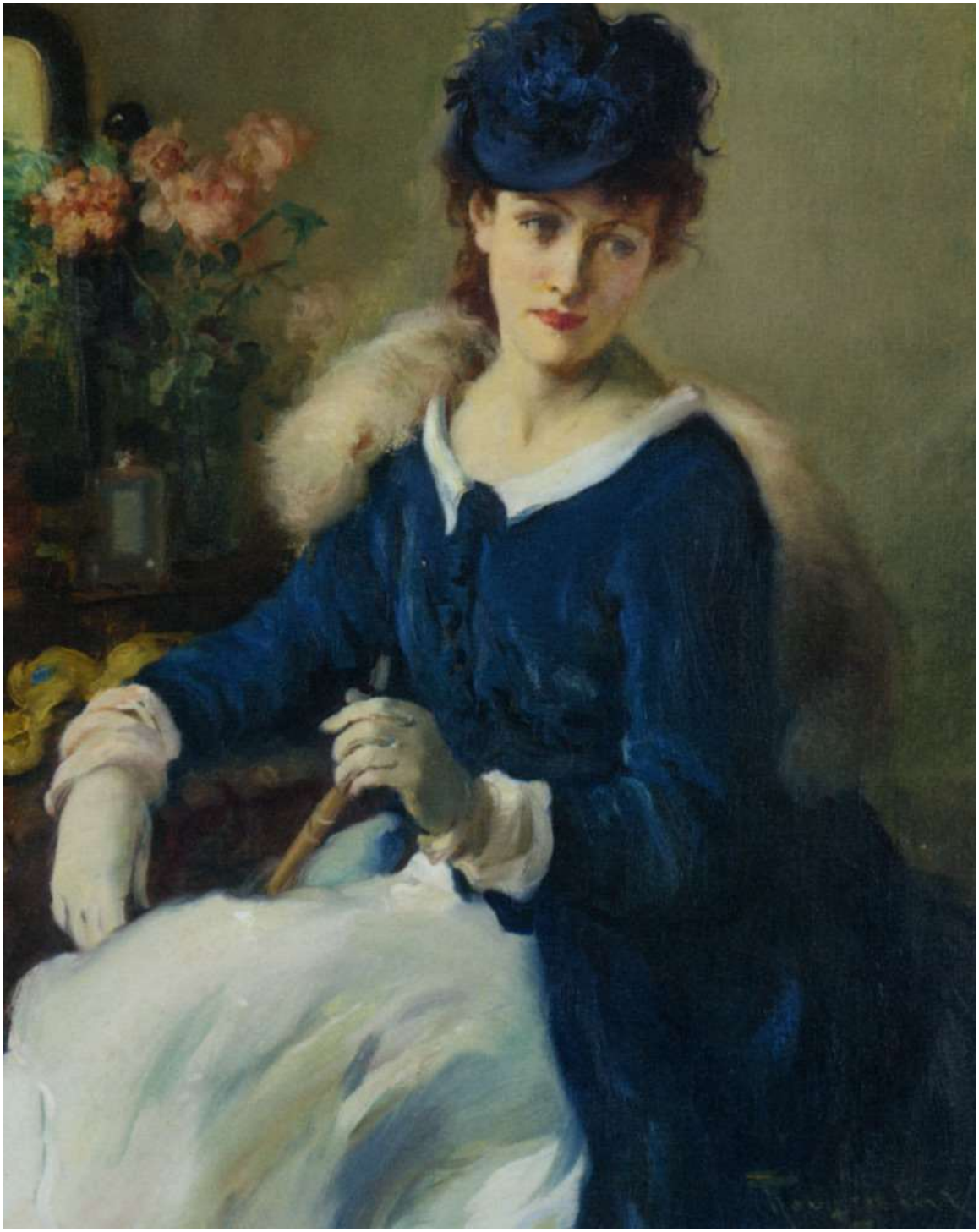
THE NORTHERN HOSPITAL

CHLORAL HYDRATE



"An Elegant Woman", oil on Canvas, Fernand Toussaint, (1873-1955). "But in the sleep which the phial procured she sank far below such half-waking visitations, sank into depths of dreamless annihilation, from which she woke each morning with an obliterated past"

The street lamps were lit, but the rain had ceased, and there was a momentary revival of light in the upper sky. Lily walked on, unconscious of her surroundings. She was still treading the buoyant ether which emanates from the high moments of life. But gradually it shrank away from her and she felt the dull pavement beneath her feet. The sense of weariness returned with accumulated force, and for a moment she felt she could walk no farther. She had reached the corner of Forty-First Street and Fifth Avenue, and she remembered that in Bryant Park, there were seats were she might rest.

