

ZUCLOPENTHIXOL



*“Skittles Players Outside an Inn” oil on oak panel c. 1660 - 63, Jan Steen.
National Gallery London*

In that same village, and in one of these very houses, there lived, many years since, while the country was yet a province of Great Britain, a simple, good-natured fellow, of the name of Rip Van Winkle....Rip Van Winkle, however, was one of those happy mortals, of foolish, well-oiled dispositions, who take the world easy, eat white bread or brown, whichever can be got with least thought or trouble, and would rather starve on a penny than work for a pound. If left to himself, he would have whistled life away in perfect contentment; but his wife kept continually dinning in his ear about his idleness, his carelessness, and the ruin he was bringing on his family.... He shrugged his shoulders, shook his head, cast up his eyes, but said nothing. This, however, always provoked a fresh volley from his wife; so that he was fain to draw off his forces, and take to the outside of the house—the only side which, in truth, belongs to a henpecked husband....Times grew worse and worse with Rip Van Winkle as years of matrimony rolled on. A tart temper never mellows with age, and a sharp tongue is the only edged tool that grows keener with constant use...Poor Rip was at last reduced almost to despair; and his only alternative, to escape from the labor of the farm ...and stroll away into the woods...As he was about to descend, he heard a voice from a distance, hallooing, “Rip Van Winkle! Rip Van Winkle!” ...

On nearer approach he was still more surprised at the singularity of the stranger's appearance. He was a short, square-built old fellow, with thick bushy hair, and a grizzled beard. His dress was of the antique Dutch fashion,- a cloth jerkin strapped round the waist, and several pair of breeches, the outer one of ample volume, decorated with rows of buttons down the sides. He bore on his shoulder a stout keg that seemed full of liquor, and made signs for Rip to approach and assist him with the load. Though rather shy and distrustful of this new acquaintance, Rip complied with his usual alacrity, and relieving one another, they clambered up a narrow gully, apparently the dry bed of a mountain torrent....On entering the amphitheater new objects of wonder presented themselves. On a level spot in the center was a company of odd-looking personages playing at ninepins. They were dressed in a quaint, outlandish fashion; some wore short doublets, others jerkins, with long knives in their belts, and most of them had enormous breeches, of similar style with that of the guide's. Their visages, too, were peculiar....They all had beards, of various shapes and colors. There was one who seemed to be the commander. He was a stout old gentleman, with a weather-beaten countenance; he wore a laced doublet, broad belt and hanger, high-crowned hat and feather, red stockings, and high-heeled shoes, with roses in them. The whole group reminded Rip of the figures in an old Flemish painting, in the parlor of Dominie Van Shaick, the village parson, which had been brought over from Holland at the time of the settlement....What seemed particularly odd to Rip was that, though these folks were evidently amusing themselves, yet they maintained the gravest faces, the most mysterious silence, and were, withal, the most melancholy party of pleasure he had ever witnessed. Nothing interrupted the stillness of the scene but the noise of the balls, which, whenever they were rolled, echoed along the mountains like rumbling peals of thunder...

As Rip and his companion approached them, they suddenly desisted from their play, and stared at him with such fixed, statue-like gaze, and such strange, uncouth countenances, that his heart turned within him, and his knees smote together. His companion now emptied the contents of the keg into large flacons, and made signs to him to wait upon the company. He obeyed with fear and trembling; they quaffed the liquor in profound silence,

and then returned to their game...By degrees Rip's awe and apprehension subsided. He even ventured, when no eye was fixed upon him, to taste the beverage, which he found had much of the flavor of excellent Holland. He was naturally a thirsty soul, and was soon tempted to repeat the draught. One taste provoked another; and he repeated his visits to the flagon so often that at length his senses were overpowered, his eyes swam in his head, his head gradually declined, and he fell into a deep sleep....On waking he found himself on the green knoll whence he had first seen the old man of the glen. He rubbed his eyes—it was a bright, sunny morning....“Surely,” thought Rip, “I have not slept here all night.”Oh! that flagon! that wicked flagon!” thought Rip; “what excuse shall I make to Dame Van Winkle?” ...

