Common Pain Killers
Miscellaneous Factoids and Information

Chemistry Inspired by Pain

February 16, 2007
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Aspirin™* - acetyl ester of naturally occurring salicylic acid

Tylenol™ - acetaminophen

*Trade mark in Canada but this was lost in the US after WWI.
Ibuprofen

Aleve

Vioxx™
Vicodin™

OxyCotin™
Percodan™ - with aspirin
Pecoset™ - with acetaminophen

Fentanyl™
Aspirin

Kolbe-Schmit Reaction

- 5th Century BC willow bark extract
- Isolated in 1828 by Henri Leroux
- First Synthesis in 1853 by LaFont
- Kolbe first did this in 1860 at 1 atm, < 50 %
- Schmit ran it under pressure in quantitative yield.

Aspirin: New Crystal Structure

Figure 1. Crystal packing of aspirin forms I, II, and S. L. Price predicted form II. (a) Form I: 1D chains sustained by alternating carboxylic acid and acetyl group centrosymmetric dimers. (b) Form II: acid dimers are connected via catemeric methyl C−H···O and phenyl C−H···O (not shown) hydrogen bonds. (c) Acetyl group C−H···O dimers in form I and catemers in form II. (d) S. L. Price predicted form II. Note the similarity with the crystal packing of form II (b).

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Tylenol™: Acetaminophen

- First made in 1874 by Harmon Morse
- Up for sale in 1955
- Cox-3 inhibitor which only is found in the brain and spin
- Converted to N-arachidonoylphenolamine which is a known CB1 activator
- Prostaglandin synthesis inhibitor

Over doses lead to liver toxicity

COX - Cyclooxygenase

Prostaglandins - responsible for the perception of pain
• Prostaglandins work with cells to promote inflammation and other function.
• COX-1 is continuously secreted in the stomach and is required for gastrointestinal health. They promote the excretion of mucus in the stomach.
• COX-2 is associated with swelling injuries
Ibuprofen

- Inhibits COX-1 and COX-2 (mostly)
- Heart failure issues
- Available by prescription in 1974 in the US
- Over the counter in 1984
- (S)-(+-).ibuprofen is the active form. The inactive can be converted in the body to the active form.
SCHEME 1. The Boots Company Synthesis of Ibuprofen—The Brown Synthesis
Vioxx™

• Vioxx (Rofecoxib)- 2.5 billion sales and withdrawn in September 30, 2004. The largest selling drug to be withdrawn.
• An apparent 4 x increase heart attack risk over Aleve™

Mg monoperoxyphthalate hexahydrate

Quantitative

82 %

86 %

54 %
Aleve™

- Naproxen - introduced in 1976
- Over the counter in 1994
- Some data indicates an increase in heart attack risk and some states it decreases the risk.
- COX1 and COX2 inhibitor
Vicodin

- Hydrocodone
- Opium derived
- Opium goes back at least 3400 BC

\[
\text{Meerwein-Ponndorf-Verley like}
\]
OxyCotin™

- Oxycodon
- Drug of choice for Russ Limbaugh
- Introduced in 1995
- 50 % more potent than Vicodin™
- Highly addictive
- From thebaine minor component of opium

\[
\text{H}_2\text{O}_2, \text{CH}_3\text{CO}_2\text{H} \\
\text{Pd/C, H}_2
\]
Fentanyl™

- Introduced in 1960’s
- Sold as a “lollipop”
- Sold as a patch and more effective if absorbed through skin or tongue
- 80 times more potent than morphine
- Commonly mixed with cocaine or heroin for an extra “kick” or to dilute down cocaine or heroin
Ultam (Tramadol)

- 10% as potent as morphine and it hits those receptors
- Mixture of enantiomers
Could Not Find in Literature - But Found on Website to Make in your Garage

\[
\begin{align*}
\text{CONH}_2 & \xrightarrow{4 \text{ Å MS}} \text{CONH} \quad & \text{99% yield} \\
& \xrightarrow{\text{NaBH}_4, \text{THF}} & \\
& \xrightarrow{1) \text{ClCH}_2 \text{CO, pyridine, 30 - 60 °C}} & \text{>90%} \\
& \xrightarrow{2) \text{HCl}} & \text{50 - 80% after recrystalization}
\end{align*}
\]
Keith’s Evaluations of Pain Killers

• Aspirin - does not work well on my headaches, but if you have injuries that involves swelling, it works well
• Acetaminophen - works ok on headaches - insufficient data on injury but little anti-inflammatory effects
• Ibuprofen - works best on tooth pain and headaches, and it works ok on injuries involving swelling.
• Vicodin™ - you still hurt badly but you just don’t care!