Acetanilide and Paracetamol

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Title:
Rise and fall of Acetanilide usage and essentiality of Paracetamol drug.

Abstract:

Acetanilide, a precursor to paracetamol, was once widely used as an analgesic and antipyretic medication. This review provides a comprehensive overview of acetanilide's history, pharmacology, and clinical use. We discuss its discovery, synthesis, and initial applications, as well as its mechanism of action, pharmacokinetics, and pharmacodynamics. Additionally, we examine the reasons for its decline in use, including concerns over toxicity, methemoglobinemia, and the development of safer alternatives. We also touch on its current status, including its use in some homeopathic preparations and potential applications in research. This review aims to provide a thorough understanding of acetanilide's past, present, and potential future, highlighting its significance in the history of pain management and its continued relevance in modern medicine.

Paracetamol (acetaminophen) is a widely used analgesic and antipyretic medication, employed to treat pain and fever. This review aims to summarize the current state of knowledge on paracetamol's pharmacology, efficacy, and safety. We discuss its mechanism of action, pharmacokinetics, and pharmacodynamics, as well as its effectiveness in various pain and fever conditions. Additionally, we examine the safety profile of paracetamol, including its potential for hepatotoxicity, allergic reactions, and interactions with other medications. We also explore recent developments in paracetamol research, including novel formulations and combination therapies. This review provides a comprehensive overview of paracetamol, highlighting its benefits and limitations, and underscoring the need for continued research into its optimal use and potential risks.

Description:

Acetanilide is an organic compound with the chemical formula C8H9NO. It is a white crystalline solid, used as:

1. *Pain reliever*: Acetanilide was one of the first non-steroidal anti-inflammatory drugs (NSAIDs), used to treat headaches, fever, and minor pains.
2. *Antipyretic*: It reduces fever by acting on the hypothalamus, the part of the brain that regulates body temperature.
3. *Analgesic*: Acetanilide has analgesic properties, making it useful for relieving mild to moderate pain.

However, due to its potential toxicity and side effects, such as:

1. *Methemoglobinemia* (elevated levels of methemoglobin in the blood)
2. *Cyanosis* (blue discoloration of skin and mucous membranes)
3. *Liver damage*

Acetanilide has largely been replaced by safer alternatives like acetaminophen (paracetamol) and ibuprofen.

It's still used in some applications, such as:

1. *Chemical synthesis*: As an intermediate in the production of dyes, pharmaceuticals, and other organic compounds.
2. *Research*: In scientific studies, acetanilide is used as a model compound to investigate various biological and chemical processes.

Remember to handle acetanilide with care, as it can be hazardous if ingested or inhaled.

Metabolite of acetanilide

The main metabolites of acetanilide are:

1. Paracetamol (Acetaminophen): The primary metabolite, accounting for about 80% of acetanilide's metabolism.
2. p-Aminophenol: A minor metabolite, formed through the hydrolysis of acetanilide.
3. N-Acetyl-p-aminophenol: Another minor metabolite, formed through the acetylation of p-aminophenol.
4. N-Hydroxyacetanilide: A minor metabolite, formed through the hydroxylation of acetanilide.

These metabolites are formed through various enzymatic reactions, including:

1. Hydrolysis: Breakdown of the amide bond in acetanilide.
2. Acetylation: Addition of an acetyl group to p-aminophenol.

3. Hydroxylation: Addition of a hydroxyl group to acetanilide.

The metabolism of acetanilide occurs mainly in the liver, through the action of enzymes such as:

1. Cytochrome P450
2. Esterases
3. Amidases

These metabolites are then excreted in the urine, with paracetamol being the primary excreted metabolite.

Aminophenol carcinogenic

Aminophenols, including p-aminophenol, have been classified as potentially carcinogenic by various organizations, including:

1. International Agency for Research on Cancer (IARC): Classified p-aminophenol as "possibly carcinogenic to humans" (Group 2B).
2. National Toxicology Program (NTP): Listed p-aminophenol as "reasonably anticipated to be a human carcinogen".
3. European Chemicals Agency (ECHA): Classified p-aminophenol as "suspected of causing cancer".

The potential carcinogenicity of aminophenols is attributed to their:

1. Metabolic activation: Conversion to reactive intermediates that can damage DNA.
2. DNA binding: Ability to bind to DNA, leading to mutations and cancer.
3. Oxidative stress: Generation of reactive oxygen species, causing cellular damage.

