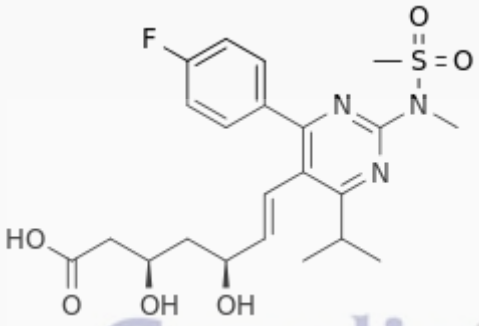
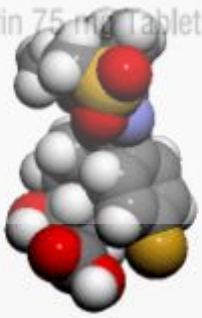
Rosuvastatin

Rosuvastatin





Systematic (IUPAC) name

5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid

Clinical data

Trade names	Crestor
AHFS/Drugs.com	monograph
MedlinePlus	a603033
Pregnancy category	AU: D US: X (Contraindicated)

Legal status	AU: Prescription Only (S4) UK: Prescription-only (POM) US: ℞-only
Routes of administration	oral
Pharmacokinetic data	
Bioavailability	20%[1]
Protein binding	88%[1]
Metabolism	Liver (CYP2C9(major) andCYP2C19-mediated; only minimally (~10%) metabolised)[1]
Biological half-life	19 hours[1]
Excretion	Faeces (90%)[1]
Identifiers	
CAS Registry Number	287714-41-4 ✓
ATC code	C10AA07
PubChem	CID: 446157
IUPHAR/BPS	2954
DrugBank	DB01098 ✓
UNII	413KH5ZJ73 ✓
KEGG	D01915 ✗
ChEBI	CHEBI:38545 ✗
ChEMBL	CHEMBL1496 ✗
PDB ligand ID	FBI (PDBe, RCSB PDB)
Chemical data	
Formula	$C_{22}H_{28}FN_3O_6S$
Molecular mass	481.539
SMILES[show]	
InChI[show]	
✗ **(what is this?)** **(verify)**	

Rosuvastatin (marketed by AstraZenecaas Crestor) 10 mg tablets

Rosuvastatin, marketed as **Crestor**, is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was developed by Shionogi. Crestor is the fourth-highest selling drug in the United States, accounting for approx. $5.2 billion in sales in 2013.[2]

Contents

[hide]

Medical uses[edit]

The primary use of rosuvastatin is for the treatment of dyslipidemia.[3] It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels.[3]

Side effects and contraindications[edit]

Side effects are uncommon. The following side effects should be reported to the prescribing doctor if they persist or get worse:[4]

- constipation
- heartburn
- dizziness
- insomnia

- depression
- joint pain
- cough
- memory loss or forgetfulness
- confusion

The following rare side effects are more serious. Like all statins, rosuvastatin can possibly cause myopathy, rhabdomyolysis. Stop taking rosuvastatin and contact the prescribing doctor if any of these occur:[4][5]

- muscle pain, tenderness, or weakness
- lack of energy
- fever
- chest pain
- jaundice: yellowing of the skin or eyes
- dark colored, or foamy urine
- pain in the upper right part of the abdomen
- nausea
- extreme tiredness
- weakness
- unusual bleeding or bruising
- loss of appetite
- flu-like symptoms
- sore throat, chills, or other signs of infection

If any signs of an allergic reaction develop, contact an emergency medical service immediately:[5]

- rash
- hives
- itching
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- numbness or tingling in fingers or toes

Rosuvastatin has multiple contraindications, conditions that warrant withholding treatment with rosuvastatin, including hypersensitivity to rosuvastatin or any component of the formulation, active liver disease, elevation of serum transaminases, pregnancy, or breast-feeding.[6] Rosuvastatin must not be taken while pregnant as it can cause serious harm to the unborn baby.[5] In the case of breastfeeding, it is unknown whether rosuvastatin is passed through breastmilk, but due to the potential of disrupting the infant's lipid metabolism, patients should not breast feed while on rosuvastatin.[5][7]

Drug interactions[edit]

The following drugs can have negative interactions with rosuvastatin and should be discussed with the prescribing doctor:[4]

- Anticoagulants ('blood thinners') can affect the removal of rosuvastatin, examples include: warfarin (Coumadin); cimetidine (Tagamet); cyclosporine (Neoral, Sandimmune); ketoconazole (Nizoral)
- Additional medications for high cholesterol such as clofibrate (Atromid-S), fenofibrate (Tricor), gemfibrozil (Lopid), and niacin (Niaspan, Niacor);
- Specific HIV protease inhibitors including atazanavir (Reyataz), taken with ritonavir (Norvir) and lopinavir and ritonavir (Kaletra); and spironolactone (Aldactone).

- Alcohol intake should be reduced while on rosuvastatin in order to decrease risk of developing liver damage.[5]
- Aluminum and magnesium hydroxide antacids such as Mylanta and Maalox, should not be taken within two hours of taking rosuvastatin[5]
- Coadministration of Rosuvastatin with Eluxadoline may increase the risk of Rhabdomyolysis and myopathy caused by the former. [8]

Structure[edit]

Rosuvastatin has structural similarities with most other synthetic statins, e.g., atorvastatin, cerivastatin and pitavastatin, but unlike other statins rosuvastatin contains sulfur.

Crestor is actually rosuvastatin calcium,[9] in which calcium replaces the hydrogen in the carboxylic acid group on the right of the two structure diagrams.

Mechanism of action[edit]

Further information: Statin

Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, having a mechanism of action similar to that of other statins.[10] Its approximate elimination half life is 19 h and its time to peak plasma concentration is reached in 3–5 h following oral administration.[11]

Putative beneficial effects of rosuvastatin therapy on chronic heart failure may be negated by increases in collagen turnover markers as well as a reduction in plasma coenzyme Q10 levels in patients with chronic heart failure.[12]

Pharmacokinetics[edit]

Absolute bioavailability of rosuvastatin is about 20% and C_{max} is reached in 3 to 5 h; administration with food did not affect the AUC. It is 88% protein bound, mainly to albumin.[13]

Rosuvastatin is metabolized mainly by CYP2C9 and not extensively metabolized; approximately 10% is recovered as metabolite. It is excreted in feces (90%) primarily and theelimination half-life is approximately 19 h.[13]

Indications and regulation[edit]

Rosuvastatin is approved for the treatment of high LDL cholesterol (dyslipidemia), total cholesterol (hypercholesterolemia), and/or triglycerides (hypertriglyceridemia).[14] In February 2010, rosuvastatin was approved by the FDA for the primary prevention of cardiovascular events.[15]

As of 2004, rosuvastatin had been approved in 154 countries and launched in 56. Approval in the United States by the FDA came on August 12, 2003.[16]

The results of the JUPITER trial (2008) suggested rosuvastatin may decrease the relative risk of heart attack and stroke in patients without hyperlipidemia, but with elevated levels of highly sensitive C-reactive protein. This could strongly impact medical practice by placing many patients on statin prophylaxis who otherwise would have been untreated.[17][18] As a result of this clinical trial, the FDA approved rosuvastatin for the primary prevention of cardiovascular events.[15]

The AURORA trial randomized 2776 patients undergoing hemodialysis due to kidney damage to receive either rosuvastatin or placebo. The randomized, double-blind study (2005 to 2009) found no difference in the two groups in the primary end-point, a combination of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. The study found no difference in all-cause mortality among this population at a mean follow-up of 3.8 years.[19]

Effects on cholesterol levels[edit]

The effects of rosuvastatin on LDL cholesterol are dose-related. Rosuvastatin 10 to 40 mg was more efficacious in improving the lipid profile of patients with hypercholesterolemia than milligram-equivalent doses of atorvastatin and milligram-equivalent or higher doses of simvastatin and pravastatin. [20]

Meta-analysis showed that rosuvastatin treatment (5 or 10 mg) is able to modestly increase levels of HDL cholesterol as well, as with other statins.[21] A study in Japanese diabetics showed the low dose (2.5 mg) can also improve HDL levels.[22] A 2014 Cochrane review determined there was good evidence for rosuvastatin lowering non-HDL levels linearly with dose.[23] HDL increases by 7% with no dose effect noted.

