

PARACETAMOL



"Candaules, King of Lydia, Shews his Wife by Stealth to Gyges, One of his Ministers, as She Goes to Bed", oil on canvas, 1830, William Etty.

In this department the exactitude of the Greeks is inconsistent, in placing the painters many Olympiads after the sculptors in bronze and chasers in metal, and putting the first in the 90th Olympiad....And then it is not equally admitted that Candaules, the last king of Lydia of the Heraclid line, who was also commonly known by the name of Myrsilus, gave its weight in gold for a picture of the painter Bularchus representing a battle with the

Magnetes. So high was the value already set on the art of painting. This must have occurred at about the time of Romulus, since Candaules died in the 18th Olympiad, or according to some accounts, in the same year as Romulus, making it clear, if I am not mistaken, that the art had already achieved celebrity, and in fact a perfection. And if we are bound to accept this conclusion, it becomes clear at the same time that the first stages were at a much earlier date, and that the painters in monochrome, whose date is not handed down to us, came considerably earlier.....

*Pliny the Elder, “The Natural Histories”, Bk XXXV; 55
77-79 A.D*

This Candaules of whom I speak was passionately in lust with his wife; and he deemed that his wife was fairer by far than all other women...and thus saying, to Gyges, “Gyges, I think that you do not believe me when I tell you of the beauty of my wife, for it happens that men’s ears are less capable of belief than are their eyes: I order you therefore to contrive a means by which you may look upon her naked!”. But Gyges cried out alarmed and said: “Master, what words of craziness are these which you utter, bidding me look upon my Queen naked?... I believe indeed that she is the fairest woman of all and I beg you please not to ask of me that which is not proper for me to do!”.

With such words as these he resisted, fearing lest some evil might come to him from this; but the King answered him thus, “Courage, Gyges! And have no fear, either of me...For I will contrive it so from the first she shall not even perceive that she has been seen by you. I will place you in the room where we sleep, behind the open door, and after I have gone in, my wife also will come to lie down. Now there is a seat near the entrance of the room, and upon this she will lay her garments as she takes them off one by one; so you will be able to secretly gaze upon her at full leisure....”

Candaules, when he considered that it was time to rest, led the protesting Gyges to his chamber; and soon after this the Queen appeared: and Gyges looked upon her after she came in and as she laid down her garments; and when she had her back turned towards him, as she went to the bed, then he slipped away from his hiding-place. But as he was sneaking away, the Queen caught sight of him, and perceiving that which had been done to her by her husband, and though struck with shame, she did not cry out,, but made out as though she had not perceived the matter at all, meaning all the time, to avenge herself upon Candaules...

At the time then she kept silent, as I say, and made no outward sign that she knew what had happened; but as soon as day had dawned, and she made ready those of her servants whom she perceived to be the most loyal to herself, and after that she sent a summons to Gyges. He then, not supposing that anything of that which had been done was known to her, came upon her summons; for he had been well accustomed before to go whenever the Queen summoned him....

*The Queen said, “There are two ways open to you, Gyges, and I give you the choice. Either you kill Candaules and possess both me and the kingdom of Lydia, or I will have **you** killed here on the spot!” Either he must die who formed this disgusting plan, or you must, who have looked upon me naked...”.*

Gyges was amazed at these words, and he began to entreat her that she should not bind him to make such a terrible choice: but as he could not prevail with her, but saw that set before him, either to slay his master or to be himself slain by others, he made the choice to live...

And she answering said, “From that same place shall the assassination be, where he displayed me naked; and we will lay hands upon him as he sleeps”... when night came on, he followed the Queen to the bedchamber; and she gave him a dagger and concealed him behind that very same door. Then afterwards, while Candaules was sleeping, Gyges snuck up to him and slew him, and so he obtained both the king’s wife and his kingdom...and in this manner the Mermnadai line obtained the kingdom of Lydia, from the Heraclid line....

