아동약물요법 적용의 기본 원리 II

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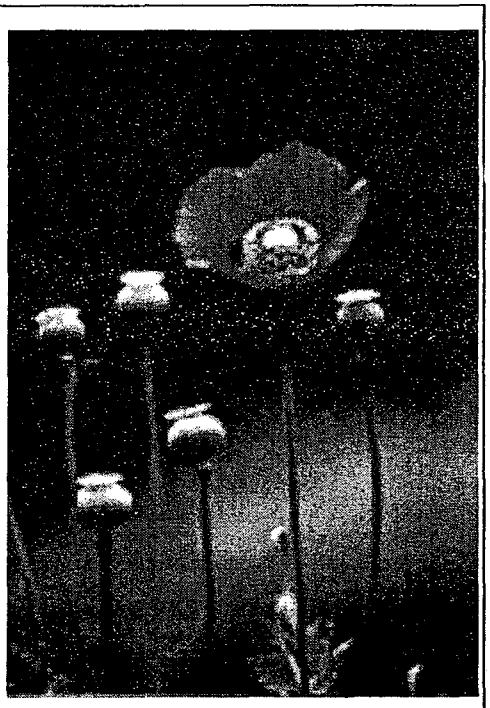
Drugs Used To Manage Pain

- **Nonnarcotic analgesics**
  - NSAIDs (Nonsteroidal Anti-inflammatory Drugs)
    - Salicylates: aspirin (acetylsalicylic acid, Bayer), methylsalicylate
    - Ibuprofen, naproxen, ketoprofen, flurbiprofen
  - Acetaminophen (Tylenol)
- **Narcotic analgesics (opioid analgesics)**
  - Controlled substances used to treat moderate to severe pain
  - Major adverse effects
    - CNS depression, respiratory depression
- **Narcotic antagonists**
  - Drugs that counteract the effects of the narcotic analgesics

- Opium poppy (*Papaver somniferum*)
- Opium (阿片, 아편)
  - Morphine: Morpheus (the Greek god of dreams)



Opium alkaloids

- **Alkaloids:** N (질소)를 함유하고 있으며 알칼리성을 나타내는 유기물질
  - Atropine, caffeine, cocaine, morphine, nicotine, quinine, etc.
- Opium contains two groups of alkaloids
  - **Phenathrenes:** morphine, codeine
  - **Benzylisoquinolines:** papaverine
- **Morphine (10%)**
- **Codeine**
- **Thebaine (paramorphine):** precursor of several semisynthetic opioid agonists and antagonists
  - Codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine, etorphine
- **Papaverine:** vasodilator
  - PDE (phosphodiesterase) inhibitor
  - Cerebral ischemia, peripheral vascular disease

Controlled Substances Act

Schedule I (C-I)
High abuse potential
No accepted medical use
heroin, marijuana,
LSD (lysergic acid diethylamide), peyote
Phencyclidine (PCP)

Schedule II (C-II)
Potential for high abuse with
severe dependence
narcotics, amphetamines, barbiturates
Opioids: morphine, meperidine (Demerol)

Schedule III (C-III)
Less abuse potential than
schedule II drugs
Potential for moderate dependence
nonbarbiturate sedatives
Nonamphetamine stimulants
Limited amounts of certain narcotics
Opioids: codeine

Schedule IV (C-IV)
Less abuse potential than schedule III drugs
Limited dependence potential
Some sedatives and anxiety agents
Diazepam (Valium)

Schedule V (C-V)
Limited abuse potential
Small amounts of narcotics (codeine) used as antitussives or antidiarrheals

Classification

- **Opiates (narcotics; 아편제제)**
  - Morphine and other natural derivatives of the opium poppy
- **Opioids (아편유사제)**
  - Opiates
  - Synthetic drugs
  - Endogenous compounds that produce morphine-like effects
    - Pentapeptides (met-enkephalin, leu-enkephalin, dynorphins, beta-endorphins)
- **Spectrum of clinical uses**
  - Analgesics, antitussives, antidiarrheal drugs
- **Strength of analgesia**
  - Strong, moderate, and weak agonists

