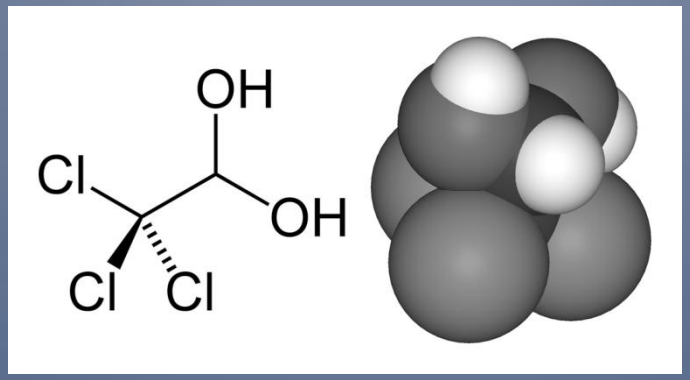
CHLORAL HYDRATE : A REVIEW



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INTRODUCTION

- 1832: discovered by Justus von Liebig in Gießen

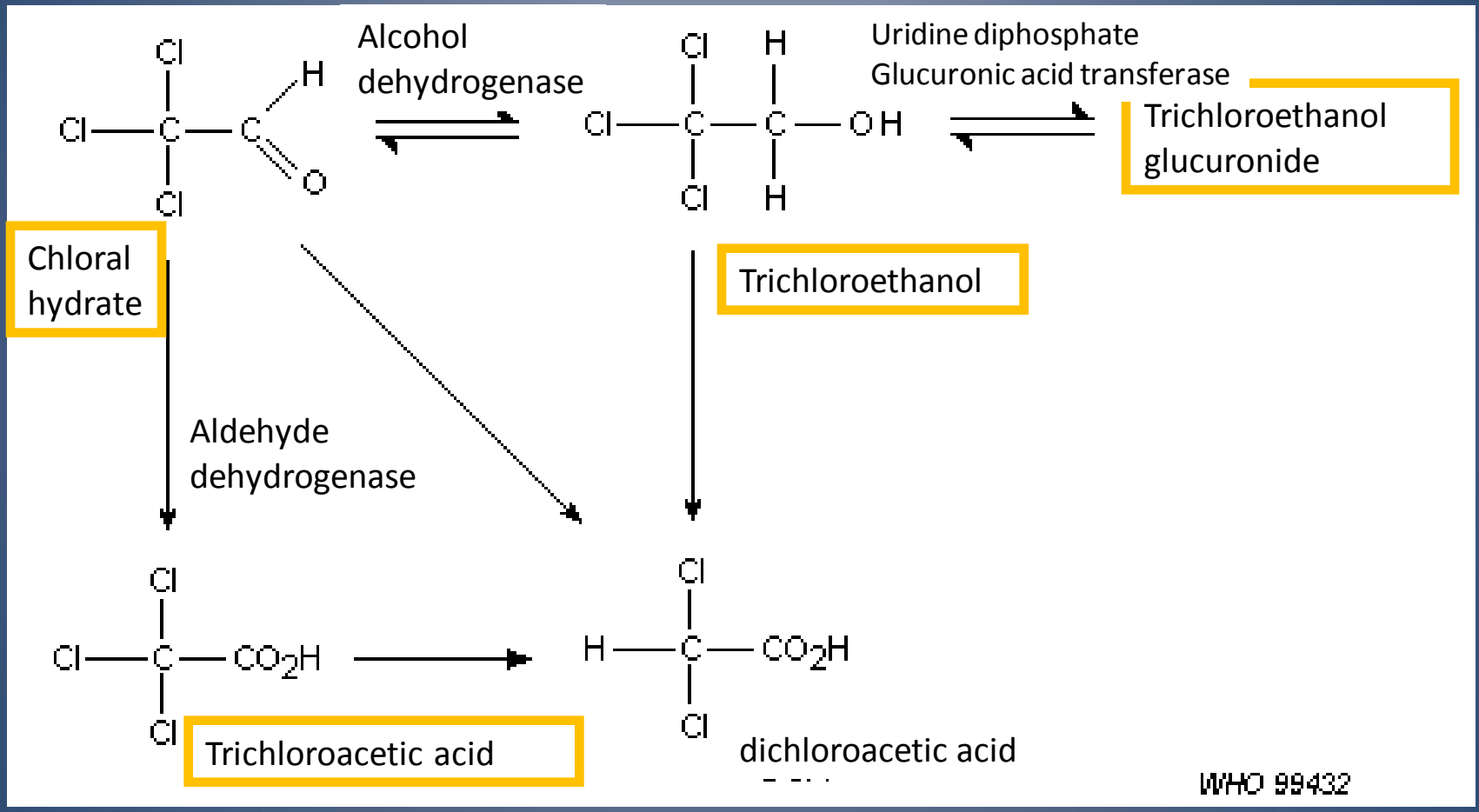
  1869: sedative property was published
- Chlorine & ethanol in acidic solution:

  $4\ Cl_2 + C_2H_5OH + H_2O \rightarrow Cl_3CCH(OH)_2 + 5\ HCl$
- For short-term sedative
- Barbiturates & benzodiazepines displaced it in the mid-20th century

METABOLISM & MECHANISM

METABOLISM

- Distribution: Protein Binding 70-80%
- Metabolization of chloral hydrate to trichloroethanol (active metabolite) in liver & erythrocytes
- Oxidation of chloral hydrate & trichloroethanol to trichloroacetic acid(inactive metabolite) in liver & kidney
- Glucuronidation of trichloroethanol to trichloroethanol glucuronide (inactive metabolism)



Marshall & Owens, 1954
Kaplan et all a., 1967

ROUTE OF ELIMINATION

- Trichloroethanol, trichloroethanol glucuronide, & trichloroacetic acid are excreted in urine(40%)

- Some trichloroethanol glucuronide may be secreted into bile & excreted in feces

- Half life: child & adult : 7-10 hours
  infant: 27.7 – 39.8 hours

MECHANISM

- Trichloroethanol enhanced $GABA_A$ receptor which is similar with benzodiazepine(BZD), non-BZD & barbiturates
  - inhibiting histaminergic cells in tuberomammillary nucleus & activating ventrolateral preoptic nucleus of hypothalamus
- Trichloroethanol had central nervous system depressant effects, but the mechanism is unknown

INDICATION

CLINICAL INDICATION-

LESS PARADOXICAL EXCITEMENT IN CHILDREN

- Alcohol withdrawal syndrome
- Electroencephalography(EEG)
- Insomnia
- Preoperative & postoperative care
- Procedural sedation
- Sedation
- Status epilepticus

DOSAGE

ADULT NORMAL DOSAGE

- Oral route
  - **Alcohol withdrawal syndrome**
    500 mg to 1 g Q6H; maximum dose: 2 g/day
  - **Insomnia**
    500 mg to 1 g; maximum dose: 2 g/day
  - **Postoperative pain**
    250 mg TIDPC, an adjunct to opiates & analgesics
  - **Sedation**
    250 mg TID PC; maximum dose: 2 g/day
- Rectal route
  - **Alcohol withdrawal syndrome**
    500 mg to 1 g Q6H; maximum dose: 2 g/day
  - **Sedation**
    250 mg TIDPC

ADULT ADJUSTED DOSAGE :
RENAL FAILURE AND GERIATRIC PATIENT

- Renal Failure
  - GFR>50mL/min: no adjustment
  - GFR<50mL/min: avoid usage

- Geriatric Patients
  - For insomnia: 250 mg/day as initial oral dose

PEDIATRIC DOSAGE

- Definition of pediatrics

早產兒	(Premature)	GA < 38 weeks
足月新生兒	(Full-term neonate)	GA 38-42 weeks
新生兒	(Neonate)	0 – 1 month
嬰兒	(Infant)	1 - 1 2 m o n t h s
幼兒	(Young child)	1 - 5 y / o
學童	(Older child)	6 - 1 2 y / o
青少年	(Adolescent)	1 3 - 1 8 y / o

- Pediatric body surface area:

$$\sqrt{\text{body weight(kg) x body height(cm)/3600}}$$

PEDIATRIC NORMAL DOSAGE

– Procedural sedation

Procedure	Dosage			
	Age	dose	repeat	Maximal dose
EEG	Neonate	25mg/kg/dose	single dose only	
	Infant & children	25-50mg/kg/dose	25-50mg/kg 30mins later	100mg/kg (infant ≤ 1g, children ≤ 2g)
Non-painful procedure	Neonate	25-50 mg/kg/dose	single dose only	
	Infant & children	50-75mg/kg/dose	25-50mg/kg 30mins later	120mg/kg (infant ≤ 1g, children ≤ 2g)

