Chloroform

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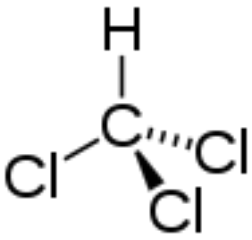
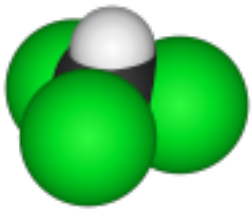
Chloroform	





IUPAC name[hide]
Chloroform

Systematic name[hide]
Trichloromethane

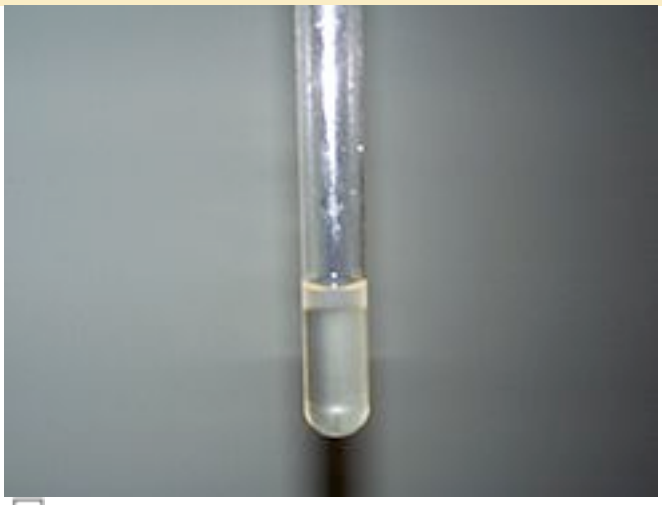
Other names[hide]
Formyl trichloride, Methane trichloride, Methyl trichloride, Methenyl trichloride, TCM, Freon 20, R-20, UN 1888

Identifiers	
CAS number	67-66-3 ✓
PubChem	6212
ChemSpider	5977 ✓
UNII	7V31YC746X ✓
EC number	200-663-8
KEGG	C13827 ✓
ChEBI	CHEBI:35255
ChEMBL	CHEMBL44618 ✓
RTECS number	FS9100000
SMILES [show]	
InChI [show]	

Properties	
Molecular formula	$CHCl_3$
Molar mass	119.38 g/mol
Appearance	Colorless liquid
Density	1.483 g/cm^3
Melting point	-63.5 °C
Boiling point	61.2 °C
Solubility in water	0.8 g/100 ml (20 °C)
Refractive index (n_D)	1.4459
Structure	
Molecular shape	Tetrahedral
Hazards	
MSDS	External MSDS
R-phrases	R22, R38, R40, R48/20/22
S-phrases	(S2), S36/37

NFPA 704	 0 2 0
Flash point	Non-flammable
U.S. Permissible exposure limit (PEL)	50 ppm (240 mg/m^3) (OSHA)
Supplementary data page	
Structure and properties	*n*, ε$_r$, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

✓ (what is this?) (verify)
Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)
Infobox references



Chloroform in its liquid state shown in a test tube

Chloroform is the organic compound with formula $CHCl_3$. The colorless, sweet-smelling, dense liquid is a trihalomethane, and is considered somewhat hazardous. Several million tons are produced annually as a precursor to Teflon and refrigerants, but its use for refrigerants is being phased out.[1]

Contents

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Occurrence

$CHCl_3$ has a multitude of natural sources, both biogenic and abiotic. It is estimated that greater than 90% of atmospheric $CHCl_3$ is of natural origin.[2]

Marine

In particular, chloroform is produced by brown seaweeds (*Laminaria digitata*, *Laminaria saccharina*, *Fucus serratus*, *Pelvetia canaliculata*, *Ascophyllum nodosum*), red seaweeds (*Gigartina stellata*, *Corallina officinalis*, *Polysiphonia lanosa*), and green seaweeds (*Ulva lactuca*, *Enteromorpha* sp., *Cladophora albida*).[3] Similarly, the macroalga *Eucheuma denticulatum*, which is cultivated and harvested on a large scale for carrageenan production, produces $CHCl_3$,[4] as do *Hypnea spinella*, *Falkenbergia hillebrandii*, and *Gracilara cornea* along with seven indigenous macroalgae inhabiting a rock pool.[5] These studies show increased $CHCl_3$ production with increased light intensity, presumably when photosynthesis is at a maximum. Chloroform is also produced by the brown alga *Fucus vesiculosus*, the green algae *Cladophora glomerata*, *Enteromorpha ahlneriana*, *Enteromorpha flexuosa*, and *Enteromorpha intestinalis*, and the diatom *Pleurosira laevis*.[6] Other studies observe $CHCl_3$ in *Fucus serratus*, *Fucus vesiculosis*, *Corallina officinalis*, *Cladophora pellucida*, and *Ulva lactuca*,[7] and *Desmarestia antarctica*, *Lambia antarctica*, *Laminaria saccharina*, *Neuroglossum ligulatum*.[8]