The melancholy pleasure ground was almost deserted when she entered it, and sank down on an empty bench in the glare of an electric street lamp. The warmth of the fire had passed out of her veins, and she told herself that she must not sit long in the penetrating dampness that struck up from the wet asphalt. But her will power seemed to have spent itself in a last great effort, and she was lost in the blank reaction which follows an untoward expenditure of energy. And besides that, what was there to go home to? Nothing but the silence of her cheerless room - that silence of the night that may be more wracking to tired nerves than the most discordant noises: that, and the bottle of chloral by her bed. The thought of the chloral was the only spot of light in the dark prospect: she could feel its lulling influence stealing over her already. But she was troubled by the thought that it was losing its power - she dared not go back to it too soon. Of late the sleep it had brought her had been more broken and less profound; there had been nights were she was perpetually floating up through it to consciousness. What if the effect of the drug should gradually fail; as all narcotics were said to fail? She remembered the chemist's warning against increasing the dose; and she had heard before of the capricious and incalculable action of the drug. Her dread of returning to a sleepless night was so great that she lingered on, hoping that excessive weariness would reinforce the waning power of the chloral…After that she continued to sit at the table, sorting her papers and writing, till the intense silence of the house reminded her of the lateness of this hour. In the street the noise of wheels had ceased, and the rumble of the "elevated" came only at long intervals through the deep unnatural hush. In the mysterious nocturnal separation from all outward signs of life, she felt herself more strangely confronted with her fate. The sensation made her brain reel, and she tried to shut out consciousness by pressing her hands against her eyes. But the terrible silence and emptiness seemed to symbolize her future-she felt as though the house, the street, the world were all empty, and she alone left sentient in a lifeless universe.

But this was the verge of delirium… she had never hung so near the dizzy brink of the unreal. Sleep was what she wanted - she remembered that she had not closed her eyes for two nights. The little bottle was at her bedside, waiting to lay its spell upon her. She rose and undressed hastily, hungering now for the touch of her pillow. She felt so profoundly tired that she thought she must fall asleep at once; but as soon as she had lain down every nerve started once more into separate wakefulness. It was though a great blaze of electric light had been turned on in her head, and her poor little anguished self shrank and cowered in it, without knowing were to take refuge. She had not imagined that such a multiplication of wakefulness was possible: her whole past was re-enacting itself at a hundred different points of consciousness. Where was the drug that could still this legion of insurgent nerves? The sense of exhaustion would have been sweet compared to this shrill beat of activities; but weariness had dropped from her as though some cruel stimulant had been forced into her veins.

She could bear it - yes, she could bear it, but what strength would be left her the next day? Perspective had disappeared - the next day pressed close upon her, and on its heels came the

days that were to follow - they swarmed around her like a shrieking mob. She must shut them out for a few hours; she must take a brief bath of oblivion. She put out her hand, and measured the soothing drops into a glass; but as she did so, she knew they would be powerless against the supernatural lucidity of her brain. She had long since raised the dose to its highest limit, but tonight she felt she must increase it. She knew she took a slight risk in doing so - she remembered the chemist's warning. If sleep came at all, it might be a sleep without waking. But after all that was but one chance in a hundred: the action of the drug was incalculable, and the addition of a few drops to the regular dose would probably do no more than procure for her the rest she so desperately needed….She did not in truth, consider the question very closely - the physical craving for sleep was her only sustained sensation. Her mind shrank from the glare of thought as instinctively as eyes contract in a blaze of light - darkness, darkness was what she must have at any cost. She raised herself in bed and swallowed the contents of the glass, then she blew out her candle and lay down.

