THE NORTHERN HOSPITAL

PALIPERIDONE OVERDOSE

Confederate Soldier, killed at the Siege of Petersburg, April 3, 1865 glass, stereograph, wet collodion, T.C Roche. (Library of Congress).

"Dear Henry; I feel more lonely and sadder than I have been in some time. Oh that I knew what the termination of this awful conflict would be. Henry, I want to see you, but don't you come. Join for the war if it is 40 years. If you get killed, tis the most honorable death. If you escape, I will rejoice. I love thee still".

Mollie Vanderberg, letter to her sweetheart at Petersburg, 1865

"...Nothing for excitement except that a few were picked off by sharpshooters. A feeling prevails that sooner or later this experience will befall us all".

Private John W. Haley, Union Soldier, 17th Maine.

"He is at rest, and we who are left are the ones to suffer"

Robert E. Lee, on hearing of the death of A.P Hill.

Grant kept moving. He slipped his army out of his trenches, crossed the Chickahominy, feinted towards Richmond, then shifted left again to the James River. His target now was Petersburg, south of the Confederate capital where he hoped to cut off Lee's supplies and destroy the army of Northern Virginia. For the first time Lee, misjudged Grant's intentions, rushing much of his army to the outskirts of Richmond to meet an attack Grant did not plan to make. Instead Union engineers laid a pontoon bridge all the way across the James in just 8 hours. On June 12th the massive army of the Potomac began to cross. It took four days.

"General Grant, I begin to see it. You will succeed. God bless you!"
(A. Lincoln).

16,000 Union troops under General William Smith were the first to reach Petersburg. The city was defended by fewer than 3,000 Confederates under General Beauregard. Smith moved slowly to the attack. Reinforcements intended to aid him got lost on the way. Still, his late afternoon assault made progress. When night fell, Petersburg seemed within the Union's grasp. General Winfield Scott Hancock urged a moonlight assault, but Smith begged off, remembering Cold Harbour. During the night Confederate reinforcements were brought up. The opportunity was gone.

"The rage of the enlisted men was devilish. The most bloodcurdling blasphemy I ever listened to, I heard that night"
(Union soldier)

In just six weeks Grant and Lee had all but crippled each other, and now both armies dug in for a siege. The burrowing would go on for 10 long months. The men lived in a 20 mile labyrinth of trenches, plagued by flies, open to rain and the fierce Virginia sun, and exposed to shell and mortar fire.

"Nothing for excitement except that a few were picked off by sharpshooters. A feeling prevails that sooner or later this experience will befall us all".
(Private John W. Haley).

Colonel Joshua Lawrence Chamberlain, one of the heroes of Gettysburg, led his regiment in an assault on Petersburg. As he turned to rally his men, a bullet smashed through his pelvis, severed arteries, nicked his bladder. He stayed on his feet, leaning on his sword with one hand and waving his men on with the other until they had all passed him by. Then he sank to the ground. Doctors did not expect him to live. In tribute to his courage Grant promoted him on the field to Brigadier General. Chamberlain's obituary appeared in the newspapers the next day.

Petersburg is a magnificent salute to the durability of men on both sides. It was just a rehearsal for World War I trench warfare, and they stood up very well to it, but the soldiers always did in that war. It's to us an almost incredible bravery, considering the casualties.
(Shelby Foote, Civil War Historian).

"June 23 1864: The demand down here for killing purposes is far ahead of the supply. Thank God however for the consolation that when the last man is killed, the war will be over. This war you know, differs from all previous wars in having no object to fight for. It can't be finished until all the men on either the one side or the other are killed. Both sides are trying to do that as fast as they can because it would be a pity to spin this affair out for two or three years longer!"
(Washington Roebling).

"Dear Henry; I feel more lonely and sadder than I have been in some time. Oh that I knew what the termination of this awful conflict would be. Henry, I want to see you, but don't you come. Join for the war if it is 40 years. If you get killed, tis the most honorable death. If you escape, I will rejoice. I love thee still".
(Mollie Vanderberg).

"Our bleeding, bankrupt, almost dying country longs for peace, shudders at the prospect of further wholesale devastation, of new rivers of human blood"
(Horace Greeley).....