Production

Chloroform was discovered by three researchers independently of one another. Chloroform was reported in 1831 by the French chemist Eugène Soubeiran, who prepared it from acetone (2-propanone) as well as ethanol through the action of chlorine bleach powder (calcium hypochlorite).[9] The American physician Samuel Guthrie prepared gallons of the material and described its "deliciousness of flavor."[10] Independently, Justus von Liebig also described the same compound.[11] All early preparations used variations of the haloform reaction. Chloroform was named and chemically characterized in 1834 by Jean-Baptiste Dumas.[12]

Industrial routes

In industry, chloroform is produced by heating a mixture of chlorine and either chloromethane or methane.[1] At 400–500 °C, a free radical halogenation occurs, converting these precursors to progressively more chlorinated compounds:

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$
$$CH_3Cl + Cl_2 \rightarrow CH_2Cl_2 + HCl$$
$$CH_2Cl_2 + Cl_2 \rightarrow CHCl_3 + HCl$$

Chloroform undergoes further chlorination to give CCl_4:

$$CHCl_3 + Cl_2 \rightarrow CCl_4 + HCl$$

The output of this process is a mixture of the four chloromethanes, chloromethane, dichloromethane, chloroform, and carbon tetrachloride, which are then separated by distillation.[1]

Deuterochloroform

An archaic industrial route to chloroform involved the reaction of acetone (or ethanol) with sodium hypochlorite or calcium hypochlorite, the aforementioned haloform reaction.[1] The chloroform can be removed from the coproducts by distillation. A related reaction is still used in the production of bromoform and iodoform. Although the haloform process is obsolete for the production of ordinary chloroform, it is used to produce $CDCl_3$.[*citation needed*] Deuterochloroform can also be prepared by the reaction of sodium deuteroxide with chloral hydrate,[*citation needed*] or from ordinary chloroform.[13]

Inadvertent formation of chloroform

The haloform reaction can also occur inadvertently in domestic settings. Sodium hypochlorite solution (chlorine bleach) mixed with common household liquids such as acetone, butanone, ethanol, or isopropyl alcohol can produce some chloroform, in addition to other compounds such as chloroacetone, or dichloroacetone.

Uses

The major use of chloroform today is in the production of the chlorodifluoromethane (R-22), a major precursor to tetrafluoroethylene:

$$CHCl_3 + 2\ HF \rightarrow CHClF_2 + 2\ HCl$$

The reaction is conducted in the presence of a catalytic amount of antimony pentafluoride. Chlorodifluoromethane is then converted into tetrafluoroethylene, the main precursor to Teflon. Before the Montreal Protocol, chlorodifluoromethane (R22) was also a popular refrigerant.

As a solvent

Chloroform is a common solvent in the laboratory because it is relatively unreactive, miscible with most organic liquids, and conveniently volatile. Chloroform is used as a solvent in the pharmaceutical industry and for producing dyes and pesticides. Chloroform is an effective solvent for alkaloids in their base form and thus plant material is commonly extracted with chloroform for pharmaceutical processing. For example, it is used in commerce to extract morphine from poppies and scopolamine from *Datura* plants. Chloroform containing deuterium (heavy hydrogen), $CDCl_3$, is a common solvent used in NMR spectroscopy. It can be used to bond pieces of acrylic glass (also known under the trade names Perspex and Plexiglas). A solvent of phenol:chloroform:isoamyl alcohol 25:24:1 is used to dissolve non-nucleic acid biomolecules in DNA and RNA extractions.

As a reagent in organic synthesis

As a reagent, chloroform serves as a source of the dichlorocarbene CCl_2 group.[14] It reacts with aqueous sodium hydroxide usually in the presence of a phase transfer catalyst to produce dichlorocarbene, CCl_2.[15][16] This reagent affects ortho-formylation of activated aromatic rings such as phenols, producing aryl aldehydes in a reaction known as the Reimer-Tiemann reaction. Alternatively the carbene can be trapped by an alkene to form a cyclopropane derivative. In the Kharasch addition chloroform forms the $CHCl_2$ free radical in addition to alkenes.

