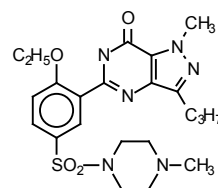


Sildenafil

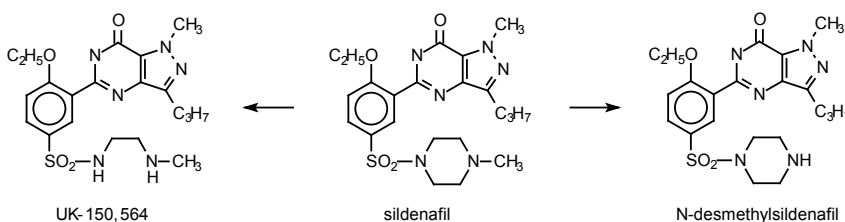


t_{1/2}: 1.4–4.5 h
Vd: 1.0–1.5 L/kg
Fb: 0.96
pKa: 8.7
b/p: 0.5

Occurrence and Usage. Sildenafil (Kamagra, Revatio, Viagra) is an inhibitor of cyclic GMP phosphodiesterase, originally developed as an antihypertensive agent, but now used frequently for the treatment of erectile dysfunction. The drug is supplied as the citrate salt in 20–100 mg tablets for oral administration. The usual adult dosage is 20 mg thrice daily in hypertensive patients and 25–100 mg no more than once daily in erectile dysfunction patients.

Blood Concentrations. A single oral 20 mg dose administered to 10 healthy men yielded an average peak plasma sildenafil concentration of 50 µg/L at 1.5 hours (Wang et al., 2005). Twenty-six healthy men given a single oral 50 mg dose achieved peak plasma concentrations averaging 206 µg/L at 1.0 hour for sildenafil and 83 µg/L at 0.9 hours for N-desmethylsildenafil (Al-Ghazawi et al., 2006). A single oral 100 mg dose given to 34 healthy fasted men yielded average peak plasma levels of 514 µg/L at 1.0 hour for sildenafil and 215 µg/L at 0.9 hours for N-desmethylsildenafil; elimination half-lives for the two species averaged 4.0 and 5.9 hours, respectively (Nichols et al., 2002). Adult male patients given a single oral 200 mg dose attained peak plasma sildenafil concentrations averaging 903 µg/L and declining with an average half-life of 3.7 hours (Milligan et al., 2002). The oral bioavailability of sildenafil averages 41% (Nichols et al., 2002). The peak plasma level, area-under-the-curve and elimination half-life of sildenafil were significantly increased by pretreatment with fluvoxamine (Hesse et al., 2005) and significantly decreased by pretreatment with bosentan (Paul et al., 2005). Advanced age, renal impairment or hepatic cirrhosis can increase both the peak plasma level and the area-under-the-curve of sildenafil by 47–100%, while the elimination half-life is increased by 14–46% (Muirhead et al., 2002a).

Metabolism and Excretion. A single oral sildenafil dose is eliminated, largely as products of biotransformation, in the feces (80%) and urine (13%). A major plasma metabolite, N-desmethylsildenafil, has about one-half of the pharmacological activity of the parent drug (Viagra, 1998). A single urinary metabolite, representing 5% of a dose, has been identified as a product of hydroxylation on the n-propyl sidechain. A product of piperazine ring fission, UK-150,564, is present in plasma at about 25% of the parent drug concentration and represents 22% of the dose in the excreta. At least 25 metabolites have been isolated in urine and feces, but the parent drug has not been detected there during single dose studies (Walker et al., 1999; Muirhead et al., 2002b).



Toxicity. Adverse effects associated with sildenafil therapy include headache, flushing, blurred vision, dyspepsia and musculoskeletal pain. The drug may potentiate the hypotensive effects of co-administered organic nitrates. A 73 year old man with severe renal disease experienced loss of consciousness and marked hypotension following a single 50 mg oral dose; peak plasma levels of 440 µg/L for sildenafil and 190 µg/L for N-desmethylsildenafil occurred at 2 and 4 hours, respectively (Wada et al., 2009). Overdosage may result in hypotension, tachycardia and cardiac arrest (Boolell et al., 1996; Viagra, 1998; Krenzelok, 2000). A 19 month old male infant who ingested as much as 300 mg of the drug developed facial flushing, mild tachycardia and priapism of approximately 24 hours duration; serum concentrations of 3900 µg/L for sildenafil and 1700 µg/L for N-desmethylsildenafil were present at 7 hours post-ingestion (Wills et al., 2007). A woman who ingested 2 g of the drug in a suicide attempt manifested weakness, dizziness, tachycardia, facial flushing, tremor and EKG changes; she was treated supportively and discharged after 12 hours (Hung and Yang, 2001).

A man with a history of heart disease and hypertension died during sexual intercourse; sildenafil was not found in his portmortem blood (detectability, 100 µg/L), but his urine contained 400 µg/L (Ng et al., 1999). In 3 similar cases involving 43–80 year old men, sildenafil was identified in postmortem blood at concentrations of 40–105 µg/L and in postmortem urine at levels of 63–246 µg/L (Dumestre-Toulet et al., 2001; Weinmann et al., 2001; Pagani et al., 2005). A 56 year old man who apparently died of an acute 600 mg oral overdose had a postmortem blood sildenafil concentration of 6270 µg/L (Tracqui et al., 2002).

Analysis. Sildenafil and its major metabolite have been measured in biofluids by liquid chromatography with ultraviolet (Cooper et al., 1997; Jeong et al., 2001), electrochemical (Al-Ghazawi et al., 2007) or mass spectrometric detection (Eerkes et al., 2002; Wang et al., 2005; Lewis et al., 2006; Vos et al., 2008). Gas chromatography-mass spectrometry has also been described (Strano-Rossi et al., 2010).

Sildenafil and N-desmethylsildenafil were stable in plasma for 48 hours at room temperature, 3 months at -20 °C and 50 days at -48 °C (Eerkes et al., 2002; Al-Ghazawi et al., 2007). They were stable in blood for 1 week at 4 °C (Lewis et al., 2006).

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