FDA advisory for East Asian patients[edit]

According to the FDA, the risk of myopathy during rosuvastatin therapy may be increased in Asian Americans:

Because Asians appear to process the drug differently, half the standard dose can have the same cholesterol-lowering benefit in those patients, though a full dose could increase the risk of side-effects, a study by the drug's manufacturer, AstraZeneca, indicated.[24]

Therefore, physicians should start Asian-American or East Asian patients at the lowest dose level.[25]

Marketing and competition[edit]

Patent protection[edit]

The main patent protecting rosuvastatin (RE37,314 - due to expire in 2016) was challenged as being an improper reissue of an earlier patent. This challenge was rejected in 2010, confirming protection until 2016.[26][27][28][29]

Marketing[edit]

The drug was billed as a "super-statin" during its clinical development; the claim was that it offers high potency and improved cholesterol reduction compared to rivals in the class. The main competitors to rosuvastatin are atorvastatin (Lipitor) and simvastatin (Zocor). However, people can also combine ezetimibe with either rosuvastatin or atorvastatin and other agents on their own, for somewhat similar augmented response rates. So far, some published information for comparing rosuvastatin, atorvastatin, and ezetimibe/simvastatin results is available, but many of the relevant studies are still in progress.[10]

First launched in 2003, sales of rosuvastatin were $129 million and $908 million in 2003 and 2004, respectively, with a total patient treatment population of over 4 million by the end of 2004.[*citation needed*] Typical per patient costs to the UK NHS are £18.03-26.02/month (compared to £0.85-1.37/month for simvastatin).

Debate and criticisms[edit]

In October 2003, several months after its introduction in Europe, Richard Horton, the editor of the medical journal *The Lancet*, criticized the way Crestor had been introduced. "AstraZeneca's tactics in marketing its cholesterol-lowering drug, rosuvastatin, raise disturbing questions about how drugs enter clinical practice and what measures exist to protect patients from inadequately investigated medicines," according to his editorial. *The Lancet's* editorial position is that the data for Crestor's superiority rely too much on extrapolation from the lipid profile data (surrogate end-points) and too little on hard clinical end-points, which are available for other statins that had been on the market longer. The manufacturer responded by stating that few drugs had been tested so successfully on so many patients. In correspondence published in *The Lancet*, AstraZeneca's CEO Sir Tom McKillop called the editorial "flawed and incorrect" and slammed the journal for making "such an outrageous critique of a serious, well-studied medicine."[30]

In 2004, the consumer interest organization Public Citizen filed a Citizen's Petition with the FDA, asking that Crestor be withdrawn from the US market. On March 11, 2005, the FDA issued a

letter to Sidney M. Wolfe, M.D. of Public Citizen both denying the petition and providing an extensive detailed analysis of findings that demonstrated no basis for concerns about rosuvastatin compared with the other statins approved for marketing in the United States.[31]

Myopathy[edit]

As with all statins, there is a concern of rhabdomyolysis, a severe undesired side effect. The FDA has indicated that "it does not appear that the risk [of rhabdomyolysis] is greater with Crestor than with other marketed statins", but has mandated that a warning about this side-effect, as well as a kidney toxicity warning, be added to the product label.[9]

Diabetes mellitus[edit]

Statins increase the risk of diabetes,[32] consistent with FDA's review of the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.[33]

Notes[edit]

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Clopidogrel

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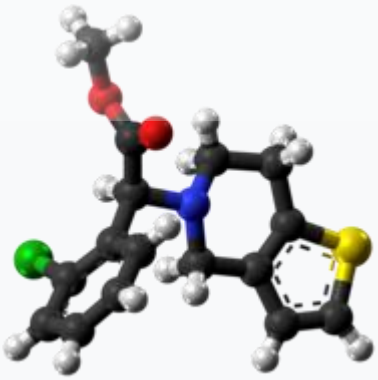
Not to be confused with Clopidol.

Clopidogrel



Clinical data	
Trade names	Plavix, others[1]
AHFS/Drugs.com	Monograph
MedlinePlus	a601040
License data	EU EMA: by INN US FDA: Plavix
Pregnancy category	AU: B1 US: B (No risk in non-human studies)

Routes of administration	by mouth
ATC code	B01AC04 (WHO)
Legal status	
Legal status	AU: S4 (Prescription only) UK: POM (Prescription only) US: ℞-only
Pharmacokinetic data	
Bioavailability	>50%
Protein binding	94–98%
Metabolism	liver
Onset of action	2 hours[2]
Elimination half-life	7–8 hours (inactive metabolite)
Duration of action	5 days[2]
Excretion	50% kidney 46% biliary
Identifiers	
IUPAC name[show]	
CAS Number	113665-84-2 ✓
PubChem CID	60606
IUPHAR/BPS	7150
DrugBank	DB00758 ✓
ChemSpider	54632 ✓
UNII	A74586SNO7

KEGG	D07729 ✓
ChEBI	CHEBI:37941 ✓
ChEMBL	CHEMBL1771 ✓
ECHA InfoCard	100.127.841
Chemical and physical data	
Formula	$C_{16}H_{16}ClNO_2S$
Molar mass	321.82 g/mol
3D model (JSmol)	Interactive image
SMILES[show]	
InChI[show]	
(verify)	

Clopidogrel, sold as the brandname **Plavix** among others,[1] is a medication that is used to reduce the risk of heart disease and stroke in those at high risk.[2] It is also used together with aspirin in heart attacks and following the placement of a coronary artery stent (dual antiplatelet therapy).[2] It is taken by mouth.[2] Onset of effects is about 2 hours and lasts for 5 days.[2]

Common side effects include headache, nausea, easy bruising, itching, and heartburn.[2] More severe side effects include bleeding and thrombotic thrombocytopenic purpura.[2] While there is no evidence of harm from use during pregnancy, such use has not been well studied.[3] Clopidogrel is in the thienopyridine-class of antiplatelet agent.[2] It works by irreversibly inhibiting a receptor called $P2Y_{12}$ on platelets.[2]

Clopidogrel was first written about in 1982 and was approved for medical use in 1998.[4] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[5] The wholesale cost in the developing world is about 0.77 to 31.59 USD per month.[6] In the United States a month of treatment costs less than 25 USD.[7]

Medical use

Clopidogrel is used to prevent heart attack and stroke in people who are at high risk of these events, including those with a history of myocardial infarction and other forms of acute coronary syndrome, stroke, and those with peripheral artery disease.

Treatment with clopidogrel or a related drug is recommended by the American Heart Association and the American College of Cardiology for people who:

- Present for treatment with a myocardial infarction with ST-elevation[8] including

    - A loading dose given in advance of percutaneous coronary intervention (PCI), followed by a full year of treatment for those receiving a vascular stent
    - A loading dose given in advance of fibrinolytic therapy, continued for at least 14 days

- Present for treatment of a non-ST elevation myocardial infarction or unstable angina[9]

    - Including a loading dose and maintenance therapy in those receiving PCI and unable to tolerate aspirin therapy
    - Maintenance therapy for up to 12 months in those at medium to high risk for which a noninvasive treatment strategy is chosen

    - In those with stable ischemic heart disease,[10] treatment with clopidogrel is described as a "reasonable" option for monotherapy in those who cannot tolerate aspirin, as is treatment with clopidogrel in combination with aspirin in certain high risk patients.