As he approached the village he met a number of people, but none whom he knew, which somewhat surprised him, for he had thought himself acquainted with everyone in the country round. Their dress, too, was of a different fashion from that to which he was accustomed. They all stared at him with equal marks of surprise, and whenever they cast their eyes upon him, invariably stroked their chins. The constant recurrence of this gesture induced Rip, involuntarily, to do the same, when, to his astonishment, he found his beard had grown a foot long!...

*The very village was altered; it was larger and more populous. There were rows of houses which he had never seen before, and those which had been his familiar haunts had disappeared. Strange names were over the doors—strange faces at the windows—everything was strange. His mind now misgave him; he began to doubt whether both he and the world around him were not bewitched....It was with some difficulty that he found the way to his own house, which he approached with silent awe, expecting every moment to hear the shrill voice of Dame Van Winkle. He found the house gone to decay—the roof fallen in, the windows shattered, and the doors off the hinges....He entered the house, which, to tell the truth, Dame Van Winkle had always kept in neat order. It was empty, forlorn, and apparently abandoned. He called loudly for his wife and children—the lonely chambers rang for a moment with his voice, and then all again was silence...Instead of the great tree that used to shelter the quiet little Dutch inn of yore, there now was reared a tall, naked pole, with something on the top that looked like a red nightcap, and from it was fluttering a flag, on which was a singular assemblage of stars and stripes; all this was strange and incomprehensible. He recognized on the sign, however, the ruby face of King George, under which he had smoked so many a peaceful pipe; but even this was singularly changed. The red coat was changed for one of blue and buff, a sword was held in the hand instead of a scepter, the head was decorated with a cocked hat, and underneath was painted in large characters, **General Washington***

“What is your name, my good woman?” asked he.

“Judith Gardenier.”

“And your father's name?”

“Ah, poor man, Rip Van Winkle was his name, but it's twenty years since he went away from home with his gun, and never has been heard of since—his dog came home without him; but whether he shot himself, or was carried away by the Indians, nobody can tell. I was then but a little girl.”

Rip had but one question more to ask; but he put it with a faltering voice:

“Where's your mother?”

“Oh, she, too, had died but a short time since; she broke a blood-vessel in a fit of passion at a New England peddler.”

There was a drop of comfort, at least, in this intelligence. The honest man could contain himself no longer. He caught his daughter and her child in his arms. “I am your father!” cried he — “Young Rip Van Winkle once — Old Rip Van Winkle now! Does nobody know poor Rip Van Winkle?”

All stood amazed until an old woman, tottering out from among the crowd, put her hand to her brow, and peering under it in his face for a moment, exclaimed “Sure enough! it is Rip Van Winkle — it is himself!Why, where have you been these twenty long years?”

It was determined, however, to take the opinion of old Peter Vanderdonk..... Peter was the most ancient inhabitant of the village, and well versed in all the wonderful events and traditions of the neighborhood. He recollected Rip at once, and corroborated his story in the most satisfactory manner. He assured the company that it was a fact, handed down from his ancestor the historian, that the Catskill Mountains had always been haunted by strange beings. It was affirmed that the great Hendrick Hudson, the first discoverer of the river and country, kept a kind of vigil there every twenty years, with his crew of the Half-moon; being permitted in this way to revisit the scenes of his enterprise, and keep a guardian eye upon the river and the great city called by his name. His father had once seen them in their old Dutch dresses playing at ninepins in a hollow of the mountain; and he himself had heard, one summer afternoon, the sound of their balls, like distant peals of thunder.

Washington Irving, “Rip Van Winkle” 1819.