As an anesthetic

Antique bottles of Chloroform

Chloroform was once a popular anesthetic; its vapor depresses the central nervous system of a patient, allowing a doctor to perform various otherwise painful procedures. In 1847, the Scottish obstetrician James Young Simpson first used chloroform for general anesthesia during childbirth. The use of chloroform during surgery expanded rapidly thereafter in Europe. In the United States, chloroform began to replace ether as an anesthetic at the beginning of the 20th century; however, it was quickly abandoned in favor of ether upon discovery of its toxicity, especially its tendency to cause fatal cardiac arrhythmia analogous to what is now termed "sudden sniffer's death". Ether is still the preferred anesthetic in some developing nations due to its high therapeutic index (~1.5–2.2) [17] and low price. One possible mechanism of action for chloroform is that it increases movement of potassium ions through certain types of potassium channels in

nerve cells.[18] Chloroform could also be mixed with other anaesthetic agents such as ether to make C.E. mixture, or ether and alcohol to make A.C.E. mixture.

Veterinary use

In veterinary medicine it is used externally to kill maggots in wounds.[*citation needed*]

Safety

Fatal oral dose of chloroform may be as low as 10 mL (14.8 g), with death due to respiratory or cardiac arrest.[19]

As might be expected for an anesthetic, chloroform vapors depress the central nervous system. It is immediately dangerous to life and health at approximately 500 ppm, according to the U.S. National Institute for Occupational Safety and Health. Breathing about 900 ppm for a short time can cause dizziness, fatigue, and headache. Chronic chloroform exposure can damage the liver (where chloroform is metabolized to phosgene) and to the kidneys, and some people develop sores when the skin is immersed in chloroform.

Animal studies have shown that miscarriages occur in rats and mice that have breathed air containing 30 to 300 ppm of chloroform during pregnancy and also in rats that have ingested chloroform during pregnancy. Offspring of rats and mice that breathed chloroform during pregnancy have a higher incidence of birth defects, and abnormal sperm have been found in male mice that have breathed air containing 400 ppm chloroform for a few days. The effect of chloroform on reproduction in humans is unknown.

Chloroform once appeared in toothpastes, cough syrups, ointments, and other pharmaceuticals, but it has been banned as a consumer product in the US since 1976.[20] Cough syrups containing Chloroform can still be legally purchased in pharmacies and supermarkets in the UK.

The US National Toxicology Program's eleventh report on carcinogens[21] implicates it as reasonably anticipated to be a human carcinogen, a designation equivalent to International Agency for Research on Cancer class 2A. The IARC itself classifies chloroform as *possibly carcinogenic to humans*, a Group 2B designation.[22] It has been most readily associated with hepatocellular carcinoma.[23][24] Caution is mandated during its handling in order to minimize unnecessary exposure; safer alternatives, such as dichloromethane, have resulted in a substantial reduction of its use as a solvent.

Conversion to phosgene

During prolonged storage in the presence of oxygen chloroform converts slowly to phosgene. To prevent accidents, commercial chloroform is stabilized with ethanol or amylene, but samples that have been recovered or dried no longer contain any stabilizer. Amylene has been found ineffective, and the phosgene can affect analytes in samples, lipids and nucleic acids dissolved in or extracted with chloroform.[25] Dissolved phosgene cannot be removed by distillation or carbon filters, but is removed by calcium hydroxide or activated alumina.[26] Suspicious samples can be tested for phosgene using filter paper (treated with 5% diphenylamine, 5% dimethylaminobenzaldehyde in alcohol, and then dried), which turns yellow in phosgene vapor. There are several colorimetric and fluorometric reagents for phosgene, and it can also be quantified with mass spectrometry.