Hundreds of Confederate soldiers were deserting every day, cold hungry, barefoot, driven by desperate letters from home....

My own corps was stretched until the men stood like a row of vedettes 15 feet apart. It was not a line, it was a mere skeleton of a line".
(Confederate General John. B Gordon)

Ulysses S. Grant and Robert E. Lee had faced one another in front of Petersburg for 9 months. Slowly, steadily Grant had extended his trenches around Petersburg. Lee's lines had been forced to stretch too, but his army was shrinking. In 9 months 60,000 Southern soldiers had deserted.

"All of us think we're whipped now. The men are ragged and are getting half rations. Some say we'll have to go to Georgey, but the men will not go there".
(Confederate soldier)

The thinning Confederate lines around Petersburg finally extended 53 miles. Grant's forces numbered 125,000. Lee's had dwindled to 35,000. Lee's only hope lay in moving his army to the southwest to link up with Johnston in the hills of North Carolina and fight on. On March 25, Confederates under John B. Gordon mounted a sudden night assault that briefly won possession of an earthwork called Fort Stedman. It was Lee's last advance. Grant counterattacked, racing around the rebel flank to block Lee's escape at Five Forks. There on April 1 he routed a Confederate division under George Pickett.

The next day Union forces attacked all along the Petersburg line. Slowly, relentlessly, and at great cost they drove the Confederates out of their trenches. Amoung the Southern dead left behind were shoeless boys as young as 14.

"The conduct of the Southern people appears many times truly noble, as exemplified for instance in the defense of Petersburg, old men with silver locks lay dead in the trenches side by side with mere boys of 13 or 14. It almost makes one sorry to have to fight against people who show such devotion for their homes and their country"
(Washington Roebling).

A.P Hill who had served Lee faithfully in a dozen battles and staved off Confederate disaster at Antietam, tried to rally his men. Two Union infantrymen shot him dead as he rode between the lines

"He is at rest, and we who are left are the ones to suffer"
(Robert E. Lee)

Petersburg, the scene of 9 months siege fell to Grant's army. As black civilians cheered the black soldiers that led the Union columns into the city, Lee's army slipped across the Appomattox River.

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

Ulysses S. Grant was close to breaking point. He rarely showed emotion, but at Cold Harbor, he is reported to have momentarily broken down. Despite superiority in numbers, Cold Harbor was yet another shattering Union defeat at the hands of Robert E. Lee. It was the only time in the entire war, Grant would admit he had made a mistake, and it was a devastating one. In just seven minutes a staggering 7,000 men had gone down. It was the most concentrated killing of the war.

Although Lee lacked the man power to crush the Army of the Potomac, it was now clear to Grant, that he could not defeat Lee in pitched battle. Now he changed tactics. For the first time in the war Lee misread his adversary. Thinking that Grant would next make directly for Richmond he began to concentrate his troops there. But Grant had no intention of repeating the Wilderness, Spotsylvania or Cold Harbor in front of Richmond. Instead he headed south towards the James River, to take the city of Petersburg, a critical transport and supply hub for the Confederate capital. If he could not defeat Lee, then he would starve him out. "General Grant, I begin to see it", Lincoln wrote to him, "You will succeed. God bless you!"

But Lee quickly understood Grant's strategy, and as usual he moved quickly. By the time Grant got to Petersburg, Lee was already waiting for him. But Grant did not attack. He dug in and continued to build up a huge investing army. The siege of Petersburg would drag on for nine long months. Slowly the Confederate army starved, and shrank from constant daily casualties, but then even worse followed. Answering desperate calls from starving families Confederates began to desert back to their homes and farms, now being devastated by William Tecumseh Sherman. Finally on March 25th, Lee sent word to Jefferson Davis, that his lines had been broken, but he would try to escape from Petersburg with what was left of his army, and link up with whatever was left of Joe Johnston's army out west. Accordingly, came the shocking news, Richmond would have to be abandoned. It was the beginning of the end for the South.

In cases of paliperidone overdose, there will be no quick victory. We must like, General Grant, change strategy to meet this situation. A direct assault with charcoal will do us no good, rather we must dig in and be prepared for a prolonged siege!

Union trench works outside Petersburg, April 1865.