Herodotus, “The Histories” I - 8 c. 450 - 420 B.C

Following the sensational discovery of the Laocoön in Rome in 1506, the reputation of Pliny the Elder’s “Natural History” as a credible source for the history of the ancient world, was never greater. Renaissance scholars went back to the work and studied it in minute detail, eager to glean even the slightest fragment of anecdote that may give a truer and clearer picture of a time long past. The Kingdom of Lydia, roughly centred on the west of today’s modern Turkey, was ancient indeed, even in the time of Pliny. Its history predicated that of the generally accepted date of the foundation of Rome by Romulus in 717 B.C. Its story falls roughly into three distinct ages, the first existing only in mythology, the second, a tantalizing mix of mythology and fact and the third that falls within the time of recorded history. What makes Pliny’s anecdote on King Candaules intriguing indeed is that this king reigned just on the threshold that divides a mythical age from a historical one, and that Pliny is able to give us a “ball park” date for the time at which this king reigned.

In his “Natural History”, he debates the apparently widely held view of the Greeks of his day that the art of painting (as it was then practiced) was developed around the time of the 90th Olympiad, which would date this cultural milestone at around 420-417 B.C, and that this art came after sculpture. However Pliny has an original source, (now long since lost), that relates a story of Candaules, the king of Lydia, that says that he paid a certain Artist, Bularchus, for his painting in the weight of his large (as we learn from an earlier anecdote, NH 7.126), work in pure gold. He dates this event to the 18th Olympiad. We learn much from this priceless anecdote. Firstly the art of painting had reached a very high degree of sophistication, as early as 708-705 B.C (i.e the 18th Olympiad), and it clearly predates the great sculptures and bronzes of the Greeks. Secondly, high-end art was greatly prized by powerful kings, a point not lost on both Artists and Princes of the Renaissance! Painting was not merely a “trade” done by anonymous workers for the glory of God, as it had come to be known during the Middle Ages, rather it was the highest form of Art produced by famous individuals, whose works were eagerly sought after by Kings and Queens. This anecdote from Pliny, did much to raise the prestige of Renaissance Artists in the eyes of powerful patrons such as the Medici of Florence. Suddenly great Princes sought to outdo one another in the brilliant works of Art they possessed, and indeed the prestige of the Artists themselves rocketed to levels not seen

since the time of the ancient Greeks. It was the brilliant rebirth of prestige of a long lost Art form.

But apart from the Arts, Pliny helped drag the history of Lydia from the age of mythology into that of recorded history. Candaules is one of the earliest kings of Lydia to enter into the historical record. We know that he was killed in some type of palace coup, and his line, the Heraclids lost the throne to a new dynasty, the Mermnadai, whose first king was a man called Gyges, and who legitimized his usurpation of the throne by marrying Candaules' widowed Queen. By Pliny, we can date this event to around 717 B.C, the generally accepted date for the foundation of Rome.

But Pliny's history, now gave an intriguing new insight into a far more ancient "History", that of the 5th century B.C Greek historian, Herodotus, who relates a story on just how exactly Gyges came to the throne! According to Herodotus, Candaules not only lusted after high-end Art, he also greatly lusted after "high end" women as well. It was said that his Queen was the most beautiful woman in all of Lydia. Yet Candaules was not satisfied with all that he had, we wanted very much to flaunt it as well, apparently ordering his close friend Gyges to gaze upon his unsuspecting wife, naked so he could prove that his boasts were true! But Candaules got far more than he than he had bargained for, or perhaps rather what he deserved. His Queen, discovered the plot, and, supposedly, could not live with the shame of some man, other than her husband, seeing her naked, and so having no particular fondness for Candaules gave Gyges a choice. "The only man who is allowed to see me naked is my husband", she informed him, "so either you become my husband....or you die!" Gyges did not hesitate, he murdered Candaules in his sleep. To modern sensibilities, the story appears like "spin" of the highest order- Gyges usurps the throne of Lydia, the Queen's honour remains intact. Of course another explanation is possible - Candaules catches his Queen, "in-flagrante" with Gyges, Gyges kills him, the Queen and Gyges live happily ever after! Sadly, unlike some other anecdotes, Pliny does not offer us any moral judgements on the characters, he merely uses them to date his theories on the development of the visual arts. In this latter, he succeeds admirably, though no paintings survive from the 8th century B.C we do know that this painting had reached a high level of sophistication by this early date. Pliny was far more correct than he could have possibly known in his assertion that "monochrome" Art, that is the very first forms of painting, would have been very much more ancient than the 8th century B.C. He would have been staggered to know, that in the cave Art of the Neolithic, the first human art is at least 30,000 years old!