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External links

- Chloroform "The Molecular Lifesaver" An article at Oxford University providing facts about chloroform.
- Concise International Chemical Assessment Document 58
- History of chloroform anesthesia
- IARC Summaries & Evaluations: Vol. 1 (1972), Vol. 20 (1979), Suppl. 7 (1987), Vol. 73 (1999)

- International Chemical Safety Card 0027
- NIOSH Pocket Guide to Chemical Hazards 0127
- National Pollutant Inventory - Chloroform and trichloromethane
- NIST Standard Reference Database
- Story on Chloroform from BBC's The Material World (28 July 2005)
- Sudden Sniffer's Death Syndrome article at Carolina Poison Center
- Calculation of vapor pressure, liquid density, dynamic liquid viscosity, surface tension of chloroform
- ChemSub Online: Chloroform - Methane, trichloro-

Fentanyl

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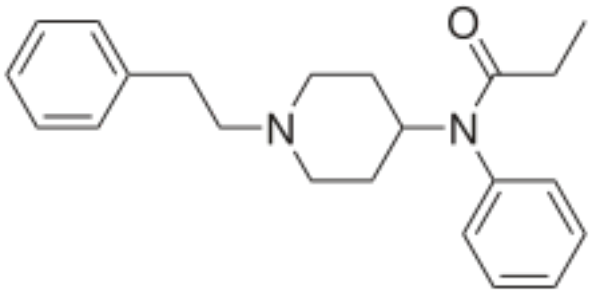
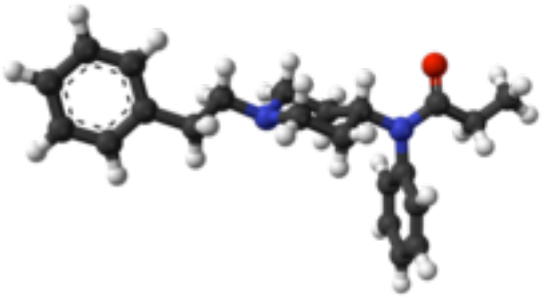
Fentanyl





Systematic (IUPAC) name
N-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenylpropanamide

Identifiers	
CAS number	437-38-7
ATC code	N01AH01 N02AB03
PubChem	CID 3345
IUPHAR ligand	1626
DrugBank	DB00813
ChemSpider	3228

UNII	UF599785JZ ✓
KEGG	D00320 ✓
ChEMBL	CHEMBL596 ✓
Chemical data	
Formula	$C_{22}H_{28}N_2O$
Mol. mass	336.471 g/mol
SMILES	eMolecules & PubChem

InChI[show]

Physical data	
Melt. point	87.5 °C (190 °F)
Pharmacokinetic data	
Bioavailability	92% (transdermal) 89% (intranasal) 50% (buccal) 33% (ingestion)
Protein binding	80-85%
Metabolism	hepatic, primarily by CYP3A4
Half-life	(IV)= 2.5 minutes Intranasal = 6.5 mins Transdermal = 7 hours (range 3–12 h)
Excretion	60% Urinary (metabolites, <10% unchanged drug)[11]
Therapeutic considerations	
Pregnancy cat.	C(US)
Legal status	? (UK) Schedule II (US)
Dependence liability	Moderate - High
Routes	TD, IM, IV, oral, sublingual, buccal

✓ **(what is this?) (verify)**

Fentanyl (also known as **fentanil**, brand names Sublimaze,[2] Actiq, Durogesic, Duragesic, Fentora, Onsolis,[3] Instanyl,[4] Abstral,[5] and others) is a potent synthetic narcotic analgesic with a rapid onset and short duration of action.[6] It is a strong agonist at the μ-opioid receptors. Historically it has been used to treat chronic breakthrough pain and is commonly used before procedures as an anesthetic in combination with a benzodiazepine.[7]

Fentanyl is approximately 80 times more potent than morphine,[8] with 100 micrograms of fentanyl approximately equivalent to 10 mg of morphine and 75 mg of pethidine (meperidine) in analgesic activity.[8] It has an LD_{50} of 3.1 milligrams per kilogram in rats, and an LD_{50} of 0.03 milligrams per kilogram in monkeys.

Fentanyl was first synthesized by Dr. Paul Janssen in 1960[9] following the medical inception of pethidine several years earlier. Janssen developed fentanyl by assaying analogues of the structurally-related drug pethidine for opioid activity.[10] The widespread use of fentanyl triggered the production of fentanyl citrate (the salt formed by combining fentanyl and citric acid in a 1:1 stoichiometry),[11] which entered the clinical practice as a general anaesthetic under the trade name Sublimaze in the 1960s. Following this, many other fentanyl analogues were developed and introduced into the medical practice, including sufentanil, alfentanil, remifentanil, and lofentanil.