….Petersburg is a magnificent salute to the durability of men on both sides. It was a rehearsal for World War I trench warfare,. (Shelby Foote).

PALIPERIDONE OVERDOSE

Introduction

Paliperidone, (trade name in Australia "**Invega**") is a second generation, "atypical" antipsychotic agent.

Paliperidone is actually **9-hydroxyrisperidone** a major *active metabolite* of **risperidone.**

It is as effective as any of the newer antipsychotic agents and has far less (if any) extrapyramidal side effects that are characteristic of the older agents.

Paliperidone **tablets** have a unique delivery system. They are composed of a trilayer core with 2 drug layers and an osmotic layer that facilitates a prolonged controlled drug delivery a 24 hour period.

In consequence the toxic manifestations of overdose with paliperidone extended release tablets, are delayed in onset, and prolonged in duration.

The *main* toxic features of overdose with extended release paliperidone include:

1. Drowsiness / reduced conscious state.

2. Significant tachycardia:

    - **Delayed onset** of **extreme** and **sustained tachycardia** (190 bpm) has been reported to occur at up to **20 hours** [4] *post* overdose in *larger* ingestions of paliperidone.

      Tachycardias can persist for up to **72 hours**.

      Tachycardias can be **posture-evoked**

3. Mild hypotension

4. Dystonias

Treatment is supportive.

See also separate document on Paliperidone in Toxicology folder.

History

Chlorpromazine was developed in 1950.

It was the first drug developed with a specific antipsychotic action and served as the prototype of the phenothiazine class of antipsychotic drugs that followed it.

The introduction of chlorpromazine during the 1950s into clinical use for schizophrenia and acute psychoses represented a significant advance in the history of psychiatry.

The "atypical" or second generation antipsychotics were developed and introduced into clinical practice during the 1990s. Olanzapine, **risperidone,** and quetiapine were introduced initially while ziprasidone and aripiprazole came onto the market in the early 2000s.

Paliperidone was introduced into clinical practice in the US in 2006.

The novel slow release delivery system of paliperidone was developed by the ALZA Corporation, which pioneered the use of osmotic pumps for oral drug delivery.

Preparations

Paliperidone as:

Extended release tablets (but capsule shaped):

- 3 mg (white, marked PAL 3)
- 6 mg (beige, marked PAL 6)
- 9 mg (pink, marked PAL 9)
- 12 mg (dark yellow, marked PAL 12)

The drug is delivered in a slow controlled fashion, via an **O**smotic Controlled **R**elease **O**ral Delivery **S**ystem (or "OROS") - **See Appendix 1 below**.

Paliperidone **palmitate** as:

Ampoules for 1 monthly IM depot administration ("Invega Sustenna"):

- 25 mg (syringe)
- 50 mg (syringe)
- 75 mg (syringe)
- 100 mg (syringe)
- 150 mg (syringe)

Ampoules for 3 monthly IM depot administration ("Invega Trinza"):

- 175 mg, 0.875 mL (syringe)

- 263 mg, 1.315 mL (syringe)
- 350 mg, 1.75 mL (syringe)
- 525 mg, 2.625 mL (syringe)

Toxicology

Features in overdose are expected to be similar to those seen with risperidone overdose, however they may be delayed in onset far more prolonged due to the sustained release nature of paliperidone preparations.

Dystonic reactions have been reported.

Neuroleptic malignant syndrome has been reported.

Pharmacokinetics

Absorption:

- Paliperidone extended release oral tablets:

  Following a single dose, the plasma concentration of paliperidone rises steadily to reach peak plasma concentrations in around 24 hours after ingestion.

  Levels are dose proportional within the recommended clinical dose range (i.e. 3 - 12 mg).

  Steady-state concentrations of paliperidone are attained within four to five days of dosing in most subjects.

  The absolute oral bioavailability of paliperidone following a administration of the extended release preparation is around 30 %.

- Paliperidone **palmitate** as IM depot preparation:

  Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation.

  Paliperidone **palmitate** → paliperidone
  ↑
  Hydrolysis

  Following a single IM (**1 monthly formulation**) dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of **13 days**. The release of the drug starts as early as day 1 (and may last for as long as 126 days).