PEDIATRIC NORMAL DOSAGE

- Sedation
  8 mg/kg or 250 mg/m^2 Q8H, maximum:500 mg/dose
- Insomnia
  50 mg/kg/day or 1.5 g/m^2; maximum: 1 g/dose
- Preoperative care
  75 mg/kg: anxiolytic effects before surgery
- Postoperative pain
  8.3 mg/kg or 250 mg/m^2, max:500 mg TID, as adjunct

PEDIATRIC NORMAL DOSAGE

- Rectal route
  - **Procedural sedation**
    EEG: 20 to 25 mg/kg
  - **Sedation**
    8mg/kg or 250 mg/m^2 Q8H; Maximum: 500 mg Q8H

ADVERSE EFFECT

INTRODUCTION

- Cardiovascular Effects
- Respiratory Effects
- Dermatologic Effects
- Gastrointestinal Effect
- Neurologic Effects
- Psychiatric Effects
- Renal Effects

CARDIOVASCULAR EFFECTS

- Cardiac dysrhythmia

  Sinus arrythmia, transient bigeminy & multifocal PVCS

  Large doses (500 to 3000 mg; 20 to 219 mg/kg)

Sing K et al, Clin Toxicol 1996; 34:101-106
Silver W et al, Pediatrics 1971; 48:32
Nordenberg A et al, Pediatrics 1971; 47:134

RESPIRATORY EFFECTS

- Respiratory arrest
  - One 45-day-old infant
    Chloral hydrate: 50 mg/kg
    Respiratory arrest 20 mins
    Caksen H et al, J Emerg Med 2003; 24(3):342-343
  - Two 24-month-old childrens
    Chloral hydrate: 80 mg/kg
    Desaturation
    Biban P et al, Pediatrics 1993; 92:461-463
  - One 22-month-old child
    Chloral hydrate: 250 mg
    Laryngospasm
    Acute obstruction of airway with cyanosis & cardiac arrest
    Seizures with sustained tonic phase & severe trismus
    Granoff DN et al, Am J Dis Child 1971; 122:170

DERMATOLOGIC EFFECTS

- Drug exanthem
  - 43 y/o woman
  - Single-dose chloral hydrate 600mg
  - Transient exanthema, leukocytosis, & thrombopenia within 1 hour of administration

Neubauer F et al, Z Ges Inn Med 1975; 30:36

- Drug-induced rash
  - 57 y/o man
  - single-dose chloral hydrate 500mg
  - Erythematous nummular, pruritic, edematous plaque

Miller LH et al, Arch Dermatol 1966; 94:60

GASTROINTESTINAL EFFECTS

- Gastrointestinal tract finding
  - Gastric irritation, occasional nausea, vomiting & diarrhea

    Sifton DW , NJ, 1998

  - Lesion of mucosa
    2 infants

    Chloral hydrate: 50mg/kg

    skin lesion around mouth

    Caksen H et al, Pediatr Dermatol 2001; 18(5):454-455

NEUROLOGIC EFFECTS

- Seizure

  2-year-old boy

  Chloral hydrate: 70 mg/kg for echography
  1st Seizures after sedation 60 minutes later

  2nd seizure after sedation 90 minutes later

Munoz M et al, J Pediatr 1997; 131(5):787-788

PSYCHIATRIC EFFECTS

- Sleep disorder

  4 patients

  Chloral hydrate: 800 mg

  Depressed REM sleep in the first 2 to 3 hours of sleep

  Evans JI et al, Br Med J , 1970; 3:310

RENAL EFFECTS

- Oliguria

  Full-term infant

  Chloral hydrate: 44mg/kg Q6H →50mg/kg Q6H

  Decreased urine output

  Anyebuno MA et al, Dev Pharmacol Ther 1991; 17:116-120

CONTRAINDICATION

CONTRAINDICATION

- Hypersensitivity to chloral hydrate
- Hepatic or renal impairment
- Severe cardiac disease
- Gastritis, esophagitis, or gastric/duodenal ulcers