In the mid 1990s, fentanyl saw its first widespread palliative use with the clinical introduction of the Duragesic patch, followed in the next decade by the introduction of the first quick-acting prescription formations of fentanyl for personal use, the Actiq lollipop and Fentora buccal tablets. Through the delivery method of transdermal patches, fentanyl is currently the most widely used synthetic opioid in clinical practice, with several new delivery methods currently in development.[12]

Contents

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History

Fentanyl was first synthesized by Paul Janssen under the label of his relatively newly formed Janssen Pharmaceutica in 1959. In the 1960s, fentanyl was introduced as an intravenous anesthetic under the trade name of Sublimaze.[*citation needed*] In the mid-1990s, Janssen Pharmaceutica developed and introduced into clinical trials the Duragesic patch, which is a formation of an inert alcohol gel infused with select fentanyl doses which are worn to provide constant administration of the opioid over a period of 48 to 72 hours. After a set of successful clinical trials, Duragesic fentanyl patches were introduced into the medical practice.

Following the patch, a flavored lollipop of fentanyl citrate mixed with inert fillers was introduced under the brand name of Actiq, becoming the first quick-acting formation of fentanyl for use with chronic breakthrough pain. More recently, fentanyl has been developed into an effervescent tab for buccal absorption much like the Actiq lollipop, followed by a buccal spray device for fast-acting relief and other delivery methods currently in development.

A new fentanyl product has been approved by the FDA for breakthrough cancer pain called Onsolis. It uses a new drug delivery technology called BEMA (fentanyl buccal soluble film) which is placed in the mouth on a small disc. There appears to be less abuse potential because the drug can not be crushed up and snorted like other fentanyl products.

Mechanism of action

Fentanyl provides most of its effects typical of other opioids (especially analgesia, euphoria, and respiratory depression) through its agonism of the μ-opioid receptors. Its strong potency in relation to that of morphine is largely due to its high lipophilicity. Because of this, it can more easily penetrate the CNS.[13]

Chemistry

Synthesis

The synthesis of fentanyl (*N*-phenyl-*N*-(1-phenethyl-4-piperidinyl)propanamide) by Janssen Pharmaceutica was achieved in four steps, starting from 4-piperidinone hydrochloride. The 4-piperidinone hydrochloride was first reacted with 2-phenylethylbromide to give N-phenethyl-4-piperidinone (NPP). Treatment of the NPP intermediate with aniline followed by reduction with sodium borohydride affording 4-anilino-*N*-phenethyl-piperidine (ANPP). Finally ANPP and propionic anhydride are reacted to form the amide product.

Analogues

The pharmaceutical industry has developed several analogues of fentanyl:

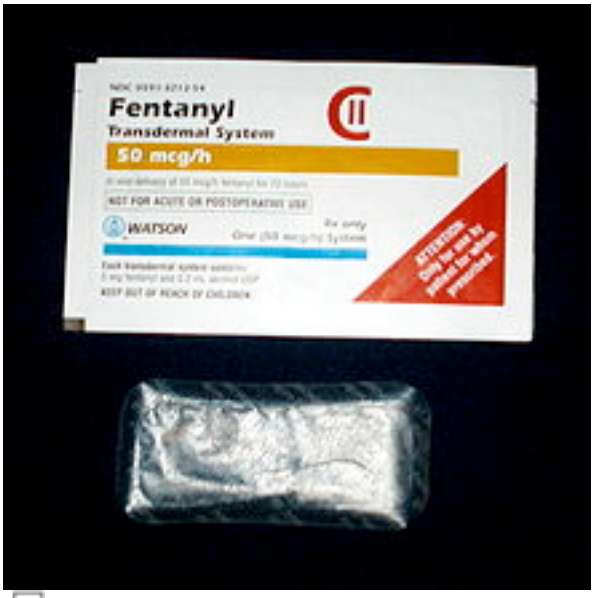
- Alfentanil (trade name **Alfenta**), an ultra-short-acting (five to 10 minute) analgesic.
- Sufentanil (trade name **Sufenta**), a potent analgesic (five to 10 times more potent than fentanyl) for use in specific surgeries and surgery in heavily opioid-tolerant/opioid-dependent patients. Its binding affinity is high enough to theoretically break through a buprenorphine blockade to offer pain relief from acute trauma in patients who are taking high-dose buprenorphine.
- Remifentanil (trade name **Ultiva**), currently the shortest-acting opioid, has the benefit of rapid offset, even after prolonged infusions.
- Carfentanil (trade name **Wildnil**) is an analogue of fentanyl with an analgesic potency 10,000 times that of morphine and is used in veterinary practice to immobilize certain large animals such as elephants.
- Lofentanil is an analogue of fentanyl with a potency slightly greater than carfentanil.