Following a single IM (**3 monthly formulation**) dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of **30-33 days**.

Distribution

- The apparent volume of distribution of the oral extended release preparation of paliperidone is 487 L.

- The plasma protein binding of paliperidone is around 75%.

  It binds primarily to α1-acid glycoprotein and albumin

- It is unknown if paliperidone crosses the human placenta.

- Paliperidone is excreted into human breast milk but only in very small amounts.

Metabolism and excretion:

- Around 30 % is metabolized in the liver, primarily by cytochrome P450 - CYP2D6 and CYP3A4 enzymes.

  Despite the large variation in the general population with regard to the ability to metabolize CYP2D6 substrates, population pharmacokinetic analyses indicated no discernable difference on the exposure and apparent clearance of paliperidone after administration of Invega between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

  Up to 70 % is excreted unchanged in the urine.

- The terminal elimination half-life of oral paliperidone is prolonged at approximately 23 hours.

  The terminal elimination half-life of IM (1 monthly) depot paliperidone is around 25 to 49 days.

Risk assessment

No deaths have been reported from paliperidone toxicity **alone** although death has been reported in the context of a mixed overdoses that have included paliperidone. [2]

The median dose for those experiencing moderate toxicity has been quoted as: [2]

- 12 mg (range 3 - 63 mg) in children under 6 years

- 25.5 mg (range 1.5 - 4600 mg) in adults

Clinical features

Extended release oral dose takes 24 hours to reach peak plasma concentrations.

The plasma half-life of oral paliperidone is 23 hours.

In consequence the toxic manifestations of overdose with paliperidone extended release tablets, are delayed in onset, and prolonged in duration.

Clinical features of paliperidone toxicity are essentially similar to those of **risperidone**.

Toxic features of overdose with extended release tablets may include:

1. CNS:
    - Sedation
    - Mild confusion
    - Coma is *uncommon* when **risperidone** is taken alone, and if present should prompt consideration of co-ingestion or alternative diagnosis.
    - Extrapyramidal effects may be seen, **acute dystonias** are relatively common.

      Extrapyramidal effects (especially in children) may be seen up to 3 days post ingestion.
2. Ocular:
    - Both miosis and mydriasis have been reported.
3. CVS:
    - Mild hypotension
        - ♥ Including orthostatic hypotension.
    - **Delayed onset** of **extreme** and **sustained tachycardia** (190 bpm) has been reported to occur at up to **20 hours** [4] *post* overdose in *larger* ingestions of paliperidone.

      Tachycardias can persist for up to **72 hours**.

      Tachycardias can be **posture-evoked**
4. Anticholinergic effects, (rare).

5. Metabolic:

    - Note that the *therapeutic* use of all antipsychotic medicines has been associated with the development of neuroleptic malignant syndrome. [2] This condition overall, however is uncommon.

6. Dystonic reactions

7. Neuroleptic malignant syndrome (rare)

Investigations

1. ECG

    - Sinus tachycardia will be the main feature
    - Look for prolonged QT or QRS intervals

2. As with any intentional overdose consider the possibility of coingestion

    - Blood alcohol level
    - Paracetamol level

Management

Management is supportive

1. Attention to any ABC issues:

    - IV access
    - Establish continuing cardiac monitoring.

2. Charcoal:

    - CNS depression is a likely consequence of significant overdose and general supportive measures should be undertaken in preference to decontamination.
    - Charcoal may be administered to patients who have been **intubated**.

3. Hypotension:

    - IV fluids are usually sufficient to correct this.
    - If blood pressure fails to resolved hypotension, vasopressors/ inotropes will be required.

4. Extreme tachycardia: [3,4]

This has been treated (without any particular success) with:

- IV fluids
- IV Mg SO_4

Adenosine does **not** appear to be effective, confirming that the tachycardia is sinus in origin. [4]

4. Dystonic reactions:

- As with risperidone, acute dystonic reactions may occur up to 2 - 3 days after acute ingestion in a patient who is not normally receiving this paliperidone.

  This need not be a reason to keep patients in hospital for 3 days but they should be warned that these reactions occur very rarely and advised to return if they develop symptoms.