Spectrum of clinical uses

- **Analgesics**
- **Antitussives (기침약, 진해제)**
  - Dextromethorphan:
  - Codeine
  - These should be used with caution in patients taking MAO inhibitors.
    - Hyperpyrexic coma, hypertension
- **Antidiarrheal drugs (지사제)**
  - Phenylpiperidines
    - Mild to moderate agonists
    - Diphenoxylate: Schedule V
      - Atropine + diphenoxylate (Lomotil)
      - 2.5 mg diphenoxylate with 0.025 mg atropine
    - Difenoxin: metabolite of diphenoxylate, Schedule IV
    - Loperamide

Functional effects associated with the main types of opioid receptor

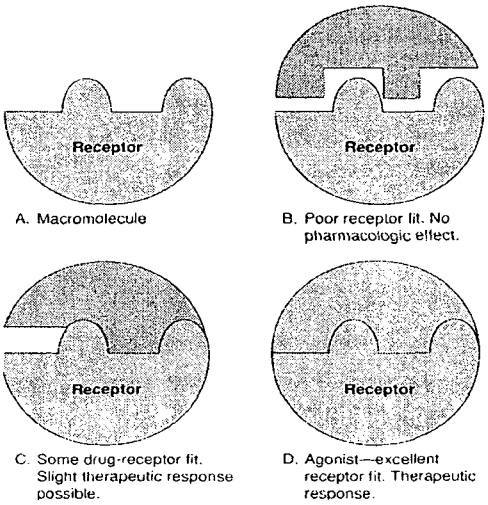
	μ	δ	κ
Analgesia			
Supraspinal	+++	-	-
Spinal	++	++	+
Peripheral	++	-	++
Respiratory depression	+++	++	-
Pupil constriction	++	-	+
Reduced GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical dependence	+++	-	+

Morphine analogs

<Phenanthrene derivatives>

- **Strong agonists:** morphine, hydromorphone, oxymorphone, heroin
- **Mild to moderate agonists: partial agonists**
  - Codeine, oxycodone, dihydrocodeine, hydrocodone
  - Partial agonists
  - Usually combined with in formulations containing aspirin or acetaminophen, and other drugs
- **Mixed agonist-antagonists:**
  - Nalbuphine: strong κ receptor agonist and a μ receptor antagonist
  - Buprenorphine: long-acting partial μ receptor agonist
- **Antagonists:** naloxone, naltrexone, nalmefene
- **Synthetic derivatives with structure unrelated to morphine**
  - **Phenylpiperidines:** meperidine (pethidine), fentanyl, sufentanil, alfentanil, remifentanil,
  - Methadone, propoxyphene, pentazocine, etorphine, levorphanol

Drug-receptor interaction (약물-수용체 상호작용)



A. Macromolecule

B. Poor receptor fit. No pharmacologic effect.

Partial agonist

C. Some drug-receptor fit. Slight therapeutic response possible.

D. Agonist—excellent receptor fit. Therapeutic response.

	Phenanthrenes	Phenylheptylamines	Phenylpiperidines	Others
Strong agonists	morphine hydromorphone oxymorphone heroin	Methadone levomethadyl acetate	Meperidine (pethidine) fentanyl sufentanil alfentanil remifentanil	levorphanol etorphine
Mild to moderate agonists (Partial agonists)	codeine oxycodone dihydrocodeine hydrocodone	dextropropoxyphene	diphenoxylate difenoxin loperamide	
Mixed agonist - antagonists	nalbuphine buprenorphine			butorphanol pentazocine dezocine
Antagonists	naloxone naltrexone nalmefene			

Pharmacodynamics

<CNS>

- Analgesia: effective in most kinds of acute and chronic pain
- Euphoria
- Sedation
- Respiratory depression
- Cough suppression
- Miosis: pinpoint pupil (by acting on Edinger-Westphal nucleus of oculomotor nerves)
- Truncal rigidity in humans
  - Circling motion & stereotyped behavior patterns in animals
- Nausea, vomiting caused by direct activation of the brain stem
  - Chemoreceptor trigger zone

Pharmacodynamics

<PNS>

- Cardiovascular system: vasodilation
  - Bradycardia, postural hypotension
  - Release of histamine (partially blocked by H_1 antagonists)
- GI tract: antidiarrheal effect
  - Decrease gastric motility and propulsive peristalsis
  - Prolong gastric emptying time
  - Decrease biliary, pancreatic, and intestinal secretion
- Contraction of gall bladder and biliary sphincter
- Skin: cutaneous dilatation by histamine release
- Renal function: depression
  - Antidiuretic effect
  - Increase of ureteral and bladder tone→ urinary retention
- Uterus: prolong labor
- Local effects by histamine release: itching and urticaria in injection sites