A number of other fentanyl analogues exist which are classified in the USA as Schedule I drugs, meaning that they have "no currently accepted medical use".[14] Many of these drugs have been sold on the street as "China White".[15] These drugs include:

- 3-Methylfentanyl (thought to be the active constituent of Kolokol-1, a chemical weapon)
- 3-Methylthiofentanyl
- Acetyl-α-methylfentanyl
- α-methylfentanyl (see below)
- α-methylthiofentanyl
- β-hydroxy-3-methylfentanyl
- β-hydroxyfentanyl
- *p*-flurorofentanyl
- Thiofentanyl[15]

Therapeutic use

Intravenous fentanyl is extensively used for anesthesia and analgesia, most often in operating rooms and intensive care units. It is often administered in combination with a benzodiazepine, such as midazolam, to produce procedural sedation for endoscopy, cardiac catheterization, oral surgery, etc. Additionally, fentanyl is often used in cancer therapy and other chronic pain management due to its effectiveness in relieving pain.



Fentanyl Transdermal System patch (50 μg/h).

It has also been found to be useful to improve the actions of local anesthetic during root canal treatment. According to E.A. Elsharrawy in the Journal of Pain Symptom Management (33; 203-207, 2007), the intraligamentary injection of 0.4 ml of fentanyl (0.05 mg/ml) was highly effective in reducing pain when used concurrently with local anesthetic for a pulpectomy procedure (where the "hot" nerve is removed).

Fentanyl transdermal patch (Durogesic/Duragesic/Matrifen) is used in chronic pain management. The patches work by releasing fentanyl into body fats, which then slowly release the drug into the bloodstream over 48 to 72 hours, allowing for long-lasting relief from pain. The patches are available in generic form and are available for lower costs. Fentanyl patches are manufactured in five patch sizes: 12 micrograms/hour, 25 μg/h, 50 μg/h, 75 μg/h, and 100 μg/h. Dosage is based on the size of the patch, since the transdermal absorption rate is generally constant at a constant skin temperature. Rate of absorption is dependent on a number of factors. Body temperature, skin type, amount of body fat, and placement of the patch can have major effects. The different delivery systems used by different makers will also affect individual rates of absorption. The typical patch will take effect under normal circumstances usually within 8–12 hours, thus fentanyl patches are often prescribed with another opiate (such as morphine or oxycodone) to handle breakthrough pain.

Fentanyl lozenges (Actiq) are a solid formulation of fentanyl citrate on a stick in the form of a lollipop that dissolves slowly in the mouth for transmucosal absorption. These lozenges are intended for opioid-tolerant individuals and are effective in treating breakthrough cancer pain. It is also useful for breakthrough pain for those suffering bone injuries, severe back pain, neuropathy, arthritis, and some other examples of chronic nonmalignant pain. The unit is a berry-flavored lozenge on a stick which is swabbed on the mucosal surfaces inside the mouth—inside of the cheeks, under and on the tongue and gums—to release the fentanyl quickly into the system. It is most effective when the lozenge is consumed in 15 minutes. The drug is less effective if swallowed, as despite good absorbance from the small intestine there is extensive first-pass metabolism, leading to an oral bioavailability of 33%. Fentanyl lozenges are available in six dosages, from 200 to 1600 μg in 200 μg increments (excluding 1000 μg and 1400 μg). These are now available in the United States in generic form,[16] through an FTC consent agreement.[17] However, most patients find it takes 10–15 minutes to use all of one lozenge, and those with a dry mouth cannot use this route. In addition, nurses are unable to document how much of a lozenge has been used by a patient, making drug records inaccurate.

Over 2008-09, a wide range of fentanyl preparations became available, including buccal tablets or patches, nasal sprays, inhalers and active transdermal patches (heat or electrical). High-quality evidence for their superiority over existing preparations is currently lacking. Some preparations such as nasal sprays and inhalers may result in a rapid response, but the fast onset of high blood levels may compromise safety (see below). In addition, the expense of some of these appliances may greatly reduce their cost-effectiveness.