She lay very still, waiting with a sensuous pleasure for the first effects of the soporific. She knew in advance what form they would take - the gradual cessation of the inner throb, the soft approach of passiveness as though an invisible hand made magic passes over her in the darkness. The very slowness and hesitancy of the effect increased its fascination: it was delicious to lean over and look down into the dim abysses of unconsciousness. Tonight the drug seemed to work more slowly than usual: each passionate pulse had to be stilled in turn, and it was long before she felt them dropping into abeyance, like sentinels falling asleep at their posts. But gradually the sense of complete subjugation came over her, and she wondered languidly what had made her feel so uneasy and excited. She saw now that there was nothing to be excited about - she had returned to her normal view of life. Tomorrow would not be so difficult after all: she felt sure that she would have the strength to meet it. She did not quite remember what it was that she had been so afraid to meet, but the uncertainly no longer troubled her. She had been unhappy, and now she was happy -she had felt herself alone, and now the sense of loneliness had vanished.

Edith Wharton, "The House of Mirth", 1905

In the closing years of the Nineteenth century Ms Lily Bart was the most beautiful woman in all of New York City. Though of modest background her unsurpassed beauty, allowed her to move in the very highest levels of society, courted by every eligible (and non-eligible) male of the super rich, yet she had reached the age of twenty nine years and remained unmarried. She was incapable of marrying for money but also incapable of living without it and she could not admit to loving a man beneath her social aspirations. Eventually she is rejected by her glittering circle of acquaintances on a false accusation of adultery and without the financial support of her repulsive suitors, who expect a "return" on their "investments", she quickly falls into a life of poverty. She wanders the streets one night in extreme agitation unable to sleep and resolves to increase her dose of "chloral" upon which she has become increasingly reliant to escape the pain of her circumstances. We never know if she dies by intention or by accident. Choral hydrate was a common sedative - hypnotic agent of the Nineteenth and early Twentieth century. It was a common cause of intentional lethal overdose, and because of its extremely narrow therapeutic index, it was also not uncommonly a cause of tragic inadvertent lethal overdose. No better example of this is described as in the last heart rending pages of Edith Wharton's 1905 magisterial social commentary, "The House of Mirth".

CHLORAL HYDRATE

Introduction

Chloral hydrate is a powerful sedative particularly in combination with other CNS depressants, including alcohol.

Its therapeutic index is extremely narrow.

It is potentially lethal due to its toxic myocardial effects as well as its CNS depressant effects.

Historical

Chloral hydrate has long been used as a hypnotic agent, at least as early as the mid Nineteenth century.

Due do its potent synergistic effects with alcohol it also gained notoriety as the "Mickey Finn" (or "knock out drops") around a century ago. It was added to an alcoholic drink in order to quickly render the drinker unconscious so that they could be robbed!

It was popular in the 1980s as a sedative for children and is still occasionally used for children undergoing procedures, but has largely lost favour to safer agents. It is no longer used as a sedative in adults because of its narrow therapeutic index.

Preparation

Chloral hydrate as:

Liquid: **100mg/ml solution (= 1 gram per 10 mls) in a 200ml bottle.**

Pharmacokinetics

Absorption:

- Oral absorption is rapid
- Bioavailability is high.
- Peak plasma concentrations occur within 30-60 minutes, but these may be delayed in overdose situations.

Distribution:

- Vd is approximately 1 L/kg.
- Protein binding is approximately 35%

Metabolism and excretion:

- There is rapid hepatic metabolism: the half life of chloral hydrate at therapeutic dosage is short at just 5 minutes.

- Chloral hydrate has an active toxic metabolite trichloroethanol (TCE). Its half-life is long at 8 to 12 hours, and probably even longer in overdose.

Pathophysiology

Chloral hydrate binds GABA-A receptors in the central nervous system.

Toxic effects include:

1. CNS:
    - CNS depression which occurs as a result of the potentiation of the effects of endogenous GABA.
2. Cardiac:
    - **Tachyarrhythmias**:

      These are due to enhanced myocardial sensitivity to the effects of endogenous catecholamines.
    - Direct myocardial depression.
3. GIT upset:
    - Due to direct corrosive effects on the gastrointestinal mucosa
4. Direct toxicity:
    - Renal impairment
    - Hepatic impairment

Risk assessment

Dose-related risk assessment of chloral hydrate is not well defined.