However, it's important to note that:

1. Risk assessment: The actual risk of cancer from exposure to aminophenols depends on various factors, including dose, duration, and individual susceptibility.
2. Regulatory measures: Many regulatory agencies have established limits and guidelines for exposure to aminophenols to minimize potential risks.

If you have concerns about exposure to aminophenols or potential health risks, consult a healthcare professional or qualified expert.

When acetanilide banned from market

Acetanilide was gradually phased out of the market in the mid-20th century due to concerns over its safety and potential toxicity. Here are some key milestones:

1. *1940s-1950s*: Reports of methemoglobinemia, cyanosis, and other adverse effects associated with acetanilide use began to surface.
2. *1950s-1960s*: Regulatory agencies, such as the US FDA, started to investigate and restrict the use of acetanilide.
3. *1963*: The FDA required warning labels on acetanilide-containing products, highlighting the risk of methemoglobinemia.
4. *1970s*: Acetanilide was largely replaced by safer alternatives like acetaminophen (paracetamol) and ibuprofen.
5. *1980s*: Many countries, including the US, Canada, and European nations, withdrew acetanilide from the market or restricted its use to prescription-only or industrial applications.
6. *1990s-present*: Acetanilide is no longer available for human use in most countries, and its use is generally limited to research, industrial, or veterinary applications.

Keep in mind that the exact timeline may vary depending on the country or region.

Difference acetaminophen and paracetamol

Acetaminophen and paracetamol are actually the same medication, with the same chemical structure and pharmacological effects. The difference lies in the name used in different regions:

1. Acetaminophen: This name is commonly used in the United States, Canada, and Japan.
2. Paracetamol: This name is widely used in Europe, Australia, New Zealand, and other parts of the world.

Both names refer to the same active ingredient, N-acetyl-p-aminophenol (APAP), which is used to relieve:

1. Pain (mild to moderate)
2. Fever
3. Headaches
4. Menstrual cramps
5. Toothaches

The difference is purely semantic, and both names are used interchangeably in medical literature and research.

Some interesting facts:

1. The name "acetaminophen" was coined by the American pharmaceutical company McNeil Consumer Products in 1950.
2. The name "paracetamol" was introduced in the UK in 1956.
3. Both names are used in different countries, but the medication remains the same.

In summary, acetaminophen and paracetamol are two names for the same medication, used to treat pain and fever.

Paracetamol (acetaminophen) was first synthesized in 1877 by German chemist Harmon Northrop Morse. However, it wasn't until the 1950s that it became widely used as a medication.

Here's a brief history:

1. *1877*: Harmon Northrop Morse synthesizes paracetamol while working at Johns Hopkins University.
2. *1887*: German chemist Josef von Mering discovers paracetamol's analgesic and antipyretic properties.
3. *1890s-1940s*: Paracetamol is used in various medications, but its use is limited due to concerns about toxicity and lack of standardization.
4. *1946*: American chemist Bernard Brodie and colleagues at the University of Michigan rediscover paracetamol's potential as a safe and effective analgesic.
5. *1950*: McNeil Consumer Products introduces paracetamol under the brand name Tylenol, marking the beginning of its widespread use.
6. *1956*: Paracetamol is introduced in the UK under the brand name Panadol.

Paracetamol was developed to address the need for a safer alternative to existing pain relievers, such as:

1. *Aspirin*: Had gastrointestinal side effects and was not suitable for children.
2. *Codeine*: Had addictive properties and was not suitable for long-term use.
3. *Morphine*: Had addictive properties and was not suitable for mild to moderate pain.

Paracetamol's invention and development were driven by the need for a reliable, effective, and safe pain reliever for widespread use.

Acetanilide use in homeopathy

Acetanilide has been still used in homeopathy, although its use is controversial and not widely accepted by the medical community.

In homeopathy, acetanilide is used in highly diluted forms, typically in potencies such as 6C, 12C, or 30C, to treat various conditions, including:

1. Headaches
2. Fever
3. Pain relief
4. Menstrual cramps
5. Toothaches

Homeopaths claim that the highly diluted solution of acetanilide retains its therapeutic properties while minimizing its toxic effects. However, there is limited scientific evidence to support its effectiveness, and many experts consider it a form of pseudoscience.

Some homeopathic products containing acetanilide are available over-the-counter, but their use is not regulated by the FDA in the same way as conventional medications.

It's essential to note that:

1. Acetanilide is toxic in large doses_.
2. Homeopathic preparations may not be standardized.
3. The effectiveness of homeopathic acetanilide has not been scientifically proven.

If you're considering using homeopathic acetanilide, consult a healthcare professional to discuss potential risks and benefits.