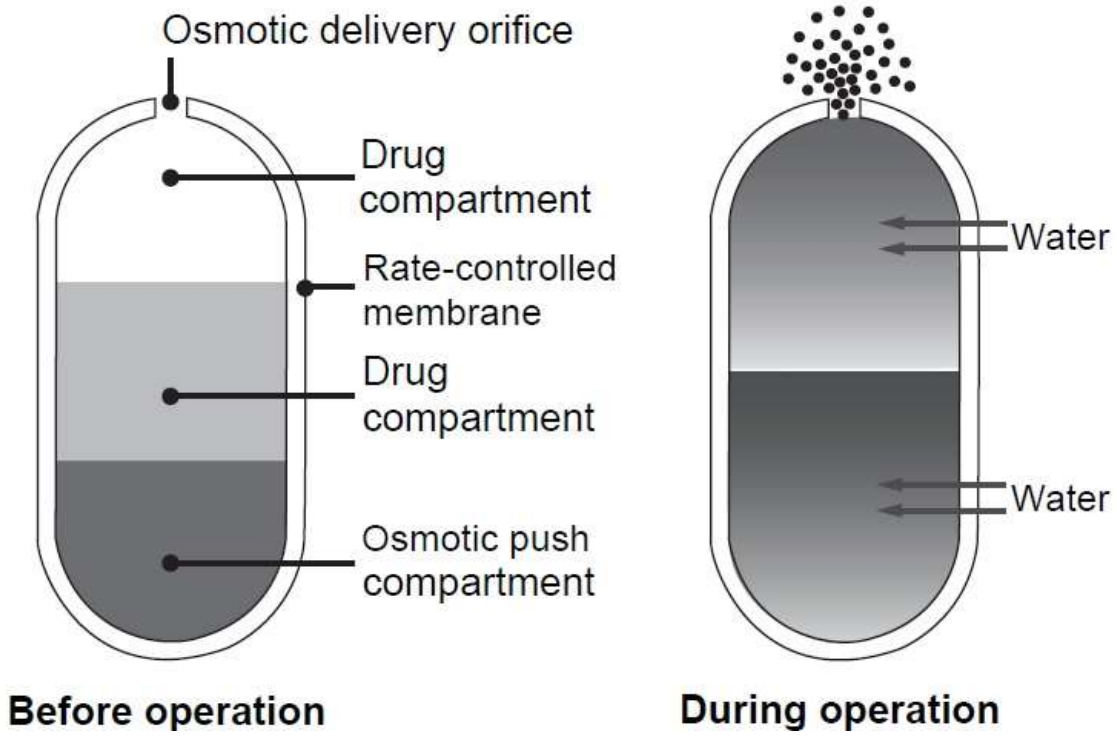
Disposition

If medical observation is required the patient should be monitored for the **onset** of or **worsening** of symptoms for *at least* **24 hours** following ingestion

On the basis of the limited evidence available, **prolonged cardiac monitoring** following ingestion of **> 0.4 mg/kg or 5-fold ingestion of the normal dose** of paliperidone has been recommended. [3]

Appendix 1

Osmotic Controlled Release Oral Delivery System (OROS):



Paliperidone is delivered slowly via a novel osmotic delivery system.

The "OROS" *(**O**smotic Controlled **R**elease **O**ral Delivery **S**ystem) is a controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it.*

As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, into an osmotic push compartment, and the resulting osmotic pressure swells this compartment and so pushes the active drug through the opening(s) in the tablet.

Multiple drug layers provide increased flexibility and control over the pattern of release of medication from the system, as opposed to the single layer, which can deliver a drug only in a zero order fashion. For example, two drug layers can be formulated with different drug concentration to provide modulation in the release rate profile.

