

Digoxin

CAS number: 20830-75-5

MF: C₄₁H₆₄O₁₄

FW: 781.0

Slightly soluble in water (64.8 mg/l); slightly soluble in diluted alcohol, pyridine, or mixture of chloroform and alcohol.

Major use

Digoxin is a cardiac glycoside derived from the plants *Digitalis purpurea* or *D. lanæ*. It is a cardiac drug widely used for the treatment of arrhythmias and heart failure [1].

Human toxicity

Digoxin is a very toxic compound, with an estimated lethal dose being only a few milligrams.

Nausea and vomiting are early signs of acute digoxin toxicity. Among other symptoms are gastro-intestinal tract (GIT) disorders, abdominal pain, diarrhea, hyperkalemia, and muscle pain and weakness.

Since digoxin is a cardiac medicine, its overdoses can have severe and multiple effects on the heart. Acute poisoning may result in sinus bradycardia, atrial and ventricular arrhythmias, and varying degrees of heart block, coma, and even death [1].

Acute exposure to digoxin can also have various neuropsychiatric effects, including drowsiness, weakness, and headache [1].

The therapeutic daily doses of digoxin are between 0.25 and 3 mg [2]. The minimum lethal dose is 10 mg/70 kg person [3].

The approximate therapeutic blood concentration is 0.001 mg/l [3]. The mean lethal serum concentration, based on the data from several handbooks, is 0.016 mg/l, and minimum lethal serum concentration is 0.0038 mg/l [4].

Kinetic data [4, 5, 6]

Absorption occurs from small intestine, probably by passive diffusion.

Peak plasma concentration after oral administration is reached after 30 min – 3 h, however, it may be prolonged after an overdose.

Volume of distribution: 6 l/kg.

Plasma protein binding is about 20%. Cardiac glycosides are widely distributed in body tissues; highest concentrations are found in the heart, kidneys, intestine, stomach, liver, and skeletal muscle. Lowest concentrations are in the plasma and brain.

The plasma half-life is in the range of 20-50 h.

The elimination half-life is 34-44 h in patients with normal renal function. The elimination half-life is decreased in patients with acute digoxin overdosage.

Metabolism and excretion

Only small amounts of digoxin are metabolized, but the extent of metabolism is variable and may be substantial in some patients. Some metabolism presumably

occurs in the liver, but digoxin is also apparently metabolized by bacteria within the lumen of the large intestine following oral administration. Digoxin undergoes stepwise cleavage of the sugar moieties to form digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, and digoxigenin [5, 6].

Excretion: The kidney excretes 60%-80% of digoxin unchanged. The rest of the drug excreted in the urine will consist of reduced metabolites (see above).

Toxicological mechanism

Cardiac cells are stimulated by the movement of sodium, potassium, and calcium into and out of the cell via the ATP pump (Na^+/K^+ -ATPase). Digoxin may attach to the ATP pump, which leads to an inhibition of ATPase and consequently to an inhibition of sodium transport, however, calcium continues to move into the cell. Toxicity results in part from loss of intracellular potassium associated with inhibition of Na^+/K^+ -ATPase [6, 7].

Target organ: heart, GIT, CNS [4].

References

1. Poisindex, Thomson Micromedex (2005).
2. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th ed., pp. 246-250. Foster City, CA, USA: Chemical Toxicology Institute.
3. Kaye, S. (1980) *Handbook of Emergency Toxicology: A Guide for the Identification, Diagnosis and Treatment of Poisoning*, 4th edn., pp. 139, also 232-235, Springfield, IL, USA.
4. Ekwall, B., Clemenson, C., Crafoord, B., Ekwall, B., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26,
5. Therapeutic Drugs (1993), Vol 1 & 2, Dollery, C., ed., London: Churchill Livingstone.
6. Medical Toxicology (2004), 3rd ed., Dart, R.C., ed., Lippincott, Williams & Wilkins.
7. *Casarett and Doull's Toxicology (The Basic Science of Poisons)*, (1986) C.D. Klaassen, M.O. Amdur, J. Doull, eds., Macmillan Publishing Company.

Written by Ada Kolman, March-April 2005; revised February 2007

ada.kolman@telia.com