5-Fluorouracil

CAS: 51-21-8
MF: $C_4H_3FN_2O_2$
MW: 130.1
It is poorly soluble in water (1:80) and almost insoluble in alcohol (1:170).

Major use
5-fluorouracil (5-FU) is an anticancer drug widely used in oncology for the treatment of carcinoma of breast, lung, liver, stomach, pancreas and colon, often in combination with other cytostatics, or in combination with surgery, or radiotherapy.

Human toxicity
The usual adult doses for the treatment of carcinomas of the colon are between 13.5 - 25 mg/kg per day, i.v., 5-6 days. Maximum tolerated dose (clinical data): 2.5 g, i.v.; 6 g, oral administration.
There are practically no data on acute toxicity of 5-FU; only few cases of over dosage are known from the clinical practice. Among adverse reactions are anorexia, nausea, vomiting, dispnea, tachycardia and hypotension, pulmonary edema, and chest pain. Neurological effect: reversible cerebellar ataxia has been reported in less than 5% of patients receiving intravenous dose [1].

Peak plasma levels of 5-fluorouracil after oral administration of the drug may vary between 0.8 and 60 mg/l (clinical data from three patients with colon cancer; reviewed in [2]). Toxic blood concentrations of 5-fluorouracil are not well established.

Kinetic data
Absorption: Oral absorption is 28%.

Volume of distribution: 0.25 ± 0.12 l/kg.
5-FU is rapidly distributed in all tissues of the body.

Plasma half-life is 5 - 15 min. The high plasma clearance of 5-fluorouracil suggests that the first-pass metabolism occurs following oral administration (reviewed in [2]).

Plasma-protein binding is 8-12%.

Radioactive 5-FU was shown to cross the blood-brain barrier readily in humans; it distributes into brain and cerebrospinal fluid.

Metabolism and excretion
5-FU is rapidly metabolized by the liver to produce biologically inactive metabolites, such as dihydrofluorouracil, α-fluoro-β-ureidopropionic acid, which are further converted to CO_2, urea and aminofluoropropionic acid, and excreted with urine. [4, 5].

Excretion: 10-15% of 5-FU is excreted intact in the urine. Non-toxic metabolites are also excreted in the urine, and 60-80% are excreted as CO_2 during 8-12 h [3].

Toxicological mechanisms

5-FU is an antimitotic agent, which is influencing cell division. It is not active as such, but it is converted into the active 5-fluoro-deoxyuridine monophosphate (FdUMP). The latter inhibits enzyme thymidylate synthetase, which results in the reduced formation of thymidine and thus DNA. Inhibition of DNA synthesis leads to the cell cycle inhibition and to block of mitosis and cell division. Fluorouracil and its metabolite FdUMP are also incorporated into RNA, which can lead to decreased RNA function and, as a consequence, to inhibition of protein synthesis [4, 5].

References

[1] Poisindex, Thomson Micromedex (2005).
[2] Phillips, T.A., Howell, A., Grieve, R.J., Welling, P.G. (1980) *Pharmacokinetics of oral and intravenous fluorouracil in humans*. J Pharm Sci 69(12), 1428-1431.
[3] Baselt RC, Cravey RH (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th ed., Foster City, CA, USA: Chemical Toxicology Institute.
[4] Dollery C, ed. (1993) *Therapeutic drugs*. Vol 1 & 2, London: Churchill Livingstone.
[5] *Ellenhorn's Medical Toxicology* (1997) William & Wilkins.

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