Opioid antagonists

- **Naloxone, naltrexone, nalmefene**
- **Clinical uses**
  - Acute opioid overdose
  - Diagnosis of physical dependence on opioids
  - Alcoholism (to decrease craving for alcohol)

	Oral absorption	Metabolism	Duration of action	Half-life
Naloxone	poor efficacy (*parenteral administration)	glucuronic conjugation in liver	1-4 hrs	1 hr
Naltrexone potency: 3x of naloxone	better efficacy	metabolized to 6-naltrexol (weak antagonist)	24 hrs	10 hrs

*Naltrexone (100 mg of oral administration) blocks the euphorigenic effect of heroin (25 mg of IV injection) for 48 hours

Opioid antagonists

Clinical uses

•Opioid induced toxicity

- **Naloxone**
  - •0.1 - 0.4 mg (IV), repeated as necessary
  - Remember the relatively short duration of action of naloxone!
- When given IV to a morphine-treated subject, the antagonist will completely and dramatically reverse the opioid effects within 1-3 min.
- **Naltrexone**
  - •Long duration o f action
  - •A 'maintenance drug' for addicts in treatment programs
  - •50 mg (PO), qod

•Diag nosis of physical dependence on opioids

•Alco holism (to decrease craving for alcohol)

- **Naltrexone**

Tramadol

- **Centrally acting analgesics:**
  - Via enhancement of serotonin neurotransmission (inhibition of serotonin reuptake)
  - By inhibiting of NE reuptake
  - By acting as weak μ-agonist
- **Advantages:**
  - Less drug abuse tendency, constipation
- **Toxicity:**
  - Seizure, nausea, dizziness, vomiting, dry mouth, sedation
- **Clinical uses:**
  - Mild to moderate pain
  - Labor pain: less neonatal respiration depression
  - Chronic neuropathic pain
  - Pregnancy Category C

Local anesthetics to prevent pain

- **EMLA cream (emulsion of lidocaine and prilocaine)**
  - Penetrates the skin to provide anesthesia to a depth of 5 mm
  - IM and SC injections, venipuncture, IV cannulation, lumbar puncture, circumcision, skin-graft harvesting, and laser dermal therapy
  - Safe and effective in newborns ≥ 37 weeks' gestation
  - Disadvantages:
    - Requires 1 hour before onset of adequate anesthesia
    - Has vasoconstirctive effect
    - May induce methhemoglobinemia
  - May take longer than an hour to achieve effective anesthesia in dark-skinned individuals.

Local anesthetics to prevent pain

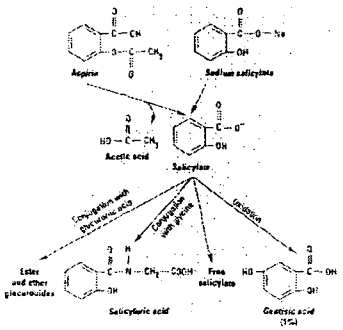
- **Numby Stuff (lidocaine iontophoresis)**
  - Provides dermal anesthesia to a depth of 10 mm within 10-20 minutes
  - Needle-free method of delivering pain medication through the use of low-level electric currents applied to the skin.
  - Emulsion which contains two anesthetics, lidocaine and epinephrine.
  - Disadvantage: tingling, itching or burning sensation from the electric current used to transport drug to the tissues
- **Vapocoolant sprays (ethylchloride or dichlorodifluoromethane)**
  - Sprayed directly onto the skin or applied to a cotton ball
  - Provides local anesthesia within 15 seconds
  - Effective in reducing injection pain in children 4-6 years of age
  - Disadvantages:
    - Brief duration of action
    - May not be effective in reducing injection pain in infants aged 2-6 months

Nonsteroidal anti-inflammatory drugs (NSAIDs)