SUBSTITUTION

Drug	Use	Dose	Route	Onset	Duration	Contraindication	Remarks
Chloral hydrate	Sedative	25-100 mg/kg	PO	30-60 mins	30-90 mins		•Vomiting •Respiratory depression
Midazolam	Sedative	0.1-0.15 mg/kg	IV	1-5 mins	30-120 min		•Respiratory depression
Ketamine	Sedative & analgesic	0.5-1 mg/kg & 2-4 mg/kg	IV IM	30-60 secs & 5-20 mins	15-20 mins & 30-40 mins	•Intracranial pressure↑ •Intraocular pressure↑ •Blood pressure↑	• Respiratory depression • Arterial hypoxaemia • Laryngospasm • Vomiting
Pento-barbital	Sedative	1-2 mg/kg Max: 5mg/kg	IV IM	1-5 mins	30-60 mins	•Acute porphyria •Acute asthma •Shock •Hypovolemia	• Respiratory depression • Arterial hypoxaemia
Par-aldehyde	Sedative	0.3ml/kg	PR	10-15 mins	8-10 hours	•Hepatic or pulmonary dysfunction	• IMI painful • Risk of abscess formation
Pethidine	Sedative & analgesic	0.5-1 mg/kg	IV IM	5-10 mins	3-4 hours		• Respiratory depression

ASSESSMENT

ASSESSMENT: BEFORE PROCEDURE

- Patient selection: ASA physical status 1 and 2 only

Physical Status	Criteria
1	Normal, healthy patient
2	Patient with mild systemic disease that does not limit normal activity
3	Patient with systemic disease that limits normal activity
4	Patient with systemic disease that is a constant threat to life
5	Moribund patient who is not expected to survive with or without operation

American Society of Anesthesiologists Physical Status classification

ASSESSMENT: BEFORE PROCEDURE

- Patient exclusion:
  - Current respiratory tract infection, unexplained fever, acute illness
  - Craniofacial anomalies that could compromise airways
  - ASA physical status 3, 4, or 5
  - History of complications with prior sedation or failed sedation
  - Failure to follow dietary precautions

American Academy of Pediatrics guidelines

ASSESSMENT: BEFORE PROCEDURE

- Dietary precautions for sedation:
  - Infants 0-5 months: no solids for 4 hrs
  - Infants 6-36 months: no solids for 6 hrs
  - Children ≥ 36 months: no solids for 8 hrs

American Academy of Pediatrics guidelines

ASSESSMENT: DURING SEDATION

- Monitoring:
  - Oxygen delivery system, suction apparatus, emergency drug, resuscitation equipment , pulse oximeter
  - Heart rate monitor
  - Intermittent recording of respiratory rate and blood pressure
  - Intermittently checking head position & chest excursions for airway patency
  - One-to-one monitoring by registered nurses trained in pediatric advanced life support

American Academy of Pediatrics guidelines

ASSESSMENT: AFTER PROCEDURE

- Discharge criteria:
  - Stable vital signs
  - Easily arousable with patent airway
  - Patient can talk, sit up unaided (if age appropriate)
  - Presedation level of response in a young or handicapped child
  - Adequate hydration
  - Minimal or no nausea

American Academy of Pediatrics guidelines

FLOWCHART

診斷:_____檢查:_____

鎮靜前評估

1. 心血管系統:□心跳血壓正常、□異常:_____
2. 呼吸系統: □呼吸型態正常、□需氧氣供應 SpO2:____%、□異常:_____
3. 現在病史: □無、□呼吸道感染、□發燒、□急性病症:_____
4. 過去病史: □無、□對 Chloral hydrate 過敏、□過去鎮靜曾發生併發症、□其他鎮定異常_____
5. 禁食時間: __小時(0-5 個月:禁食 4 小時,6-36 個月:禁食 6 小時,≥ 36 個月:禁食 8 小時)
6. ASA 分級:(僅 ASA grade I 與 II 者可進行鎮靜)

□I: 正常健康病人	□IV:重度系統疾病
□II: 輕度系統疾病,不會限制身體功能	□V: 有立即死亡風險
□III:中度系統疾病,會限制身體功能	□VI:緊急狀態

7. 整體評估: □可進行鎮靜、□因上述評估未通過,不建議鎮靜

評估者:_____日期:_____年_____月_____日_____時_____分

3. 生命徵象紀錄:

時間	心跳(/分)	血氧濃度(%)	備註
_____時_____分			
_____時_____分			
_____時_____分			

紀錄者:_____日期:_____年_____月_____日_____時_____分

_____時_____分

2. 復甦評估: □生命徵象穩定、□意識清醒、□可深呼吸或大哭、□可移動四肢、□無噁心嘔吐
3. 整體評估: □可離院或回病房、□建議繼續觀察生命徵象及復甦狀態,____分鐘後再評估

評估者:_____日期:_____年_____月_____日_____時_____分

REFERRENCES

- Micromedex
- Clinical guideline for sedation in children and young people, National Institute for health and Care Excellence(NICE), 2010
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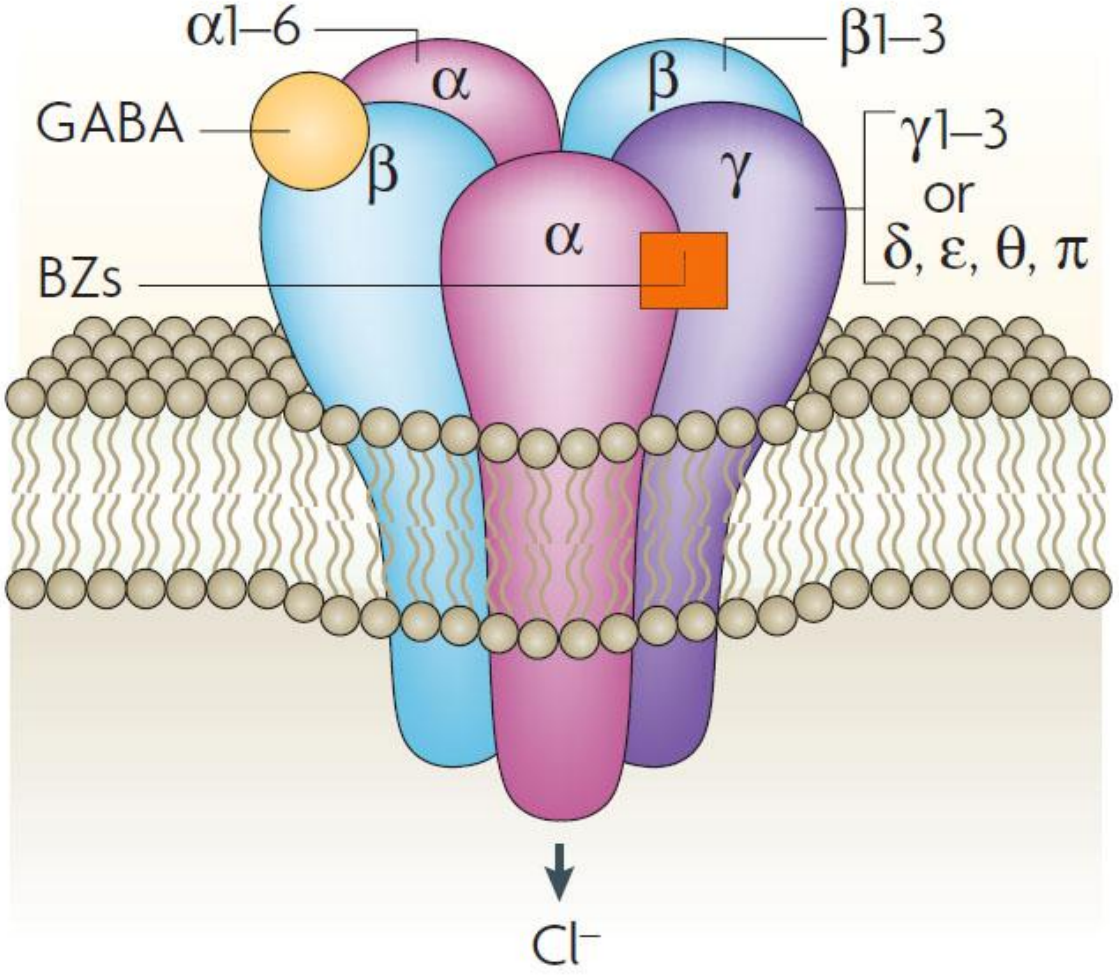
- Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update, Paediatr Anaesth. 2008 Jan;18(1):9-10
- Procedural sedation and analgesia in children. Lancet 2006; 367(9512):766-780


Thanks for your listening

$GABA_A$ receptor



Jacob et al., Nature Reviews Neuroscience, 2008