Paracetamol is the world's most widely used analgesic, antipyretic agent. So commonly is it used, so readily is it available, it is quite literally the Queen of all the simple oral analgesic agents! And yet its potentially toxic effects are virtually unknown by the general public, whose perception of it is generally one of harmlessness. It is frequently used inappropriately in routine dosing on the principal of "more is better". Similarly for the dramatic gesture of overdose it is taken, when no real intention to die is in the mind of the overdoser, just a goodly dose of "secondary gain". Yet paracetamol is not benign in either of these situations! As the story of King Candaules informs us, inappropriate use of the Queen can lead to drastic unintended consequences not dreamed of - death!

PARACETAMOL

Introduction

Paracetamol (or in North American parlance, **acetaminophen**) is a very widely used mild analgesic and antipyretic agent.

In overdose paracetamol is potentially lethal, (a fact, fortunately, not widely appreciated by the lay public).

Although it is only a mild analgesic agent it has a number of significant advantages over other analgesic agents, (as below).

See also separate Document on:

- **Paracetamol Overdose (in Toxicology folder)**

Advantages

- No respiratory depression
- No CNS depression
- No constipation
- No GIT mucosal damage
- Allergic reactions are very rare
- Does not cause analgesic nephropathy with long term use.

Disadvantages

- Should not be used in significant liver failure/ disease.

Chemistry

Paracetamol is a para-aminophenol derivative

Preparations

Paracetamol as:

Tablets:

- **500 mg** (*immediate release*)
- **665mg** (*modified release*).

Modified tablets should not be chewed or crushed before swallowing. Each contains **665 mg** of paracetamol and provides up to 8 hours pain relief; **3 times** daily dosing appears to be clinically equivalent to immediate release paracetamol which is taken **4 times daily.**¹

Some formulations (such as “**Panadol Osteo**”) incorporate a *combined* formulation for an immediate release and a sustained release dose of paracetamol as **69% modified-release** and **31% immediate-release** paracetamol in each 665 mg tablet.

Liquid:

- A wide range of concentrations available for paediatric use.
 - ♥ Most commonly: **125 mg/ 5mls, 240 mg/ 5mls.**

Suppositories:

- Generally available in **125 mg, 250 mg** and **500 mg** strengths.

Ampoules:

- Vials containing paracetamol **10 mg/mL of 50 mL, 100 mL**
Therefore **1gram of paracetamol in 100 ml.**

Composite:

- Note that paracetamol is frequently present in a large number of **composite medications**, most commonly in combination with codeine in many cough and cold products.

Mechanism of Action

The exact mechanism of action of paracetamol is uncertain but is thought to involve complex actions on **prostaglandin synthesis**.

Analgesic effects may include inhibition of central prostaglandins

The antipyretic effect is probably related to reduced production of prostaglandins within the hypothalamus

Pharmacodynamics

Actions include:

1. Analgesic:

- Mild to moderate efficacy
2. Antipyretic

Paracetamol has **negligible** anti-inflammatory effects.

Pharmacokinetics

Absorption:

Paracetamol can be given **orally, rectally and intravenously.**

Orally:

- Paracetamol is rapidly absorbed from the small intestine.
- The onset of pain relief is approximately 30 minutes after oral administration.²
- Peak serum concentrations occur within 2 hours for standard tablet or capsule formulations and within 30 minutes for liquid preparations.
- Peak serum concentrations after therapeutic doses do not usually exceed 130 micromol/L.