Rip Van Winkle had fallen asleep for 22 years! When he awakens he finds the world has changed beyond recognition. His village is unrecognizable. The American Revolution has occurred and he gets into trouble for toasting King George and not recognizing George Washington. He tries to make himself known to a woman, who turns out to be his daughter, now grown up with her own children. She finally recognized him much to her amazement. The oldest citizen on the village is summoned and confirms that indeed the old stranger is Rip Van Winkle who had gone missing over two decades ago. The old man recounts a strange legend that the ghosts of the explorer Henry Hudson and his crew still haunt the Catskill Mountains. Rip rejoices that he has slept long enough to outlive his nagging wife as well as a great war between the colonies and England.

The story of Rip Van Winkle retells an ancient storytelling motif of a man who sleeps decades of his life away in just a single night. Interestingly this motif appears across many cultures and traditions. The Jewish Talmudic tells of Honi M’agel who falls asleep for 70 years. In the Christian tradition there is the story of “The Seven Sleepers of Ephesus” who sleep for 200 years, while in the Islamic tradition the Koran tells the story of the Ashabu Al-Kahf who sleep in a cave for 309 years. In all cases the protagonists awaken find themselves in a in a better world then the one they previously knew..

In the Emergency Department we may send our disturbed patients into a prolonged and restful slumber by use of the magical spell of zuclopenthixol, by which we may hope they will awaken some distant time later to a world they find very much better!

ZUCLOPENTHIXOL

Introduction

Zuclopenthixol is a second generation (or “atypical”) thioxanthene neuroleptic antipsychotic agent.

It is available in a variety of forms including:

1. Oral tablet form:
 - **Zuclopenthixol dihydrochloride**, (trade name in Australia; **Clopixol**)
2. Long acting parenteral IM depot forms:
 - **Zuclopenthixol acetate**: *a relatively short acting intramuscular depot preparation*, (trade name in Australia; **Clopixol-Acuphase**)
 - **Zuclopenthixol decanoate**: *a long acting intramuscular depot preparation*.

In the ED setting, **Zuclopenthixol acetate** may be useful in the following circumstances:

There is a prolonged stay in the ED

- The patient is requiring repeated doses of anti-psychotic to control agitation and will therefore benefit from a longer acting agent.
- The patient is not *severely* disturbed, (the onset of action is slow) but would benefit from some ongoing IM sedation/ anti-psychotic medication.
- The patient is not “neuroleptic naive”, i.e they have received a neuroleptic agent in the past without significant adverse effect. (As the agent is long acting any adverse effect is likely to be similarly prolonged)

It should only be administered after **specialist psychiatric assessment** has confirmed the presence of a primary psychotic disorder or there is clear evidence of a psychotic illness, and there is a high likelihood of recurrent agitation and aggression

Clopixol-Acuphase has a slow onset of action (over hours) and duration of action of two to three days.

It is therefore not a suitable agent for immediate containment, especially in situations where the effect of the drug needs to be time limited and reversible.

Chemistry

Zuclopenthixol is a **thioxanthene** neuroleptic antipsychotic agent.

Classification

Antipsychotic drugs have been classified as conventional or atypical, or first generation or second generation.

In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the development of neuroleptic malignant syndrome.

Some of the second generation antipsychotics, including quetiapine. may improve the **negative** symptoms of schizophrenia (e.g. blunted affect, decreased speech, lack of motivation) better than the older generation of antipsychotics.

Preparation

Tablets:

- **Zuclopendixol dihydrochloride** 10 mg.

Ampoules:

- **Zuclopendixol acetate** 50 mg/mL, 1 mL, 2 mL
- **Zuclopendixol decanoate** 200 mg/mL, 1 mL

Mechanism of Action

Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system).

Evidence suggests:

- All effective antipsychotics block D₂ receptors
- Differential blockade of other dopamine receptors (e.g. D₁) may influence therapeutic and adverse effects.
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT₂ antagonism with some agents.

Pharmacokinetics

Absorption:

- The absolute bioavailability after oral administration of **zuclopendixol dihydrochloride** tablets is about 50 %.

- **Zuclopenthixol acetate** is slowly released from the oil and is rapidly hydrolysed to the active substance, zuclopenthixol, upon reaching the body water phase.

