid-induced sedation.

IV. Corticosteroids (Devor et al. 1985; Bruera et al. 1985; Watkins and Maier 2002)
   A. Understand the literature supporting the use of corticosteroids in certain pain states.
      1. Know the role of these drugs in the management of pain and other symptoms related to cancer (controlled studies in pain and nausea, anecdotal reports in lassitude, anorexia, and others).
      2. Be aware of the laboratory evidence supporting the use of steroids in reducing both the magnitude and effects of nerve injury.
3. Understand the importance of immunological activation of the central nervous system during chronic pain syndromes and the potential for modification of this response by corticosteroids.

B. Understand the reasons for the limited role played by these drugs in the management of nonmalignant pain syndromes and their substantial potential for toxicity with short- or long-term use.

V. Muscle relaxants and antispasticity drugs (Dellemijn and Fields 1994; Arrezzo 2002; Dodick 2003; van Tulder et al. 2003; Raj 2003; Gobel 2004)

A. Know the potential indications for muscle relaxants as a short-term treatment for muscle spasm from a variety of causes.

B. Know the specific drugs used as systemic muscle relaxants and antispasticity agents.
   1. Be aware of the pharmacology of specific drugs such as dantrolene, baclofen, and orphenadrine.
   2. Understand the potential for using these drugs in combination.

C. Know the data supporting the use of muscle relaxant drugs for common musculoskeletal pain syndromes.
   1. Be aware of the paucity of controlled studies.
   2. Be aware of the lack of evidence of long-term benefit.
   3. Understand that drug selection is empirical.

D. Know the appropriate dosing regimens and toxicity associated with these drugs.

E. Know the clinical pharmacology of botulinum toxin.
   1. Be aware of the peripheral anti-spasticity effects and central analgesic effects of botulinum toxin.
   2. Be aware of the different subtypes of botulinum toxin.
   3. Be aware of the evidence supporting the use of botulinum toxin in headache of various etiologies, musculoskeletal pain syndromes, and the pain of neurological disease.
   4. Be aware of the dosing regimens and potential side effects of botulinum toxin.

VI. NMDA antagonists (Mercadante et al. 2000; Hocking and Cousins 2003)

A. Understand the theoretical basis for the use of NMDA antagonist drugs in chronic pain states.

B. Be aware of the clinical pharmacology of ketamine.
   1. Be aware of the use of ketamine in refractory neuropathic pain.
   2. Be aware of the use of ketamine in opioid resistance/tolerance.
   3. Be aware of the spectrum of side-effects associated with the use of ketamine (e.g., dysphoria, hallucinations, psychosis) and appropriate management strategies.
   4. Be aware of appropriate oral and parenteral dosing regimens for ketamine.

VII. Local anesthetics and membrane-stabilizing drugs (Lindstrom and Lindblom 1987; Dejgard et al. 1988; Chabal et al. 1989; Rowbotham et al. 1991; Galer et al. 1993; Strichartz 1995)

A. Be aware of the evidence demonstrating the efficacy of certain antiarrhythmic drugs (e.g., mexiletine, tocainide) in neuropathic pain.

B. Know the rationale for the use of these drugs in neuropathic pain.
   1. Understand that they block voltage-dependent sodium channels in a manner similar to some anticonvulsants (e.g., carbamazepine and lamotrigine).
   2. Be familiar with the evidence from human and animal studies demonstrating sodium channel accumulation in damage to peripheral nerves and reduction in spontaneous and evoked activity in animal neuroma models.

C. Know the dosing regimens for these agents.
D. Be aware of the possibility for serious or irreversible toxicity with these agents (e.g., blood dyscrasias, malignant cardiac arrhythmias in susceptible patients).

VIII. Sympatholytic drugs (Verdugo and Ochoa 1994; Verdugo, Campero and Ochoa 1994; Jadad et al. 1995).
   A. Know the rationale for the use of sympatholytic drugs in the management of sympathetically maintained pain.
   B. Be aware of the limited and contradictory evidence for the use of these drugs in clinical pain management.

IX. Miscellaneous adjuvant analgesics (Fromm et al. 1984; Khan et al. 1999; Devers and Galer 2000; Robbins 2000; Campbell et al. 2001; Mason et al. 2004; Silberstein 2004).
   A. Know that baclofen is effective in trigeminal neuralgia and is often used for other neuropathic lancinating pain.
   B. Understand the difficulty in interpreting evidence relating to the use of cannabinoids as analgesics.
      1. Be aware of the evidence indicating that cannabinoids have analgesic activity but that this activity is compromised by significant side effects.
      2. Understand that the scientific debate relating to therapeutic use of cannabinoids is generally subservient to the concurrent political debate.
   C. Know that drugs modifying serotonergic pathways (pizotifen, methysergide, and triptan drugs) are of proven efficacy for migraine headache.
   D. Understand the basis for the analgesic effects of alpha-2 adrenergic agents (clonidine, tizanidine, dexmedetomidine) together with the use of these agents via the oral, parenteral, and neuroaxial routes.
   E. Be aware of the evidence from controlled studies for the use of topical agents in neuropathic pain syndromes such as diabetic neuropathy and postherpetic neuralgia.
      1. Be aware of the use of lidocaine patch technology in relieving the symptoms of localized neuropathic pain.
      2. Be aware of the use of capsaicin in both low- and high-potency preparations in the management of neuropathic, musculoskeletal, and arthritic pain.

REFERENCES

Dellemijn PL, Fields HL. Do benzodiazepines have a role in chronic pain management? Pain 1994; 57:137–152.
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