Rectally:

- The recommended rectal and oral doses are generally the same; however, the rectal dose required to produce a plasma concentration may be higher than that using the oral route, and rectal absorption can be erratic.

IV:

- Following **IV administration**, onset of action is within **5 to 10 minutes**, **peak effect is at one hour**, and **duration is 4 to 6 hours.**¹

Distribution:

- The volume of distribution of paracetamol is approximately 1 L/kg.

Distribution is to most tissues and usually occurs within 4 hours of ingestion for standard preparations and two hours for liquid preparations.
- It is not extensively bound to plasma proteins, at 10-25 %.
- Paracetamol can cross the human placenta.
- Paracetamol is excreted into human breast milk in small amounts.

Metabolism and excretion:

The elimination half-life is 1.5 - 3 hours.

20 % of an ingested dose undergoes first pass metabolism by sulphation in the gut wall.

The remainder then undergoes hepatic metabolism via two pathways:

- 90% undergoes hepatic metabolism to inactive conjugates of sulphate and glucuronide, which are excreted in the urine.
- 10% is metabolized by cytochrome P450 oxidation to give a highly reactive metabolite N-acetyl-p-benzoquinoneimine, (NAPQI).

This in turn is immediately bound by intracellular glutathione and is then eliminated in the urine as inactive mercapturic metabolites.

Large doses of paracetamol may saturate sulphate and glucuronide conjugation mechanisms. Once this occurs, there will be increased metabolism via the cytochrome P450 pathway.

When glutathione depletion reaches a critical level (believed to be about 30 % of normal stores) NAPQI begins to bind to other intracellular proteins resulting in hepatocyte damage.

Indications

Indications for paracetamol are:

1. Mild analgesia
2. Antipyretic

Note that in the case of **osteoarthritis**, regular paracetamol alone is the preferred longer treatment but in general very much under-used.²

Contraindications/ Precautions

These include:

1. Liver disease/ those with low reserves of **hepatic glutathione**:
 - In patients with chronic or active hepatic disease, especially those with hepatocellular insufficiency, including those with chronic alcoholism or chronic malnutrition, paracetamol should be avoided or otherwise used with caution, (e.g. the dose should not exceed **3 grams** per day).

2. Those with allergies to paracetamol, (very rare).
3. Do not exceed the **maximal daily dose of 4 grams**:

The **total** 24 hourly dose of paracetamol for adults should not exceed 4 grams /day.

It is important to consider the contribution of *all* paracetamol-containing medications, including nonprescription, oral or PR (per rectum) forms of the drug to this total daily paracetamol dose prior to administering other dose forms.

If the daily dose of paracetamol from **all sources** exceeds the maximum, hepatic injury may occur.

Pregnancy:

Paracetamol is a Class A drug with respect to pregnancy.

Class A drugs are drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Maternal use of paracetamol has not been associated with an increased risk of congenital malformations.

Paracetamol is safe to use during pregnancy.

Several systematic reviews have suggested there may be a link between prenatal paracetamol exposure and an increased risk of childhood asthma. However, further investigations are needed to confirm these findings.

Breast Feeding:

Small amounts of paracetamol are excreted into breast milk (9), but these amounts are unlikely to pose harmful effects in breastfed infants.

Paracetamol is safe to use during breastfeeding.

Adverse Reactions

Paracetamol, in usual therapeutic dosing, is generally considered a very safe analgesic with a low incidence of adverse effects compared with other drugs.

The following may be seen:

1. Hypersensitivity skin reactions, e.g. rash, fixed drug eruption, toxic epidermal necrolysis and Stevens-Johnson syndrome, (rare).
2. Allergic reactions, (rare).
3. Mild reversible elevation in liver transaminases.

Dosing

Oral dosing:

Adults:

- Paracetamol **500 mg to 1 gram every 4 to 6 hours**, to a generally accepted maximum of **4 grams per day**.¹
- **Sustained release preparations (i.e “Panadol Osteo”)** for **adults and children over 12 years**.
 - ♥ **Two tablets**, swallowed whole, 3 times a day, i.e **8 hourly** (maximum of **6 tablets** in any **24 hours**).
 - ♥ These tablets must not be crushed.