As no first pass metabolism occurs when a drug is administered **parenterally**, zuclopenthixol decanoate can be administered in lower doses than oral zuclopenthixol.

Maximum serum concentrations of zuclopenthixol are reached, on average, **24 to 36 hours** after intramuscular (IM) injection, followed by a gradual decline.

- Zuclopenthixol decanoate is slowly released from the oil depot and is rapidly hydrolysed to the active substance, zuclopenthixol, upon reaching the body water phase.

Whereas zuclopenthixol itself is relatively short acting, the decanoate ester in oil provides a predictable, slow release preparation of the active constituent.

Maximum serum concentrations of zuclopenthixol are reached **3 - 7 days** following IM injection.

Distribution:

- The apparent volume of distribution is 20 L/kg
- Protein binding approximately 98% at concentrations above the therapeutic range.

Metabolism and excretion:

- Zuclopenthixol is metabolized in the liver to inactive metabolites.

Pharmacodynamics

Clopixol has specific anti-psychotic effects and non-specific sedative effects.

In addition to its antipsychotic effect, zuclopenthixol also has a non-specific sedative effect on accompanying symptoms such as agitation, restlessness, hostility or aggression.

Zuclopenthixol induces dose dependent sedation.

Tolerance to the non-specific sedative effect develops rapidly.

Depot **IM zuclopenthixol acetate** has an onset of action within **2 hours**?

Peak effect is achieved approximately **24 hours after injection**

Indications

Indications include:

- 1 Acute psychoses and chronic psychoses.
2. Acute mania.

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Contraindications/ Precautions

These include:

1. Antipsychotic naïve patients.
 - Caution when using depot preparations.
2. Caution when used in association with other CNS depressants.
3. Parkinsonism
4. Convulsive disorders, (may lower seizure threshold)
5. Caution in the elderly
6. Caution in patients at risk of increased QT interval:

- Many antipsychotics can prolong the QTc interval, which could lead to life-threatening arrhythmias (torsades de pointes).

People already treated with a drug that prolongs the QTc interval, or who have hypokalaemia, hypomagnesaemia, hypocalcaemia, kidney failure, heart failure or a congenital disposition, are more prone to prolongation of the QTc interval secondary to antipsychotic treatment.

Pregnancy

Zuclopenthixol is a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Breastfeeding

Caution, insufficient data

Adverse Effects

These include:

1. CNS
 - Sedation
 - Extrapyrmidal reactions:
 - ♥ Dystonic reactions
 - ♥ Akathisia
 - ♥ Tardive dyskinesia
2. CVS:
 - Orthostatic hypotension.
 - Prolonged QT syndrome/ arrhythmias.
3. Neuroleptic malignant syndrome.
4. Weak anticholinergic effects.

Dosing¹

Oral:

Acute psychoses/ acute mania:²

- *Oral*, adult, 10 - 50 mg daily in divided doses.

Doses of up to 75 mg daily may be needed in severe cases.

Chronic psychoses:²

- *Oral*, adult, 20 - 40 mg daily, usually at night.

IM:

If **zuclopenthixol acetate** is considered appropriate, use:

- **Zuclopenthixol acetate 50 to 150 mg IM as a single dose.**

This can be repeated every 2 to 3 days if necessary (a repeat dose may be needed 24 hours after the first dose), up to a maximum of 400 mg per course given over no more than 4 doses.

Treat for a **maximum of 2 weeks** before switching to an alternative zuclopenthixol formulation or another antipsychotic drug

References

1. eTG Complete - March 2015
 - Psychotropic Therapeutic Guidelines ed 7 (2) 2013
2. Zuclopenthixol in Australian Medicines Handbook Website, Accessed July 2015.
3. Zuclopenthixol hydrochloride in MIMs 1 may 2014.
4. Zuclopenthixol acetate in MIMs 1 May 2014.
5. Zuclopenthixol decanoate in MIMs 1 May 2014.

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