The upper limit of therapeutic dosing is considered to be **50 mg/ kg.**

> 100 mg/kg (i.e twice the upper limit of therapeutic dosing) is associated with a high risk of coma and life threatening arrhythmias.

In general terms for adults:

0.5 to 1.0 gram:	Sedation
1.5-2.0 grams:	Strong sedation
3.5 -10 grams:	Potentially lethal dose (primarily due to tachyarrhythmias)
	Potentially lethal arrhythmias have been documented in near-therapeutic doses of as little as 1.5 grams in young children.
	There have been documented cases of adult survivors of ingestions of up to 35 grams.

Clinical features

Acute overdose:

Toxic effects occur quickly- within **30 minutes.**

Effects include:

1. Chloral hydrate is said to induce the smell of pears on the breath.
2. GIT upset:
    - Nausea, vomiting, abdominal pain.
3. Neurological:
    - Depressed conscious state.
    - Miosis
4. Airway:
    - Reduced reflexes with potential for aspiration.
5. Cardiovascular:
    - Catecholamine hypersensitivity resulting in tachyarrhythmias, including:
        - ♥ Sinus tachycardia
        - ♥ SVT
        - ♥ Multi-focal VPBs

- ♥ Atrial ectopics

Ultimately:

- ♥ Polymorphic VT/ VF / asystole

- Myocardial depression with cardiogenic shock.

6. Hypothermia.

Chronic use:

Chronic users who abruptly discontinue chloral hydrate may develop a withdrawal syndrome.

Tolerance may develop with 1-2 weeks of regular use.

Investigations

Blood tests:

1. FBE
2. U&Es/ glucose
3. LFTs/ INR
4. Consider co-ingestion, Paracetamol level and blood alcohol level
5. TCE levels can be measured retrospectively in forensic cases.

ECG:

- A 12 lead ECG should be done to document any arrhythmias.
- Serial ECGs are also essential to monitor for any effects.

Plain radiology

- CXR:
  - ♥ A CXR may be done if aspiration is suspected.
- AXR:
  - ♥ Chloral hydrate is radio-opaque and so an AXR may help confirm a recent ingestion.

Management

1. ABC issues

    - Attention to any immediate ABC issues
    - Early intubation is indicated for those showing signs of significant toxicity.

2. Monitoring

    - Establish **continuous ECG monitoring.**

3. Charcoal

    - This should **not** be given, because of the potential of CNS depression and arrhythmias.

      It may be given *following* intubation.

4. Hypotension:

    - Fluid therapy
    - Inotropic agents are problematic due to their potential to aggravate the tachyarrhythmias induced by chloral hydrate, and are best avoided if possible.

5. Tachyarrhythmias:

    Tachyarrhythmias tend to be resistant to conventional antiarrhythmic agents.

    These are best treated with **beta blocking agents**, which reduce the increased catecholamine sensitivity of the myocardium that leads to tachyarrhythmias.

    Options include:

    - **IV metoprolol**
    - **IV esmolol infusion**

6. Flumazenil:

    - This has been reported to be effective in improving the conscious state.

      However it is *not* recommended as given the life threatening nature of the CVS effects, early intubation and ventilation is preferred.

7. Hemodialysis:

- Renal dialysis may increase the elimination of chloral hydrate, given its low volume of distribution.

- It has been used in massive overdoses of chloral hydrate, however clinical efficacy is uncertain.

8. Endoscopy:

   - Patients with indications of possible corrosive gastrointestinal injury such as drooling, odynophagia, vomiting, abdominal pain should be kept nil-by-mouth and have upper GIT endoscopy performed within 24 hours of ingestion.

Disposition

Asymptomatic patients should be observed for at least 4 hours following ingestion.

All patients should have ECG monitoring.

References

1. Graham SR et al. Overdose with chloral hydrate: a pharmacological and therapeutic review. Med J Aust. 1988 Dec 5-19; 149 (11-12): 686 - 8.

2. Chloral hydrate in L Murray et al. Toxicology Handbook 3rd ed 2015.

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Reviewed July 2015