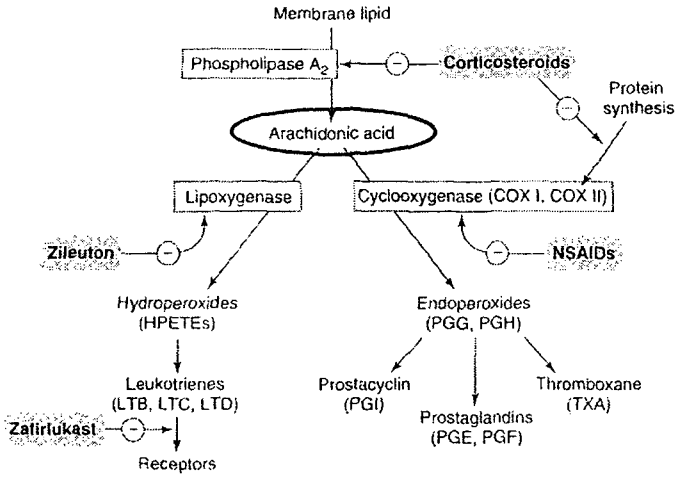
- **NSAIDs (비스테로이드성 항염증약물)**
  - Anti-inflammatory action
  - Antipyretic action
  - Analgesic action
  - **Ibuprofen**
    - Advil, Nuprin, Motrin, 부루펜시럽
  - **Salicylates**
    - Aspirin (acetylsalicylic acid, ASA)
    - Sodium salicylate
    - Salicylic acid
    - Methylsalicylate
      - 제놀쿨파스 (Zenol Cool Cataplasma):
        - Diphenhydramine HCl 10 mg, Methylsalicylate 160 mg,
        - Camphor 80 mg, menthol 140 mg, Thymol 20 mg
    - Diflunisal

Salicylates

- Williow bark extracts
  - Aspen Willow
  - Babylon weeping willow (수양버들)
  - 1763, salicin
- Aspirin (acetylsalicylic acid; ASA), 1899



Synthesis of eicosanoids and sites of inhibitory effects of corticosteroids, NSAIDs, and leukotriene antagonist drugs



Cyclooxygenase (COX)

- **COX-1**
  - Predominantly constitutive (although activity is increased 2-4 fold by inflammatory stimuli)
  - Present in most tissues, especially stomach, platelets, kidney
- **COX-2**
  - Inducible
  - 10-20 fold by inflammatory stimuli in many cells including macrophages, synoviocytes (윤활막세포), chondrocytes (연골세포), fibroblasts (섬유모세포), endothelial cells (내피세포)
- **Selective COX-2 inhibitors**
  - Celecoxib (Celebrex)
  - Rofecoxib (Vioxx, Merck): withdrawn from the market (2004. 9. 30)
  - Meloxicam (Mobic)
  - Etoricoxib, valdecoxib

Aspirin (acetylsalicylic acid, ASA; Bayer Aspirin)

- **Pharmacokinetics:**
  - **A:** PO and rectal
  - **M:** hydrolyzed in liver, GI tract, and plasma; then further hepatic metabolism
  - **E:** metabolites excreted in urine
  - Rapidly metabolized to salicylate after ingestion
- **Pharmacodynamics**
  - Nonselective inhibitor of COX-1 and COX-2
- **Drawbacks and side effects**
  - Contraindicated in gout (it inhibits the elimination of uric acid by the kidney)
  - Contraindicated in children with viral infections: Reye's syndrome (RS, 라이증후군)
  - Gastritis, increased bleeding time, hypersensitivity
  - Salicylate poisoning

Methylsalicylate (Ben-Gay)

- **Lipid soluble oil**
  - Known as oil of wintergreen
  - Very irritating to tissues: external use only!
  - Absorbed through the skin: **cataplasm**
  - Produces effects similar to oral sodium salicylate
  - **Rubefacient** [causing redness (as of the skin)] to produce cutaneous vasodilation
- **Clinical Uses:**
  - Topical analgesic (draws blood flow to ease myalgias)
  - OTC preparations employed topically to alleviate local muscle soreness and to produce local vasodilation (heat)
- **Drawbacks and side effects:**
  - Can be a contributing factor in salicylate poisoning

Acetaminophen (paracetamol) [Tylenol, Datril, Panadol]

- **Actions:**
  - Analgesic and antipyretic actions
- **Clinical Uses:**
  - To relieve mild to moderate pain
  - To reduce fever
  - Particularly useful for those with
    - Aspirin allerg y
    - Bleeding disorders (bleeding ulcer or hemophilia)
    - Anticoagulant therap y
- **Adverse reactions:**
  - Skin eruptions, urticaria (hives), hemolytic anemia, pancytopenia, hypoglycemia
  - Jaundice
  - Hepatotoxicity
    - Acety lcysteine (Acetadote, Mucomyst)

