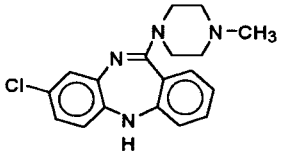
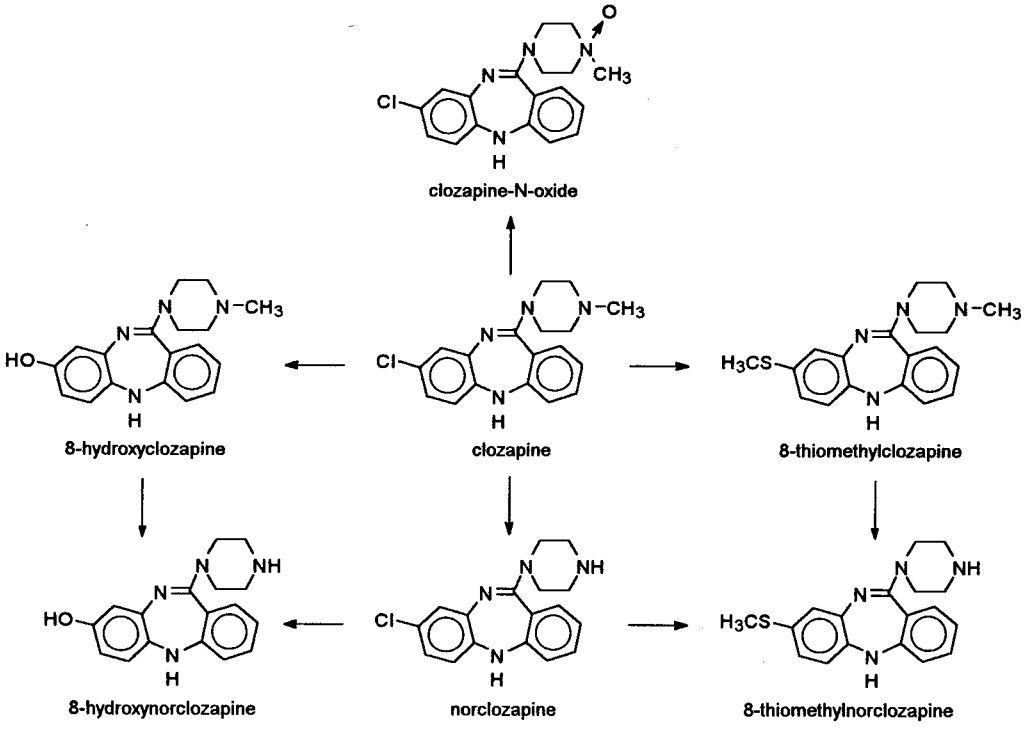
Clozapine



T½: 4.5–7.5 hr
Vd: 5 L/kg
Fb: 0.95
pKa: ?

Occurrence and Usage. Clozapine (Clozaril, Leponex) is an antipsychotic drug available in the U.S. since 1989 for the treatment of severely ill schizophrenic patients who do not respond to standard antipsychotic drug treatment. Due to the significant risk of agranulocytosis, the drug is available only through a distribution system that ensures weekly hematological monitoring. Clozapine is available in tablets of 25 and 100 mg as the free base for oral administration. It is recommended that therapy begin with doses of 12.5 mg once or twice a day, with a gradual increase to 300–450 mg/day by the end of 2 weeks.

Blood Concentrations. A single 100 mg dose given to 12 patients resulted in an average peak plasma clozapine level of 0.14 mg/L (range, 0.07–0.34) after 1.5 hours (Ackenheil, 1989). Plasma clozapine concentrations after the usual clinical doses range from 0.06–1.0 mg/L, with average levels of about 0.2–0.4 mg/L (Choc et al., 1987; Cheng et al., 1988; Ackenheil, 1989; Haring, 1989). In a study involving patients given an average dose of 384 mg/day, the patients who did not improve after weeks of therapy usually had a blood clozapine concentration less than 0.35 mg/L, whereas responders had a blood concentration greater than 0.35 mg/L (Perry et al., 1991). In 25 patients on chronic therapy with the drug at an average daily dose of 3.1 mg/kg (217 mg/70 kg), steady-state plasma levels averaged 0.23 mg/L for clozapine, 0.19 mg/L for norclozapine, and 0.05 mg/L for clozapine-N-oxide (Volpicelli et al., 1993).



Metabolism and Excretion. Clozapine is almost completely metabolized prior to excretion, undergoing N-demethylation, N-oxidation, oxidation of the chlorine-containing ring and thiomethyl conjugation (Schmutz and Eichenberger, 1982). At least 80% of the dose appears in the urine or feces as metabolites; the 2 major plasma metabolites, norclozapine and clozapine-N-oxide, are not believed to have significant pharmacological activity (Ackenheil, 1989).

Toxicity. Adverse reactions to chronic therapy with clozapine have involved hematologic disorders and tardive dyskinesia. Acute overdosage can cause hypotension, cardiac arrhythmias, respiratory depression, coma and death. Two adult patients who developed seizures after accidental overdoses with clozapine exhibited plasma levels of 1.3 and 2.2 mg/L (Simpson and Cooper, 1978). In a nonfatal suicidal attempt in which the subject ingested 2250 mg of clozapine, a blood clozapine concentration of 2.9 mg/L was determined 2.5 hours after ingestion, when the patient was somnolent yet agitated (Wolf and Otten, 1991).

In 2 deaths attributed to clozapine intoxication, a blood clozapine concentration of 4.5 mg/L was found in one, and a plasma clozapine concentration of 3.2 mg/L in the other (Vesterby et al., 1980). The following concentrations were measured postmortem in 3 adult patients following intentional overdosage; one case involved the ingestion of 2000 mg of drug (Meeker et al., 1992; Osciewicz, 1992; Sidebotham, 1992):

Clozapine Concentrations in Fatal Cases (mg/L or mg/kg)

	Blood	Brain	Liver	Urine	Gastric
Average	4.8	7.5	48	11	20 mg
(Range)	(1.6–7.1)	(7.5)	(19–82)	(11)	(1.1–54)

Analysis. Clozapine can be determined in biological specimens by gas chromatography employing nitrogen-selective detection (Heipertz et al., 1977) and by liquid chromatography (Haring et al., 1988; Humpel et al., 1989; Lovdahl et al., 1991; Weigmann and Heimke, 1992; Chung et al., 1993; Volpicelli et al., 1993). Gas chromatography-mass spectrometry offers a sensitive and specific method for the analysis of clozapine and its metabolites in biological samples (Bondesson and Lindstrom, 1988).

References

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