It is also used, along with acetylsalicylic acid (ASA, aspirin), for the prevention of thrombosis after placement of a coronary stent[11] or as an alternative antiplatelet drug for people intolerant to aspirin.[12]

Clopidogrel's benefit is primarily in those who smoke cigarettes (25% benefit), with only slight (8%) benefit in those who do not smoke cigarettes.[13]

Consensus-based therapeutic guidelines also recommend the use of clopidogrel rather than ASA for antiplatelet therapy in people with a history of gastric ulceration, as inhibition of the synthesis of prostaglandins by ASA can exacerbate this condition. In people with healed ASA-induced ulcers, however, those receiving ASA plus the proton pump inhibitor esomeprazole had a lower incidence of recurrent ulcer bleeding than those receiving clopidogrel.[14] However, prophylaxis with proton pump inhibitors along with clopidogrel following acute coronary syndrome may increase adverse cardiac outcomes, possibly due to inhibition of CYP2C19, which is required for the conversion of clopidogrel to its active form.[15][16][17] The European Medicines Agency has issued a public statement on a possible interaction between clopidogrel and proton pump inhibitors.[18] However, several cardiologists have voiced concern that the studies on which these warnings are based have many limitations and that it is not certain whether an interaction between clopidogrel and proton pump inhibitors is real.[19]

Adverse effects

Serious adverse drug reactions associated with clopidogrel therapy include:

- Thrombotic thrombocytopenic purpura (incidence: four per million patients treated)[20][21]
- Hemorrhage – the annual incidence of hemorrhage may be increased by the coadministration of aspirin.[22]

In the CURE trial, people with acute coronary syndrome without ST elevation were treated with aspirin plus clopidogrel or placebo and followed for up to one year. The following rates of major bleed were seen:[21]

- Any major bleeding: clopidogrel 3.7%, placebo 2.7%
- Life-threatening bleeding: clopidogrel 2.2%, placebo 1.8%
- Hemorrhagic stroke: clopidogrel 0.1%, placebo 0.1%

The CAPRIE trial compared clopidogrel monotherapy to aspirin monotherapy for 1.6 years in people who had recently experienced a stroke or heart attack. In this trial the following rates of bleeding were observed.[21]

- Gastrointestinal hemorrhage: clopidogrel 2.0%, aspirin 2.7%

- Intracranial bleeding: clopidogrel 0.4%, aspirin 0.5%

In CAPRIE, itching was the only adverse effect seen more frequently with clopidogrel than aspirin. In CURE, there was no difference in the rate of non-bleeding adverse events.[21]

Rashes and itching were uncommon in studies (between 0.1 and 1% of people); serious hypersensitivity reactions are rare.[23]

Interactions

Clopidogrel generally has a low potential to interact with other pharmaceutical drugs. Combination with other drugs that affect blood clotting, such as aspirin, heparins and thrombolytics, showed no relevant interactions. Naproxen did increase the likelihood of occult gastrointestinal bleeding, as might be the case with other nonsteroidal anti-inflammatory drugs. As clopidogrel inhibits the liver enzyme CYP2C9 in cellular models, it has been theorized that it might increase blood plasma levels of drugs that are metabolized by this enzyme, such as phenytoin and tolbutamide. Clinical studies showed that this mechanism is irrelevant for practical purposes.[23]

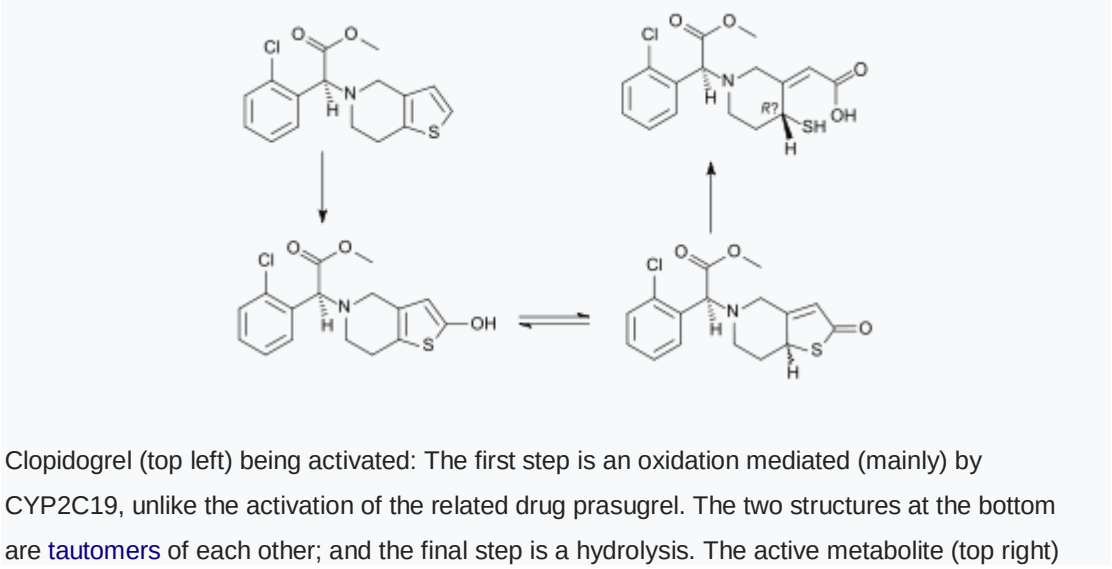
In November 2009, the FDA announced that clopidogrel should be used with caution in people using the proton pump inhibitors omeprazole or esomeprazole,[24][25] but pantoprazole appears to be safe.[26] The newer antiplatelet agent prasugrel has minimal interaction with (es)omeprazole, hence might be a better antiplatelet agent (if no other contraindications are present) in people who are on these proton pump inhibitors.[27]

Pharmacology

Mechanism of action

Clopidogrel is a prodrug, which is activated in two steps, first by CYP2C19, CYP1A2 and CYP2B6, then by CYP2C19, CYP2C9, CYP2B6 and CYP3A.[28] The active metabolite then specifically and irreversibly inhibits the $P2Y_{12}$ subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin.[28] Platelet inhibition can be demonstrated two hours after a single dose of oral clopidogrel, but the onset of action is slow, so a loading dose of either 600 or 300 mg is administered when a rapid effect is needed.[29]

Pharmacokinetics and metabolism



Clopidogrel (top left) being activated: The first step is an oxidation mediated (mainly) by CYP2C19, unlike the activation of the related drug prasugrel. The two structures at the bottom are tautomers of each other; and the final step is a hydrolysis. The active metabolite (top right)

has *Z* configuration at the double bond C3–C16 and possibly *R* configuration at the newly asymmetric C4.[30]

After repeated oral doses of 75 mg of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet-inhibiting effect, are very low and, in general, are below the quantification limit (0.258 µg/l) beyond two hours after dosing.[*citation needed*]

Clopidogrel is activated in the liver by cytochrome P450 enzymes, including CYP2C19. Due to opening of the thiophene ring, the chemical structure of the active metabolite has three sites that are stereochemically relevant, making a total of eight possible isomers. These are: a stereocentre at C4 (attached to the —SH thiol group), a double bond at C3—C16, and the original stereocentre at C7. Only one of the eight structures is an active antiplatelet drug. This has the following configuration: *Z* configuration at the C3—C16 double bond, the original *S* configuration at C7,[30] and, although the stereocentre at C4 cannot be directly determined, as the thiol group is too reactive, work with the active metabolite of the related drug prasugrel suggests the *R*-configuration of the C4 group is critical for $P2Y_{12}$ and platelet-inhibitory activity.[*citation needed*]

The active metabolite has an elimination half-life of about 0.5 to 1.0 h, and acts by forming a disulfide bridge with the platelet ADP receptor. Patients with a variant allele of CYP2C19 are 1.5 to 3.5 times more likely to die or have complications than patients with the high-functioning allele.[31][32][33]

Following an oral dose of ^{14}C-labeled clopidogrel in humans, about 50% was excreted in the urine and 46% in the feces in the five days after dosing.

- Effect of food: Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.
- Absorption and distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75-milligram clopidogrel (base), with peak plasma levels (about 3 mg/l) of the main circulating metabolite occurring around one hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is not saturable *in vitro* up to a concentration of 110 µg/ml.