On July 16, 2009 the FDA approved Onsolis (BEMA Fentanyl) for breakthrough cancer pain. Onsolis incorporates "bioerodible mucoadhesive" technology, a small soluble film that contains fentanyl which is placed on the inside cheek of the mouth.

In palliative care, transdermal fentanyl has a definite, but limited, role for:

- Patients already stabilized on other opioids who have persistent swallowing problem and cannot tolerate other parenteral routes such as subcutaneous administration.
- Patients with moderate to severe renal failure.
- Troublesome adverse effects on morphine, hydromorphone or oxycodone.

Fentanyl is sometimes given intrathecally as part of spinal anesthesia or epidurally for epidural anesthesia and analgesia. Because of fentanyl's high lipid solubility, its effects are more localized than morphine and some clinicians prefer to use the morphine to get a wider spread of analgesia.

Adverse effects

Fentanyl's major side effects (more than 10% of patients) include diarrhea, nausea, constipation, dry mouth, somnolence, confusion, asthenia (weakness), and sweating and, less frequently (3 to 10% of patients), abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, hallucinations, anxiety, depression, flu-like symptoms, dyspepsia (indigestion), dyspnea (shortness of breath), hypoventilation, apnea, and urinary retention. Fentanyl use has also been associated with aphasia.[18]

Despite being a more potent analgesic, fentanyl tends to induce less nausea, as well as less histamine-mediated itching, in relation to morphine.[13]

The fentanyl patch has been associated with altered mental state leading to aggression in an anecdotal case report.[19]

Like other lipid-soluble drugs, the pharmacodynamics of fentanyl are poorly understood. The manufacturers acknowledge there is no data on the pharmacodynamics of fentanyl in elderly, cachectic or debilitated patients, frequently the type of patient for whom transdermal fentanyl is being used. This may explain the increasing number of reports of respiratory depression events since the late 1970s.[20][21][22][23][24][25][26] In 2006 the U.S. Food and Drug Administration began investigating several respiratory deaths, but doctors in the United Kingdom had to wait until September 2008 before being warned of the risks with fentanyl.[27]

The precise reason for sudden respiratory depression is unclear, but there are several hypotheses:

- Saturation of the body fat compartment in patients with rapid and profound body fat loss (patients with cancer, cardiac or infection-induced cachexia can lose 80% of their body fat).
- Early carbon dioxide retention causing cutaneous vasodilatation (releasing more fentanyl), together with acidosis which reduces protein binding of fentanyl, releasing yet more fentanyl.
- Reduced sedation, losing a useful early warning sign of opioid toxicity and resulting in levels closer to respiratory depressant levels.

Fentanyl has a therapeutic index of 270.[28]

Illicit use

Fentanyl powder seized by a Lake County Deputy Sheriff in Painesville, Ohio, where a male subject had been discovered unresponsive and struggling to breathe.[29]

Illicit use of pharmaceutical fentanyls first appeared in the mid-1970s in the medical community and continues in the present. United States authorities classify fentanyl as a narcotic. To date, more than 12 different analogues of fentanyl have been produced clandestinely and identified in the U.S. drug traffic. The biological effects of the fentanyls are similar to those of heroin, with the exception that many users report a noticeably less euphoric "high" associated with the drug and stronger sedative and analgesic effects.[*citation needed*]

The use of fentanyl has caused death. Because the effects of fentanyl last for only a very short time, regular users may become addicted very quickly.[*citation needed*] Additionally, fentanyl may be hundreds of times more potent than street heroin, and tends to produce significantly worse respiratory depression, making it somewhat more dangerous than heroin to users. Fentanyl is most commonly used orally, but like heroin, can also be smoked, snorted or injected. Fentanyl is sometimes sold as heroin, often leading to overdoses. Many fentanyl overdoses are initially classified as heroin overdoses.[30]

Fentanyl is normally sold on the black market in the form of transdermal fentanyl patches such as Duragesic, diverted from legitimate medical supplies. The patches may be cut up and eaten, or the gel from inside the patch smoked. To prevent the removal of the fentanyl base, Janssen-Cilag, the inventor of the Fentanyl patch, designed the Durogesic patch. The Durogesic patches contain their fentanyl throughout the plastic matrix instead of gel incorporated into a reservoir on the patch. Manufacturers such as Mylan and Sandoz have also produced Durogesic-style fentanyl patches that contain the chemical in a silicone matrix, preventing the removal of the fentanyl-containing gel present in other products. The plastic matrix makes the patches far less suitable to transbuccal use and far more difficult to use illicitly than its gel-filled counterpart.[31]

Another dosage form of fentanyl that has appeared on the streets are the Actiq fentanyl lollipops, which are sold under the street name of "percopop". The pharmacy retail price ranges from US$10 to US$30 per unit (based on strength of lozenge), with the black market cost anywhere from US$15 to US$40 per unit, depending on the strength.