Children:

- 20 mg/kg loading dose, then **15 mg/kg** 4 - 6 hourly.
- Usual daily maximum of 90 mg/kg for 48 hours then 60 mg/kg thereafter.⁶
- For infants < 10 Kg, the maximal daily dose should not exceed 30mg/kg per 24 hours.⁴

See also Appendix 1 below for oral dosing charts for children.

Rectal Dosing:

The recommended rectal and oral doses are generally the same; (15 mg/kg every 4 - 6 hours) however, the rectal dose required to produce a plasma concentration may be higher than that using the oral route, and rectal absorption can be erratic.¹

The oral route is preferred to the rectal route whenever possible.²

Intravenous Dosing:

This is essentially the same as oral dosing, give: **1 gram IV 4 hourly - 6 hourly** (to a maximum of 4grams per 24 hours)

Intravenous doses should be infused slowly over **15 minutes**.

Appendix 1

Paracetamol Dosing Chart for Children (15mg/kg):

Weight (kg)	Dose in mls Panadol (Double Strength) 240 mg / 5ml (48 mg/ 1ml) Dose 15mg / kg = 0.3125 mls/kg	Dose in mls Panadol (Normal Strength) 125 mg / 5ml =25 mg/ml Dose 15mg / kg = 0.6 mls/kg	Total Dose in mg, (Regardless of paracetamol strength) 15 mg/kg
10	3.125 mls	6 mls	150 mg
11	3.4 mls	6.6 mls	165 mg
12	3.75 mls	7.2 mls	180 mg
13	4 mls	7.8 mls	195 mg
14	4.3 mls	8.4 mls	210 mg
15	4.6 mls	9 mls	225 mg
16	5 mls	9.6 mls	240 mg
17	5.3 mls	10.2 mls	255 mg
18	5.6 mls	10.8 mls	270 mg
19	5.9 mls	11.4 mls	285 mg
20	6.25 mls	12 mls	300 mg
21	6.5 mls	12.6 mls	315 mg
22	6.8 mls	13.2 mls	330 mg
23	7.1 mls	13.8 mls	345 mg
24	7.5 mls	14.4 mls	360 mg
25	7.8 mls	15 mls	375 mg
26	8.1 mls	15.6 mls	390 mg
27	8.4 mls	16.2 mls	405 mg
28	8.7 mls	16.8 mls	420 mg
29	9 mls	17.4 mls	435 mg
30	9.3 mls	18 mls	450 mg
31	9.6 mls	18.6 mls	465 mg
32	10 mls	19.2 mls	480 mg
33	10.5 mls	19.8 mls	495 mg
34	10.6 mls	20.4 mls	510 mg
35	11.1 mls	21 mls	525 mg

Paracetamol Dosing Chart for Children (20mg/kg):

Weight (Kg)	Paracetamol –	
	Dose (mg)	Dose (mls)
10	200 mg	4.16 mls
11	220 mg	4.6 mls
12	240 mg	5 mls
13	260 mg	5.4 mls
14	280 mg	5.85 mls
15	300 mg	6.25 mls
16	320 mg	6.66 mls
17	340 mg	7.08 mls
18	360 mg	7.5 mls
19	380 mg	7.9 mls
20	400 mg	8.3 mls
21	420 mg	8.75 mls
22	440 mg	9.2 mls
23	460 mg	9.6 mls
24	480 mg	10 mls
25	500 mg	10.4 mls
26	520 mg	10.8 mls
27	540 mg	11.25 mls
28	560 mg	11.7 mls
29	580mg	12.1 mls
30	600 mg	12.5 mls
31	620 mg	12.9 mls
32	640 mg	13.3 mls
33	660 mg	13.75 mls
34	680 mg	14.2 mls
35	700 mg	14.6 mls

References

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2. Paracetamol in Australian Medicines Handbook, October 2013
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