Acetanilide homeopathic triturations

In homeopathy, acetanilide triturations refer to the process of diluting and potentizing acetanilide to create a homeopathic remedy. Here's an overview of the process:

1. *Mother Tincture*: Acetanilide is dissolved in a solvent, usually ethanol or water, to create a mother tincture.
2. *Trituration*: The mother tincture is then subjected to a process called trituration, where it is:
   - Diluted with lactose or sucrose (1:10 or 1:100)
   - Ground and mixed repeatedly (usually 3-6 times)
   - Left to sit for a period (hours or days) to allow the mixture to "mature"
3. *Potentization*: The trituration is then potentized by further diluting and succussing (shaking) the mixture to create higher potencies (e.g., 6C, 12C, 30C).
4. *Final Product*: The resulting trituration is then filled into capsules, tablets, or liquids for use as a homeopathic remedy.

Homeopathic triturations of acetanilide are often labeled as:

Acetanilidum (Latin name)
Acetanilide 6C, 12C, 30C (indicating the potency)

Keep in mind that:

Homeopathic triturations are highly diluted and may not contain measurable amounts of acetanilide.
The effectiveness of homeopathic acetanilide triturations has not been scientifically proven.
Homeopathic products are not regulated by the FDA in the same way as conventional medications.

If you have questions or concerns, consult a healthcare professional or a licensed homeopath.

Use of acetanilide in homeopathy

In homeopathy, acetanilide is used to treat various conditions, including:

1. *Headaches*: Acetanilide is used to treat headaches, especially those accompanied by fever, fatigue, or menstrual cramps.
2. *Fever*: It's used to reduce fever and relieve associated symptoms like headache, fatigue, and general weakness.
3. *Pain relief*: Acetanilide is used to treat mild to moderate pain, such as toothaches, menstrual cramps, and joint pain.
4. *Menstrual issues*: It's used to treat menstrual cramps, heavy bleeding, and other symptoms associated with PMS.
5. *Toothaches*: Acetanilide is used to relieve toothache pain, especially when accompanied by fever or swelling.
6. *Neuralgia*: It's used to treat neuralgia, a condition characterized by sharp, stabbing pains in the face or head.
7. *Anxiety and stress*: Acetanilide is sometimes used to treat anxiety, stress, and restlessness.

Homeopaths often prescribe acetanilide in potencies such as 6C, 12C, or 30C, and the dosage may vary depending on the individual's symptoms and condition.

Please note that:

- Homeopathic uses of acetanilide are not supported by scientific evidence.
- Acetanilide can be toxic in large doses, and homeopathic preparations may not be standardized.
- Consult a healthcare professional or licensed homeopath before using homeopathic acetanilide.

Utility of paracetamol worldwide

Paracetamol (acetaminophen) is one of the most widely used medications globally, with a vast range of applications. Here are some examples of its utility worldwide:

1. *Pain relief*: Paracetamol is used to treat mild to moderate pain, including headaches, toothaches, menstrual cramps, and muscle aches.
2. *Fever reduction*: It's widely used to reduce fever in people of all ages, especially in children.
3. *Cold and flu*: Paracetamol is often used to relieve symptoms of cold and flu, such as headache, fever, and body aches.
4. *Menstrual relief*: It's used to treat menstrual cramps, heavy bleeding, and other symptoms associated with PMS.
5. *Post-vaccination pain*: Paracetamol is sometimes recommended to relieve pain and fever after vaccination.
6. *Chronic pain management*: It's used in combination with other medications to manage chronic pain conditions like arthritis, fibromyalgia, and lower back pain.
7. *Pediatric care*: Paracetamol is a common medication used in pediatric care to treat fever, pain, and discomfort in children.
8. *Emergency medicine*: It's used in emergency situations to treat acute pain, fever, and headache.
9. *Travel medicine*: Paracetamol is often included in travel kits to treat pain, fever, and other symptoms associated with travel-related illnesses.
10. *Low-cost alternative*: In many developing countries, paracetamol is a low-cost alternative to other pain relief medications, making it a vital component of primary healthcare.

Overall, paracetamol's utility lies in its:

- Wide availability
- Low cost
- Effectiveness in relieving pain and fever
- Safety profile (when used as directed)
- Versatility in treating various conditions

Its global utility is a testament to its importance as a medication.

What happens if production of paracetamol stopped ?

If the production of paracetamol were to suddenly stop, it would have significant consequences on public health and the pharmaceutical industry. Here are some potential effects:

1. Shortages and rationing: Immediate shortages would lead to rationing, prioritizing patients with severe pain or fever.