Non-medical use of fentanyl by individuals without opiate tolerance can be very dangerous and has resulted in numerous deaths.[32] Even those with opiate tolerances are at high risk for overdoses. Once the fentanyl is in the user's system it is extremely difficult to stop its course because of the nature of absorption. Illicitly synthesized fentanyl powder has also appeared on the United States market. Because of the extremely high strength of pure fentanyl powder, it is very difficult to dilute appropriately, and often the resulting mixture may be far too strong and, consequently, very dangerous.

Some heroin dealers mix fentanyl powder with heroin to increase potency or compensate for low-quality heroin. In 2006, illegally manufactured, non-pharmaceutical fentanyl often mixed with cocaine or heroin caused an outbreak of overdose deaths in the United States, heavily concentrated in the cities of Chicago, Detroit, and Philadelphia.[33] Baltimore, Pittsburgh, St. Louis, Milwaukee, Camden, New Jersey,[34] Little Rock, and Dallas[35] were also affected. The mixture of fentanyl and heroin is known as "magic" or "the bomb," among other names, on the street.[36]

Several large quantities of illicitly produced fentanyl have been seized by U.S. law enforcement agencies. In June 2006, 945 grams of 83% pure fentanyl powder was seized by Border Patrol agents in California from a vehicle which had entered from Mexico.[37] Mexico is the source of much of the illicit fentanyl for sale in the U.S. However, in April 2006 there was one domestic fentanyl lab discovered by law enforcement in Azusa, California. The lab was a source of counterfeit 80-mg OxyContin tablets containing fentanyl instead of oxycodone, as well as bulk fentanyl and other drugs.[38][39]

The "China White" form of fentanyl refers to any of a number of clandestinely produced analogues, especially α-methylfentanyl (AMF).[40] This Department of Justice document lists "China White" as a synonym for a number of fentanyl analogues, including 3-methylfentanyl and α-methylfentanyl,[41] which today are classified as Schedule I drugs in the United States.[15] Part of the motivation for AMF is that despite the extra difficulty from a synthetic standpoint, the resultant drug is relatively more resistant to metabolic degradation. This results in a drug with an increased duration.[42]

Military use

A derivative of fentanyl may have been used as the Moscow hostage crisis chemical agent.[43]

The Danish Army is also using the fentanyl stick in military operations as a pain killer. In the documentary film "Armadillo" (2010), a medic mentions the actual use of fentanyl on a severely wounded Danish soldier in Afghanistan.[*citation needed*]

United States Air Force Pararescue uses lollipops with fentanyl.[44]

Mossad agents used levofentanyl in their 1997 attempt to kill Hamas leader Khalid Mishal.[45]

Overdoses, recalls, and legal action

A number of fatal fentanyl overdoses have been directly tied to the drug over the past several years. In particular, manufacturers of time-release fentanyl patches have come under scrutiny for defective products. While the fentanyl contained in the patches was safe, a malfunction of the patches caused an excessive amount of fentanyl to leak and become absorbed by patients, resulting in life-threatening side effects and even death.[46][47]

Manufacturers of fentanyl transdermal pain patches have voluntarily recalled numerous lots of their patches, and the U.S. Food and Drug Administration (FDA) has issued public health advisories related to fentanyl patch dangers. Manufacturers affected include Janssen Pharmaceutica Products, L.P.; Alza Corporation; Actavis South Atlantic, LLC; Sandoz; and Cephalon, Inc.[48]

On May 24, 2009, Wilco's former guitarist Jay Bennett died in his sleep of an overdose of the drug via Duragesic time-release patches, which he was prescribed.[49]

In 2010, Slipknot's bassist Paul Gray died after accidentally overdosing on a mixture of fentanyl and morphine, after struggling with substance abuse problems for many years.[50]

An inquest jury found by a majority verdict of 3-2 that an overdose of fentanyl was responsible for the death by misadventure of Anita Chan Lai-ling, 69, who died on October 17, 2007, after she was given an overdose of the powerful fentanyl.[51]

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