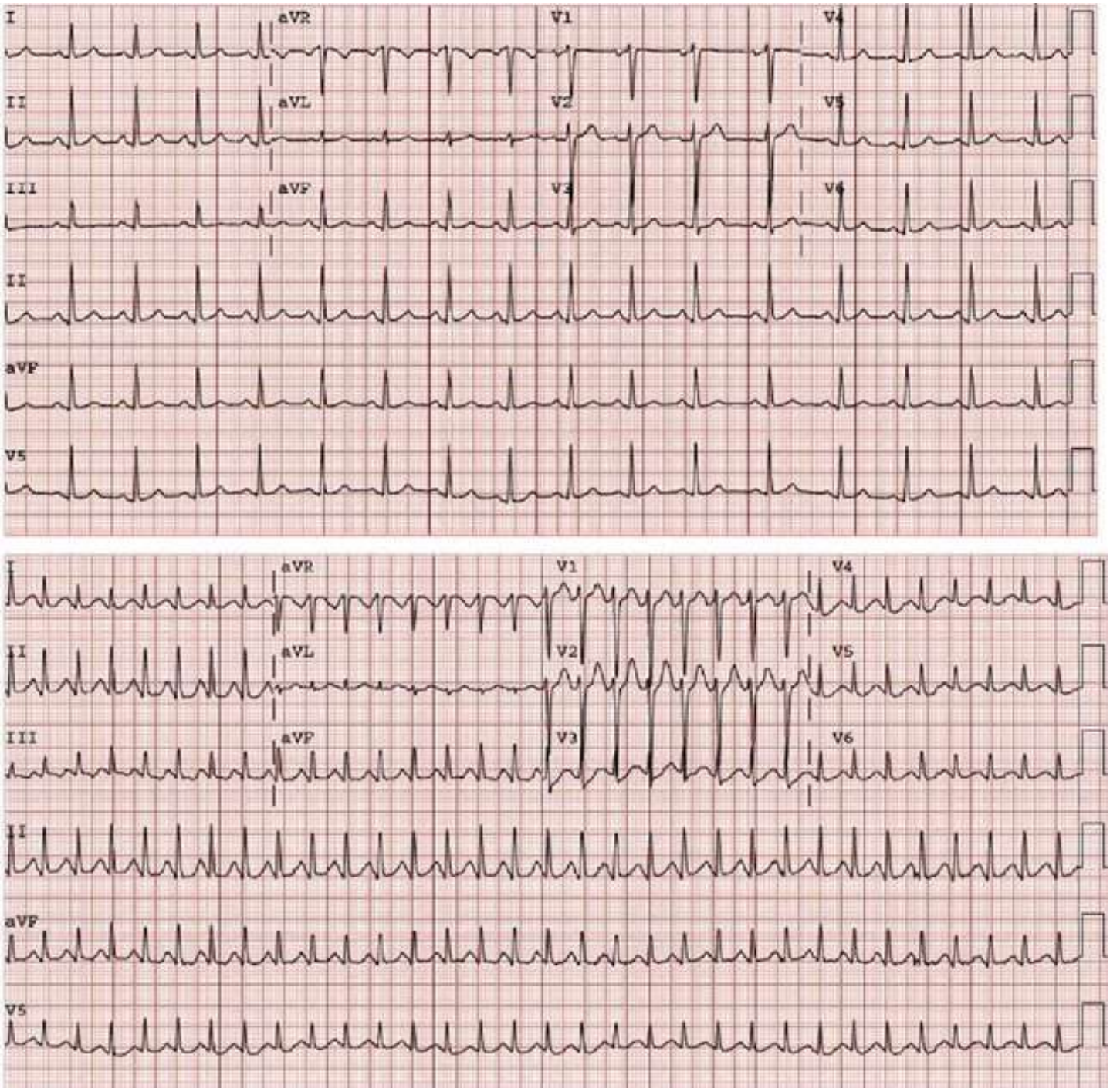
Osmotic release systems have a number of major advantages over other controlled-release mechanisms.

They are significantly less affected by factors such as pH, food intake, GI motility, and differing intestinal environments. Using an osmotic pump to deliver drugs has additional inherent advantages regarding control over drug delivery rates.

This allows for much more precise drug delivery over an extended period of time, which results in much more predictable pharmacokinetics.

However, osmotic release systems are relatively complicated, somewhat difficult to manufacture, and may cause irritation or even blockage of the GI tract due to prolonged release of irritating drugs from the non-deformable tablet.

Appendix 2



Above: ECG at presetation **1 hour** after ingestion of 180 mg of extended release paliperidone, by a 14 year old female.

Below: Her ECG at **20 hours** post ingestion! (*Levine et al*).

References

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