2. Increased use of alternatives; Other pain relievers like ibuprofen, aspirin, or opioids might see increased use, potentially leading to overuse or misuse.
3. Price increases: Remaining stockpiles would become more expensive due to high demand and low supply.
4. Black market emergence: A black market for paracetamol could emerge, with potential counterfeit or adulterated products.
5. Impact on vulnerable populations: The elderly, children, and those with chronic conditions would be disproportionately affected due to their reliance on paracetamol.
6. Delays in medical procedures: Some medical procedures, like surgeries or vaccinations, might be delayed or postponed due to the unavailability of paracetamol for post-procedure pain management.
7. Economic impact: The pharmaceutical industry would face significant economic losses, potentially leading to job losses and facility closures.
8. Research and development disruption: Ongoing research and development of new paracetamol-based medications or formulations would be halted or delayed.
9. Global health implications: The World Health Organization (WHO) might need to intervene to address the global shortage, potentially leading to international cooperation and agreements.
10. Long-term consequences: A prolonged shortage could lead to changes in prescribing practices, patient behavior, and the development of new treatment protocols.

It's essential to note that pharmaceutical companies and regulatory agencies have contingency plans in place to mitigate such scenarios. However, a global paracetamol production stoppage would still have far-reaching consequences.

What are major impurities present in paracetamol

Paracetamol (acetaminophen) can contain various impurities, including:

1. *4-Aminophenol*: A known impurity in paracetamol, formed during synthesis or degradation.
2. *4-Acetoxyacetanilide*: A related compound that can be present due to incomplete synthesis or degradation.
3. *N-Hydroxyacetaminophen*: A metabolite of paracetamol, potentially present as an impurity.
4. *Acetanilide*: A precursor in paracetamol synthesis, potentially present in small amounts.
5. *p-Chloroacetanilide*: A possible impurity, formed during synthesis or degradation.
6. *Phenol*: A known impurity in some paracetamol products, potentially introduced during manufacturing.
7. *Heavy metals*: Trace amounts of heavy metals like lead, mercury, or arsenic can be present due to contamination.
8. *Residual solvents*: Small amounts of solvents like ethanol, methanol, or acetone can remain from the manufacturing process.
9. *Polymorphic forms*: Paracetamol can exist in different polymorphic forms, which may affect its stability or efficacy.
10. *Degradation products*: Paracetamol can degrade over time, forming impurities like 4-aminophenol or N-hydroxyacetaminophen.

These impurities can arise from various sources, including:

- Synthesis or manufacturing processes
- Raw materials or starting compounds
- Degradation or decomposition
- Contamination during processing or storage

Regulatory agencies like the FDA and EMA set limits for these impurities in paracetamol products to ensure safety and efficacy. Manufacturers must test for and control these impurities to meet regulatory standards.

Conclusion:

Paracetamol (acetaminophen) is indeed one of the fastest-selling drugs globally, due to its:

1. Wide availability
2. Over-the-counter (OTC) status
3. Low cost
4. Effectiveness in relieving pain and fever
5. Safety profile (when used as directed)

Some interesting sales data:

1. Over 30 billion doses sold worldwide annually
2. $13.7 billion in global sales (2020)
3. 200 million prescriptions written in the US alone (2020)
4. Available in over 100 countries
5. Sold under various brand names, including Tylenol, Panadol, and Calpol

Its widespread use and sales make paracetamol a staple in many medicine cabinets and healthcare settings worldwide. So the quality of this drug must have to be checked frequently. Though Acetanilide is carcinogenic, the Acetanilide derivative mentioned in doi: 10.1038/srep29487 is an inhibitor of Hepatitis C Virus replication.

Keywords (1): acetanilide, analgesic, antipyretic, pharmacology, history, toxicity, methemoglobinemia.

Keywords (2): paracetamol, acetaminophen, analgesic, antipyretic, pharmacology, efficacy, safety, hepatotoxicity.

Autobiography: **Available in https://doi.org/10.5281/zenodo.13197704**

Reference:

https://doi.org/10.1038/srep29487

https://doi.org/10.5281/zenodo.12739871

Acknowledgement:

Andrea Magri, Alexander A.Ozerov,

Vera L.Tunitskaya,

Valdimir T.Valuev-Elliston, Ahmed Wahid,

Mario Pirisi, Peter Simmonds,

Alexander V.Ivanov,

Mikhail S.Novikov, Arvind H.Patel.