- Metabolism and elimination: *In vitro* and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

In March 2010, the U.S. FDA added a boxed warning to Plavix alerting that the drug can be less effective in people unable to metabolize the drug to convert it to its active form.[34][35]

Pharmacogenetics

CYP2C19 is an important drug-metabolizing enzyme that catalyzes the biotransformation of many clinically useful drugs, including antidepressants, barbiturates, proton pump inhibitors, and antimalarial and antitumor drugs. Clopidogrel is one of the drugs metabolized by this enzyme.

Several recent landmark studies have proven the importance of 2C19 genotyping in treatment using clopidogrel. In March 2010, the FDA put a black box warning on Plavix to make patients and healthcare providers aware that CYP2C19-poor metabolizers,

representing up to 14% of patients, are at high risk of treatment failure and that testing is available.[34] Patients with variants in cytochrome P-450 2C19 (CYP2C19) have lower levels of the active metabolite of clopidogrel, less inhibition of platelets, and a 3.58-times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke; the risk was greatest in CYP2C19 poor metabolizers.[36]

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Aspirin

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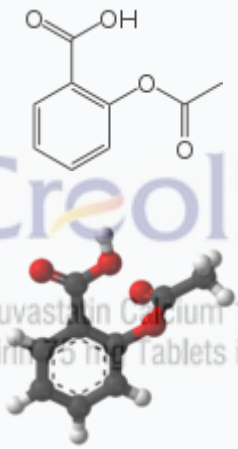
Aspirin

INN: **acetylsalicylic acid**



Clinical data	
Pronunciation	acetylsalicylic acid /əˌsiːtəlˌsælɪˈsɪlɪk/
Trade names	Bayer Aspirin, many others
Synonyms	2-acetoxybenzoic acid acetylsalicylate acetylsalicylic acid O-acetylsalicylic acid, Aspirin (BAN UK), Aspirin (USAN US)
AHFS/Drugs.com	Monograph
MedlinePlus	a682878
License data	EU EMA: by INN US FDA: Aspirin
Pregnancy category	AU: C US: C (Risk not ruled out) D in the 3rd trimester

Routes of administration	by mouth, rectal, lysine acetylsalicylate may be given intravenously or intramuscularly
ATC code	A01AD05 (WHO) B01AC06 (WHO), N02BA01 (WHO)
Legal status	
Legal status	AU: S2 (Pharmacy only) except when given intravenously (in which case it is schedule 4), used in animal medicine (schedule 5/6) or when the dose is higher than usual. UK: General sales list (GSL, OTC) US: OTC
Pharmacokinetic data	
Bioavailability	80–100%[2]
Protein binding	80–90%[1]
Metabolism	Liver, (CYP2C19 and possibly CYP3A), some is also hydrolysed to salicylate in the gut wall.[1]
Elimination half-life	Dose-dependent; 2 h to 3 h for low doses (100 mg or less), 15 h to 30 h for large doses.[1]
Excretion	Urine (80–100%), sweat, saliva, feces[2]
Identifiers	
IUPAC name[show]	
CAS Number	50-78-2 ✓
PubChem CID	2244
IUPHAR/BPS	4139
DrugBank	DB00945 ✓
ChemSpider	2157 ✓
UNII	R16CO5Y76E

KEGG	D00109 ✓
ChEBI	CHEBI:15365 ✓
ChEMBL	CHEMBL25 ✓
PDB ligand	AIN (PDBe, RCSB PDB)
ECHA InfoCard	100.000.059
	Chemical and physical data
Formula	$C_9H_8O_4$
Molar mass	180.158 g/mol[3]
3D model (JSmol)	Interactive image
Density	1.40 g/cm^3
Melting point	136 °C (277 °F) [3]
Boiling point	140 °C (284 °F) (decomposes)
Solubility in water	3 mg/mL (20 °C)
SMILES[show]	
InChI[show]	
	(verify)

Aspirin, also known as **acetylsalicylic acid** (**ASA**), is a medication used to treat pain, fever, or inflammation.[4] Specific inflammatory conditions in which aspirin is used include Kawasaki disease, pericarditis, and rheumatic fever.[4] Aspirin given shortly after a heart attack decreases the risk of death.[4] Aspirin is also used long-term to help prevent heart attacks, ischaemic strokes, and blood clots in people at high risk.[4] It may also decrease the risk of certain types of cancer, particularly colorectal cancer.[5] For pain or fever, effects typically begin within 30 minutes.[4] Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) and works similar to other NSAIDs but also suppresses the normal functioning of platelets.[4]

One common adverse effect is an upset stomach.[4] More significant side effects include stomach ulcers, stomach bleeding, and worsening asthma.[4] Bleeding risk is greater among those who are older, drink alcohol, take other NSAIDs, or are on other blood thinners.[4] Aspirin is not recommended in the last part of pregnancy.[4] It is not generally recommended in children

with infections because of the risk of Reye syndrome.[4] High doses may result in ringing in the ears.[4]

A precursor to aspirin in the form of leaves from the willow tree has been used for its health effects for at least 2,400 years.[6][7] In 1853, chemist Charles Frédéric Gerhardt treated the medicine sodium salicylate with acetyl chloride to produce acetylsalicylic acid for the first time.[8] For the next fifty years, other chemists established the chemical structure and came up with more efficient methods to make it.[8]:69–75 In 1897, scientists at the Bayer company began studying acetylsalicylic acid as a less-irritating replacement medication for common salicylate medicines.[8]:69–75 By 1899, Bayer had named it "Aspirin" and sold it around the world.[9] Aspirin's popularity grew over the first half of the twentieth century leading to competition between many brands and formulations.[10] The word *Aspirin* was Bayer's brand name; however, their rights to the trademark were lost or sold in many countries.[10]

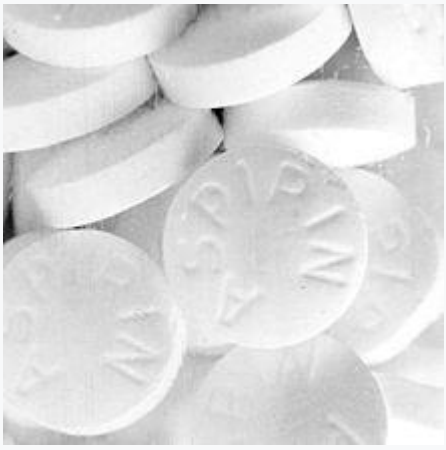
Aspirin is one of the most widely used medications globally, with an estimated 40,000 tonnes (44,000 tons) (50 to 120 billion pills) consumed each year.[6][11] It is on the World Health Organization's (WHO's) List of Essential Medicines, the safest and most effective medicines needed in a health system.[12] As of 2014 the wholesale cost in the developing world is $0.002 to $0.025 USD per dose.[13] As of 2015 the cost for a typical month of medication in the United States is less than $25.00 USD.[14] It is available as a generic medication.[4]

Medical use

Aspirin is used in the treatment of a number of conditions, including fever, pain, rheumatic fever, and inflammatory diseases, such as rheumatoid arthritis, pericarditis, and Kawasaki disease.[15] Lower doses of aspirin have also been shown to reduce the risk of death from a heart attack, or the risk of stroke in some circumstances.[16][17][18] There is some evidence that aspirin is effective at preventing colorectal cancer, though the mechanisms of this effect are unclear.[19] In the United States low dose aspirin is deemed reasonable in those between 50 and 70 years old who have a more than 10% risk of cardiovascular disease and are not at an increased risk of bleeding who are otherwise healthy.[20]

Pain

Aspirin 325 mg / 5 grains for pain



Uncoated aspirin tablets, consisting of about 90% acetylsalicylic acid, along with a minor amount of inert fillers and binders

Aspirin is an effective analgesic for acute pain, but is generally considered inferior to ibuprofen for the alleviation of pain because aspirin is more likely to cause gastrointestinal bleeding.[21] Aspirin is generally ineffective for those pains caused by

muscle cramps, bloating, gastric distension, or acute skin irritation.[22] As with other NSAIDs, combinations of aspirin and caffeine provide slightly greater pain relief than aspirin alone.[23] Effervescentformulations of aspirin, such as Alka-Seltzer or Blowfish,[24] relieve pain faster than aspirin in tablets,[25] which makes them useful for the treatment of migraines.[26] Topical aspirin may be effective for treating some types of neuropathic pain.[27]

Headache

Aspirin, either by itself or in a combined formulation, effectively treats certain types of a headache, but its efficacy may be questionable for others. Secondary headaches, meaning those caused by another disorder or trauma, should be promptly treated by a medical provider.