Salicylism

- A group of commonly occurring toxic effects of excessive dosage with salicylic acid or its salts, usually marked by sweating, vomiting, epigastric pain, tinnitus, and blurring of vision.
- Aspirin
- Topical application of salicylic acid in keratolytics
- Ingestion of methylsalicylate (oil of wintergreen)

<Presentation>

- In adults, early respiratory alkalosis & later metabolic acidosis

<Complications>

- Disturbance of electrolytes: hypokalemia, hypernatremia, hyperglycemia
- Pulmonary edema & acute renal failure
- Hypoprothrombinemia is very rare.
- Significant GI bleedings are surprisingly infrequent in salicylate poisoning

Salicylism

<Management>

- Gastric lavage
- Oral or IV rehydration with particular attention to potassium supplements
- Oral activated charcoal: 50 g q4h
- Alkalization: $NaHCO_3$(1.26%) over 2 hours and repeated to keep the urinary pH > 7.5
- Hemodialysis

Drug	Half-life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Aspirin	0.25	< 2%	1200–1500 mg tid
Salicylate[1]	2–19	2–30%	See footnote 2
Apazone	15	62%	600 mg bid
Celecoxib	11	27%[3]	100–200 mg bid
Diclofenac	1.1	< 1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	< 1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	< 1%	300 mg tid
[illegible]	2	< 1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	< 1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[4]
Meclofenamate	3	2–4%	100 mg qid
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone[5]	26	1%	1000–2000 mg qd[6]
[illegible]	14	< 1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[6]
Piroxicam	57	4–10%	20 mg qd[6]
Rofecoxib	17	72%[3]	12.5–50 mg qd
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

[1]Major anti-inflammatory metabolite of aspirin.
[2]Salicylate is usually given in the form of aspirin
[3]Total urinary excretion including metabolites.
[4]Recommended for treatment of acute (eg, surgical) pain only.
[5]Nabumetone is a prodrug; the half-life and urinary excretion are for its active metabolite.
[6]A single daily dose is sufficient because of the long half-life.

Status epilepticus (SE)

- Defined as recurrent or continuous seizure activity lasting longer than 30 minutes in which the patient does not regain baseline mental status
- Involuntary alterations of consciousness or motor activity
- Consumption of oxygen, glucose, and energy substrates (eg, ATP, phosphocreatine) is significantly increased in cerebral tissue during seizures.
- Unremitting seizure ⇒ respiratory compromise & rhabdomyolysis
- **Frequency:**
  - 70% of children younger than 1 year who are subsequently diagnosed with epilepsy present with status epilepticus as the initial symptom of their illness
  - In children with epilepsy, 20% have status epilepticus within 5 years of diagnosis
  - 5% of children with febrile seizures present with status epilepticus
- **Mortality/Morbidity:** 10-15% (USA)

Protocol for SE management

Time post onset	Treatment
Onset	Ensure adequate ventilation/O_2
2-3 min.	Secure IV line, rapid assessment, blood draw
4-5 min.	Lorazepam 4 mg (0.1 mg/kg) or diazepam 10 mg (0.2 mg/kg) over 2 minutes via second IV line or rectal diazepam
7-8 min.	Thiamine 100 mg, 50% glucose 25 mg IV
	Phenytoin or fosphenytoin 10-15 mg/kg IV at a usual rate of 0.5-1.5 mg/kg per min (maximum total dose of 20 mg/kg in 24 h)
	Pyridoxine 100-200 mg IV in children under 18 months
10 min.	Can repeat lorazepam or diazepam if seizures ongoing

Protocol for SE management (Cont.)

Time post onset	Treatment
30-60 min.	EEG monitoring unless status ended and patient waking up
40 min.	Phenobarbital 20 mg/kg at ≤ 5 mg per minute (0.75 mg/kg per minute)
70 min.	Pentobarbital 3-5 mg/kg load, 1 mg/kg per hour infusion
	OR
	Propofol 3-5 mg/kg load, 5-10 mg/kg/hr initial infusion then 103 mg/kg/hr
	OR
	Midazolam 0.2 mg/kg load, 0.25-2 mg/kg infusion