Among primary headaches, the International Classification of Headache Disorders distinguishes between tension headache (the most common), migraine, and cluster headache. Aspirin or other over-the-counter analgesics are widely recognized as effective for the treatment of tension headache.[28]

Aspirin, especially as a component of an aspirin/paracetamol/caffeine combination, is considered a first-line therapy in the treatment of migraine, and comparable to lower doses of sumatriptan. It is most effective at stopping migraines when they are first beginning.[29]

Fever

Like its ability to control pain, aspirin's ability to control fever is due to its action on the prostaglandin system through its irreversible inhibition of COX.[30] Although aspirin's use as an antipyretic in adults is well established, many medical societies and regulatory agencies (including the American Academy of Family Physicians, the American Academy of Pediatrics, and the U.S. Food and Drug Administration (FDA)) strongly advise against using aspirin for treatment of fever in children because of the risk of Reye's syndrome, a rare but often fatal illness associated with the use of aspirin or other salicylates in children during episodes of viral or bacterial infection.[31][32][33] Because of the risk of Reye's syndrome in children, in 1986, the FDA required labeling on all aspirin-containing medications advising against its use in children and teenagers.[34]

Inflammation

Aspirin is used as an anti-inflammatory agent for both acute and long-term inflammation,[35] as well as for treatment of inflammatory diseases, such as rheumatoid arthritis.[15]

Heart attacks and strokes

Aspirin is an important part of the treatment of those who have had a myocardial infarction (heart attack).[36] One trial found that among those likely having an ST-segment elevation MI, aspirin saves the life of 1 in 42 by reducing the 30-day death rate from 11.8% to 9.4%.[37] There was no difference in major bleeding, but there was a small increase in minor bleeding amounting to roughly 1 in every 167 people given aspirin.[37]

High risk

For people who have already had a heart attack or stroke, taking aspirin daily for two years prevented 1 in 50 from having a cardiovascular problem (heart attack, stroke, or death), but also caused non-fatal bleeding problems to occur in 1 of 400 people.[38][39][40]

Lower risk

In those with no previous history of heart disease, aspirin decreases the risk of a non-fatal myocardial infarction but does not change the overall risk of death.[41] One study found that among those who have never had a heart attack or stroke, taking aspirin daily for 1 year prevents 1 in 1,667 from having a non-fatal heart attack or stroke, but caused 1 in 3,333 to have a non-fatal bleeding event. However, the study population were at relatively higher risk than those who had never had a heart attack or stroke.[42]

Aspirin appears to offer little benefit to those at lower risk of heart attack or stroke—for instance, those without a history of these events or with pre-existing disease. Some studies recommend aspirin on a case-by-case basis,[43][44] while others have suggested the risks of other events, such as gastrointestinal bleeding, were enough to outweigh any potential benefit, and recommended against using aspirin for primary prevention entirely.[45]Aspirin has also been suggested as a component of a polypill for prevention of cardiovascular disease.[46][47]

Complicating the use of aspirin for prevention is the phenomenon of aspirin resistance.[48][49] For people who are resistant, aspirin's efficacy is reduced.[50] Some authors have suggested testing regimens to identify people who are resistant to aspirin.[51]

After surgery

After percutaneous coronary interventions (PCIs), such as the placement of a coronary artery stent, a U.S. Agency for Healthcare Research and Quality guideline recommends that aspirin be taken indefinitely.[52] Frequently, aspirin is combined with an ADP receptor inhibitor, such as clopidogrel, prasugrel, or ticagrelor to prevent blood clots. This is called dual antiplatelet therapy (DAPT). United States and European Union guidelines disagree somewhat about how long, and for what indications this combined therapy should be continued after surgery. U.S. guidelines recommend DAPT for at least 12 months, while EU guidelines recommend DAPT for 6–12 months after a drug-eluting stent placement.[53] However, they agree that aspirin be continued indefinitely after DAPT is complete.

Cancer prevention

Aspirin is thought to reduce the overall risk of both getting cancer and dying from cancer.[54] This effect is particularly beneficial for colorectal cancer (CRC)[19][55][56][57] but must be taken for at least 10–20 years to see this benefit.[58] It may also slightly reduce the risk of endometrial cancer,[59] breast cancer, and prostate cancer.[60]

Some conclude the benefits are greater than the risks due to bleeding in those at average risk.[54] Others are unclear if the benefits are greater than the risk.[61][62] Given this uncertainty, the 2007 United States Preventive Services Task Force guidelines on this topic recommended against the use of aspirin for prevention of CRC in people with average risk.[63] Nine years later however, the USPSTF issued a grade B recommendation for the use of low-dose aspirin (75 to 100 mg/day) “for the primary prevention of CVD [cardiovascular disease] and CRC in adults 50 to 59 years of age who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years”.[64]

Other uses

Aspirin is a first-line treatment for the fever and joint-pain symptoms of acute rheumatic fever. The therapy often lasts for one to two weeks, and is rarely indicated for longer periods. After fever and pain have subsided, the aspirin is no longer necessary, since it does not decrease the incidence of heart complications and residual rheumatic heart disease.[65][66] Naproxen has been shown to be as effective as aspirin and less toxic, but due to the limited clinical experience, naproxen is recommended only as a second-line treatment.[65][67]

Along with rheumatic fever, Kawasaki disease remains one of the few indications for aspirin use in children[68] in spite of a lack of high quality evidence for its effectiveness.[69]

Low-dose aspirin supplementation has moderate benefits when used for prevention of pre-eclampsia.[70][71] This benefit is greater when started in early pregnancy.[72]

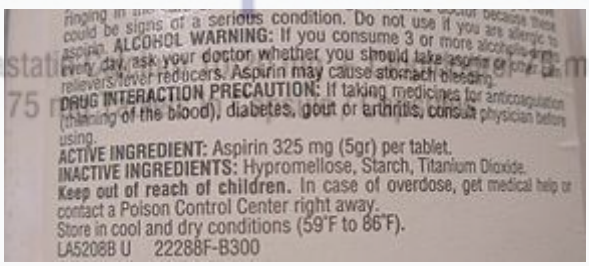
Resistance

For some people, aspirin does not have as strong an effect on platelets as for others, an effect known as aspirin-resistance or insensitivity. One study has suggested women are more likely to be resistant than men,[73] and a different, aggregate study of 2,930 people found 28% were resistant.[74] A study in 100 Italian people, though, found, of the apparent 31% aspirin-resistant subjects, only 5% were truly resistant, and the others were noncompliant.[75] Another study of 400

healthy volunteers found no subjects who were truly resistant, but some had "pseudoresistance, reflecting delayed and reduced drug absorption".[76]

Dosage

Coated 325 mg (5-grain) aspirin tablets



The 5-grain aspirin. The usage guidance label on a bottle of aspirin indicates that the dosage is "325 mg (5 gr)".

Adult aspirin tablets are produced in standardised sizes, which vary slightly from country to country, for example 300 mg in Britain and 325 mg (or 5 grains) in the United States. Smaller doses are based on these standards, *e.g.*, 75 mg and 81 mg tablets. The 81 mg (1¼-grain) tablets are commonly called "baby aspirin" or "baby-strength", because they were originally—but no longer—intended to be administered to infants and children.[77] No medical significance occurs due to the slight difference in dosage between the 75 mg and the 81 mg tablets.

In general, for adults, doses are taken four times a day for fever or arthritis,[78] with doses near the maximal daily dose used historically for the treatment of rheumatic fever.[79] For the prevention of myocardial infarction (MI) in someone with documented or suspected coronary artery disease, much lower doses are taken once daily.[78]

March 2009 recommendations from the USPSTF on the use of aspirin for the primary prevention of coronary heart disease encourage men aged 45–79 and women aged 55–79 to use aspirin when the potential benefit of a reduction in MI for men or stroke for women outweighs the potential harm of an increase in gastrointestinal hemorrhage.[80] The WHI study said regular low dose (75 or 81 mg) aspirin female users had a 25% lower risk of death from cardiovascular disease and a 14% lower risk of death from any cause.[80] Low-dose aspirin use was also associated with a trend toward lower risk of cardiovascular events, and lower aspirin doses (75 or 81 mg/day) may optimize efficacy and safety for people requiring aspirin for long-term prevention.[80]

In children with Kawasaki disease, aspirin is taken at dosages based on body weight, initially four times a day for up to two weeks and then at a lower dose once daily for a further six to eight weeks.[81]

Adverse effects

Contraindications

Aspirin should not be taken by people who are allergic to ibuprofen or naproxen,[82][83] or who have salicylate intolerance[84][85] or a more generalized drug intolerance to NSAIDs, and caution should be exercised in those with asthma or NSAID-precipitated bronchospasm. Owing to its effect on the stomach lining, manufacturers recommend people with peptic ulcers, mild diabetes, or gastritis seek medical advice before using aspirin.[82][86] Even if none of these conditions is present, the risk of stomach bleeding is still increased when aspirin is taken with alcohol or warfarin.[82][83] People with hemophilia or other bleeding tendencies should not take aspirin or other salicylates.[82][86] Aspirin is known to cause hemolytic anemia in people who have the genetic disease glucose-6-phosphate dehydrogenase deficiency, particularly in large doses and depending on the severity of the disease.[87] Use of aspirin during dengue fever is not recommended owing to increased bleeding tendency.[88] People with kidney disease, hyperuricemia, or gout should not take aspirin because it inhibits the kidneys' ability to excrete uric acid, thus may exacerbate these conditions. Aspirin should not be given to children or adolescents to control cold or influenza symptoms, as this has been linked with Reye's syndrome.[89]

Gastrointestinal

Enteric-coated 325 mg aspirin pills

Aspirin use has been shown to increase the risk of gastrointestinal bleeding.[90] Although some enteric-coated formulations of aspirin are advertised as being "gentle to the stomach", in one study, enteric coating did not seem to reduce this risk.[90] Combining aspirin with other NSAIDs has also been shown to further increase this risk.[90] Using aspirin in combination with clopidogrel or warfarin also increases the risk of upper gastrointestinal bleeding.[91]

Blockade of COX-1 by aspirin apparently results in the upregulation of COX-2 as part of a gastric defense[92] and that taking COX-2 inhibitors concurrently with aspirin increases the gastric mucosal erosion.[93] Therefore, caution should be exercised if combining aspirin with any "natural" supplements with COX-2-inhibiting properties, such as garlic extracts, curcumin, bilberry, pine bark, ginkgo, fish oil, resveratrol, genistein, quercetin, resorcinol, and others.

In addition to enteric coating, "buffering" is the other main method companies have used to try to mitigate the problem of gastrointestinal bleeding. Buffering agents are intended to work by preventing the aspirin from concentrating in the walls of the stomach, although the benefits of buffered aspirin are disputed. Almost any buffering agent used in antacids can be used; Bufferin, for example, uses magnesium oxide. Other preparations use calcium carbonate.[94]

Taking it with vitamin C has been investigated as a method of protecting the stomach lining. Taking equal doses of vitamin C and aspirin may decrease the amount of stomach damage that occurs compared to taking aspirin alone.[95][96]

Central effects

Large doses of salicylate, a metabolite of aspirin, cause temporary tinnitus (ringing in the ears) based on experiments in rats, via the action on arachidonic acid and NMDA receptors cascade.[97]

Reye's syndrome

Main article: Reye's syndrome

Reye's syndrome, a rare but severe illness characterized by acute encephalopathy and fatty liver, can occur when children or adolescents are given aspirin for a fever or other illness or infection. From 1981 through 1997, 1207 cases of Reye's syndrome in people younger than 18 were reported to the U.S. Centers for Disease Control and Prevention. Of these, 93% reported being ill in the three weeks preceding the onset of Reye's syndrome, most commonly with a respiratory infection, chickenpox, or diarrhea. Salicylates were detectable in 81.9% of children for whom test results were reported.[98] After the association between Reye's syndrome and aspirin was reported, and safety measures to prevent it (including a Surgeon General's warning, and changes to the labeling of aspirin-containing drugs) were implemented, aspirin taken by children declined considerably in the United States, as did the number of reported cases of Reye's syndrome; a similar decline was found in the United Kingdom after warnings against pediatric aspirin use were issued.[98] The U.S. Food and Drug Administration now recommends aspirin (or aspirin-containing products) should not be given to anyone under the age of 12 who has a fever,[89] and the UK National Health Service recommends children who are under 16 years of age should not take aspirin, unless it is on the advice of a doctor.[99]

Skin

For a small number of people, taking aspirin can result in symptoms resembling an allergic reaction, including hives, swelling, and headache. The reaction is caused by salicylate intolerance and is not a true allergy, but rather an inability to metabolize even small amounts of aspirin, resulting in an overdose.

Aspirin and other NSAIDs, such as ibuprofen, may delay the healing of skin wounds.[100] Aspirin may however help heal venous leg ulcers that have not healed following usual treatment.[101]

Other adverse effects

Aspirin can induce swelling of skin tissues in some people. In one study, angioedema appeared one to six hours after ingesting aspirin in some of the people. However, when the aspirin was taken alone, it did not cause angioedema in these people; the aspirin had been taken in combination with another NSAID-induced drug when angioedema appeared.[102]

Aspirin causes an increased risk of cerebral microbleeds having the appearance on MRI scans of 5 to 10 mm or smaller, hypointense (dark holes) patches.[103][104] Such cerebral microbleeds are important, since they often occur prior to ischemic stroke or intracerebral hemorrhage, Binswanger disease, and Alzheimer's disease.[*original research?*]

A study of a group with a mean dosage of aspirin of 270 mg per day estimated an average absolute risk increase in intracerebral hemorrhage (ICH) of 12 events per 10,000 persons.[105] In comparison, the estimated absolute risk reduction in myocardial infarction was 137 events per 10,000 persons, and a reduction of 39 events per 10,000 persons in ischemic stroke.[105] In cases where ICH already has occurred, aspirin use results in higher mortality, with a dose of about 250 mg per day resulting in a relative risk of death within three months after the ICH around 2.5 (95% confidence interval 1.3 to 4.6).[106]

Aspirin and other NSAIDs can cause abnormally high blood levels of potassium by inducing a hyporeninemic hypoaldosteronic state via inhibition of prostaglandin synthesis; however, these agents do not typically cause hyperkalemia by themselves in the setting of normal renal function and euvolemic state.[107]

Aspirin can cause prolonged bleeding after operations for up to 10 days. In one study, 30 of 6499 people having elective surgery required reoperations to control bleeding. Twenty had diffuse bleeding and 10 had bleeding from a site. Diffuse, but not discrete, bleeding was associated with the preoperative use of aspirin alone or in combination with other NSAIDS in 19 of the 20 diffuse bleeding people.[108]

On 9 July 2015, the FDA toughened warnings of increased heart attack and stroke risk associated with nonsteroidal anti-inflammatory drugs (NSAID). Aspirin is an NSAID but is not affected by the new warnings.[109]

Overdose

Main article: Aspirin poisoning

Aspirin overdose can be acute or chronic. In acute poisoning, a single large dose is taken; in chronic poisoning, higher than normal doses are taken over a period of time. Acute overdose has a mortality rate of 2%. Chronic overdose is more commonly lethal, with a mortality rate of 25%;[110] chronic overdose may be especially severe in children.[111] Toxicity is managed with a number of potential treatments, including activated charcoal, intravenous dextrose and normal saline, sodium bicarbonate, and dialysis.[112] The diagnosis of poisoning usually involves measurement of plasma salicylate, the active metabolite of aspirin, by automated spectrophotometric methods. Plasma salicylate levels in general range from 30–100 mg/l after usual therapeutic doses, 50–300 mg/l in people taking high doses and 700–1400 mg/l following acute overdose. Salicylate is also produced as a result of exposure to bismuth subsalicylate, methyl salicylate, and sodium salicylate.[113][114]

Interactions

Aspirin is known to interact with other drugs. For example, acetazolamide and ammonium chloride are known to enhance the intoxicating effect of salicylates, and alcohol also increases the gastrointestinal bleeding associated with these types of drugs.[82][83] Aspirin is known to displace a number of drugs from protein-binding sites in the blood, including the antidiabetic drugs tolbutamide and chlorpropamide, warfarin, methotrexate, phenytoin, probenecid, valproic acid (as well as interfering with beta oxidation, an important part of valproate metabolism), and other NSAIDs. Corticosteroids may also reduce the concentration of aspirin. Ibuprofen can negate the antiplatelet effect of aspirin used for cardioprotection and stroke prevention.[115] The pharmacological activity of spironolactone may be reduced by taking aspirin, and it is known to compete with penicillin G for renal tubular secretion.[116] Aspirin may also inhibit the absorption of vitamin C.[117][118][*unreliable medical source?*][119]

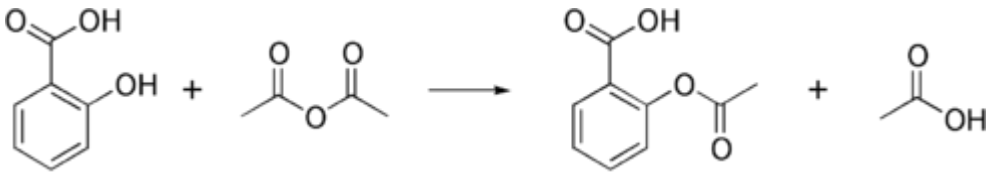
Chemical properties

Aspirin decomposes rapidly in solutions of ammonium acetate or the acetates, carbonates, citrates, or hydroxides of the alkali metals. It is stable in dry air, but gradually hydrolyses in contact with moisture to acetic and salicylic acids. In solution with alkalis, the hydrolysis proceeds rapidly and the clear solutions formed may consist entirely of acetate and salicylate.[120]

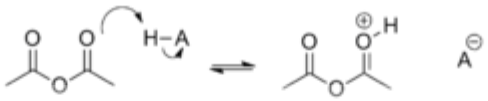
Like flour mills, factories that make aspirin tablets must pay attention to how much of the powder gets into the air inside the building, because the powder-air mixture can be explosive. The National Institute for Occupational Safety and Health (NIOSH) has set a recommended exposure limit in the United States of 5 mg/m^3 (time-weighted average).[121] In 1989, the Occupational Safety and Health Administration (OSHA) set a legal permissible exposure limit for aspirin of 5 mg/m^3, but this was vacated by the AFL-CIO v. OSHAdecision in 1993.[122]

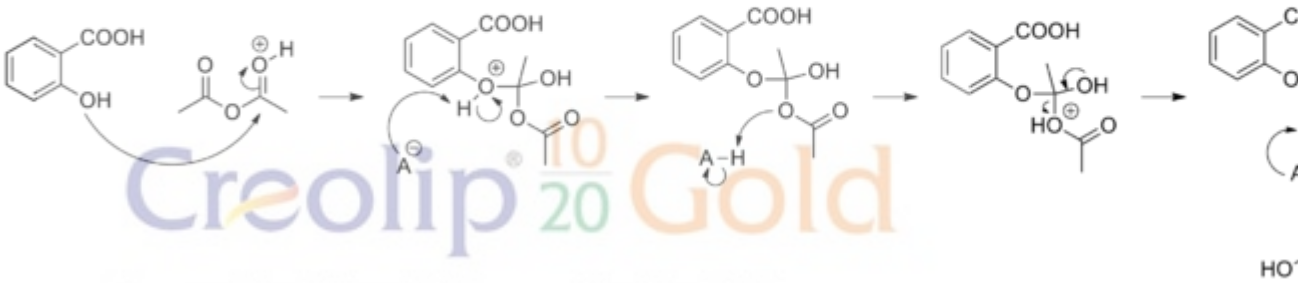
Synthesis

The synthesis of aspirin is classified as an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns salicylic acid's hydroxyl group into an ester group (R-OH → R-OCOCH$_3$). This process yields aspirin and acetic acid, which is considered a byproduct of this reaction. Small amounts of sulfuric acid (and occasionally phosphoric acid) are almost always used as a catalyst. This method is commonly employed in undergraduate teaching labs.[123]



Reaction mechanism





Formulations containing high concentrations of aspirin often smell like vinegar[124] because aspirin can decompose through hydrolysis in moist conditions, yielding salicylic and acetic acids.[125]

Physical properties

Aspirin, an acetyl derivative of salicylic acid, is a white, crystalline, weakly acidic substance, with a melting point of 136 °C (277 °F),[3] and a boiling point of 140 °C (284 °F).[126] Its acid dissociation constant (pK_a) is 3.5 at 25 °C (77 °F).[127]

Polymorphism

Polymorphism, or the ability of a substance to form more than one crystal structure, is important in the development of pharmaceutical ingredients. Many drugs are receiving regulatory approval for only a single crystal form or polymorph. For a long time, only one crystal structure for aspirin was known. That aspirin might have a second crystalline form was suspected since the 1960s. The elusive second polymorph was first discovered by Vishweshwar and coworkers in 2005,[128] and fine structural details were given by Bond *et al.*[129]A new crystal type was found after attempted cocrystallization of aspirin and levetiracetam from hot acetonitrile. The form II is only stable at 100 K and reverts to form I at ambient temperature. In the (unambiguous) form I, two salicylic molecules form centrosymmetric dimers through the acetyl groups with the (acidic) methyl proton to carbonyl hydrogen bonds, and in the newly claimed form II, each salicylic molecule forms the same hydrogen bonds with two neighboring molecules instead of one. With respect to the hydrogen bonds formed by the carboxylic acid groups, both polymorphs form identical dimer structures.[*citation needed*]

Mechanism of action

Main article: Mechanism of action of aspirin

Discovery of the mechanism

In 1971, British pharmacologist John Robert Vane, then employed by the Royal College of Surgeons in London, showed aspirin suppressed the production of prostaglandins and thromboxanes.[130][131] For this discovery he was awarded the

1982 Nobel Prize in Physiology or Medicine, jointly with Sune Bergström and Bengt Ingemar Samuelsson.[132]

Prostaglandins and thromboxanes

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase (COX; officially known as prostaglandin-endoperoxide synthase, PTGS) enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the PTGS enzyme (Suicide inhibition). This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors.

Low-dose aspirin use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks in people who have had a heart attack, unstable angina, ischemic stroke or transient ischemic attack.[133] 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.[134]

Prostaglandins, local hormones produced in the body, have diverse effects, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are caused primarily by blood clots, and low doses of aspirin are seen as an effective medical intervention for acute myocardial infarction.

COX-1 and COX-2 inhibition

At least two different types of cyclooxygenases, COX-1 and COX-2, are acted on by aspirin. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory.[135][*verification needed*] Newer NSAID drugs, COX-2 inhibitors (coxibs), have been developed to inhibit only PTGS2, with the intent to reduce the incidence of gastrointestinal side effects.[11]

However, several of the new COX-2 inhibitors, such as rofecoxib (Vioxx), have been withdrawn in the last decade, after evidence emerged that PTGS2 inhibitors increase the risk of heart attack and stroke.[136][137] Endothelial cells lining the microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically, PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Furthermore, aspirin, while inhibiting the ability of COX-2 to form pro-inflammatory products such as the prostaglandins, converts this enzyme's activity from a prostaglandin-forming cyclooxygenase to a lipoxygenase-like enzyme: aspirin-treated COX-2 metabolizes a variety of polyunsaturated fatty acids to hydroperoxy products which are then further metabolized to specialized proresolving mediators such as the aspirin-triggered lipoxins, aspirin-triggered resolvins, and aspirin-triggered maresins. These mediators possess potent anti-inflammatory activity. It is proposed that this aspirin-triggered transition of COX-2 from cyclooxygenase to lipoxygenase activity and the consequential formation of specialized proresolving mediators contributes to the anti-inflammatory effects of aspirin.[138][139][140]

Additional mechanisms

Aspirin has been shown to have at least three additional modes of action. It uncouples oxidative phosphorylation in cartilaginous (and hepatic) mitochondria, by diffusing from the inner membrane space as a proton carrier back into the mitochondrial matrix, where it ionizes once again to release protons.[141] Aspirin buffers and transports the protons. When high doses are given, it may actually cause fever, owing to the heat released from the electron transport chain, as opposed to the antipyretic action of aspirin seen with lower doses. In addition, aspirin induces the formation of NO-radicals in the body, which have been shown in mice to have an independent mechanism of reducing inflammation. This reduced leukocyte adhesion is an important step in the immune response to infection; however, evidence is insufficient to show aspirin helps to fight infection.[142] More recent data also suggest salicylic acid and its derivatives modulate signaling through NF-κB.[143] NF-κB, a transcription factor complex, plays a central role in many biological processes, including inflammation.

Aspirin is readily broken down in the body to salicylic acid, which itself has anti-inflammatory, antipyretic, and analgesic effects. In 2012, salicylic acid was found to activate AMP-activated protein kinase, which has been suggested as a possible explanation for some of the effects of both salicylic acid and aspirin.[144][145] The acetyl portion of the aspirin molecule has its own targets. Acetylation of cellular proteins is a well-established phenomenon in the regulation of protein function at the post-translational level. Aspirin is able to acetylate several other targets in addition to COX isoenzymes.[146][147] These acetylation reactions may explain many hitherto unexplained effects of aspirin.

Pharmacokinetics

Acetylsalicylic acid is a weak acid, and very little of it is ionized in the stomach after oral administration. Acetylsalicylic acid is quickly absorbed through the cell membrane in the acidic conditions of the stomach. The increased pH and larger surface area of the small intestine causes aspirin to be absorbed more slowly there, as more of it is ionised. Owing to the formation of concretions, aspirin is absorbed much more slowly during overdose, and plasma concentrations can continue to rise for up to 24 hours after ingestion.[148][149][150]

About 50–80% of salicylate in the blood is bound to albumin protein, while the rest remains in the active, ionized state; protein binding is concentration-dependent. Saturation of binding sites leads to more free salicylate and increased toxicity. The volume of distribution is 0.1–0.2 L/kg. Acidosis increases the volume of distribution because of enhancement of tissue penetration of salicylates.[150]

As much as 80% of therapeutic doses of salicylic acid is metabolized in the liver. Conjugation with glycine forms salicyluric acid, and with glucuronic acid to form two different glucuronide esters. The conjugate with the acetyl group intact is referred to as the *acyl glucuronide*; the deacetylated conjugate is the *phenolic glucuronide*. These metabolic pathways have only a limited capacity. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large salicylate doses, the kinetics switch from first-order to zero-order, as metabolic pathways become saturated and renal excretion becomes increasingly important.[150]

Salicylates are excreted mainly by the kidneys as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%), and acyl glucuronides (5%), gentisic acid (< 1%), and 2,3-dihydroxybenzoic acid.[151] When small doses (less than 250 mg in an adult) are ingested, all pathways proceed by first-order kinetics, with an elimination half-life of about 2.0 h to 4.5 h.[152][153] When higher doses of salicylate are ingested (more than 4 g), the half-life becomes much longer (15 h to 30 h),[154] because the biotransformation pathways concerned with the formation of salicyluric acid and salicyl phenolic glucuronide become saturated.[155] Renal excretion of salicylic acid becomes increasingly important as the metabolic pathways become saturated, because it is extremely sensitive to changes in urinary pH. A 10- to 20-fold increase in renal clearance occurs

when urine pH is increased from 5 to 8. The use of urinary alkalinization exploits this particular aspect of salicylate elimination.[156]

History

Main article: History of aspirin

1923 advertisement

Medicines made from willow and other salicylate-rich plants appear in clay tablets from ancient Sumer as well as the Ebers Papyrus from ancient Egypt.[8]:8–13[10] Hippocrates referred to their use of salicylic tea to reduce fevers around 400 BC, and were part of the pharmacopoeia of Western medicine in classical antiquity and the Middle Ages.[10] Willow bark extract became recognized for its specific effects on fever, pain and inflammation in the mid-eighteenth century.[157] By the nineteenth century pharmacists were experimenting with and prescribing a variety of chemicals related to salicylic acid, the active component of willow extract.[8]:46–55

In 1853, chemist Charles Frédéric Gerhardt treated sodium salicylate with acetyl chloride to produce acetylsalicylic acid for the first time;[8]:46–48 in the second half of the nineteenth century, other academic chemists established the compound's chemical structure and devised more efficient methods of synthesis. In 1897, scientists at the drug and dye firm Bayer began investigating acetylsalicylic acid as a less-irritating replacement for standard common salicylate medicines, and identified a new way to synthesize it.[8]:69–75 By 1899, Bayer had dubbed this drug Aspirin and was selling it around the world.[9]:27 The word *Aspirin* was Bayer's brand name, rather than the generic name of the drug; however, Bayer's rights to the trademark were lost or sold in many countries. Aspirin's popularity grew over the first half of the twentieth century leading to fierce competition with the proliferation of aspirin brands and products.[10]

Aspirin's popularity declined after the development of acetaminophen/paracetamol in 1956 and ibuprofen in 1962. In the 1960s and 1970s, John Vane and others discovered the basic mechanism of aspirin's effects,[8]:226–231while clinical trials and other studies from the 1960s to the 1980s established aspirin's efficacy as an anti-clotting agent that reduces the risk of clotting diseases.[8]:247–257 The initial large studies on the use of low-dose aspirin to prevent heart attacks that were published in the 1970s and 1980s helped spur reform in clinical research ethics and guidelines for human subject research and US federal law, and are often cited as examples of clinical trials that included only men, but from which people drew general conclusions that did not hold true for women.[158][159][160]

Aspirin sales revived considerably in the last decades of the twentieth century, and remain strong in the twenty-first with widespread use as a preventive treatment for heart attacks and strokes.[8]:267–269

Trademark

Bayer lost its trademark for Aspirin in the United States in 1918 because it had failed to use the name for its own product and had for years allowed the use of "Aspirin" by other manufacturers .[161] Today, aspirin is a generic trademark in many countries.[162] Aspirin, with a capital "A", remains a registered trademark of Bayer in Germany, Canada, Mexico, and in over 80 other countries, for acetylsalicylic acid in all markets, but using different packaging and physical aspects for each.[163][164]

Compendial status

- United States Pharmacopeia[165]
- British Pharmacopoeia[166]

Veterinary medicine

Aspirin is sometimes used in veterinary medicine as an anticoagulant or to relieve pain associated with musculoskeletal inflammation or osteoarthritis. Aspirin should only be given to animals under the direct supervision of a veterinarian, as adverse effects—including gastrointestinal issues—are common. An aspirin overdose in any species may result in salicylate poisoning, characterized by hemorrhaging, seizures, coma, and even death.[167]

Cats and dogs

Dogs are better able to tolerate aspirin than cats are.[168] Cats metabolize aspirin slowly because they lack the glucuronide conjugates that aid in the excretion of aspirin, making it potentially toxic if dosing is not spaced out properly.[167][169] No clinical signs of toxicosis occurred when cats were given 25 mg/kg of aspirin every 48 hours for 4 weeks,[168] but the recommended dose for relief of pain and fever and for treating blood clotting diseases in cats is 10 mg/kg every 48 hours to allow for metabolization.[167][170]

Cattle and horses

Aspirin has shown some promise in the treatment of laminitis in horses.[171]

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