Toxicity. The spectrum of toxic effects produced by maneb is quite diverse. Contact dermatitis has been reported in exposed workers and their spouses (Manuzzi et al., 1988; Piraccini et al., 1991). Acute renal failure was described after short-term casual use (Koizumi et al., 1979; de Carvalho et al., 1989). A man who walked unprotected through a field he had sprayed twice with maneb several days earlier exhibited ataxia, confusion, dysarthria, loss of consciousness and seizures; he recovered completely within 2 weeks (Israeli et al., 1983). A 7 year old girl who played in an agricultural field that had been treated with maneb experienced nausea, vomiting, hypothermia and status epilepticus that resolved within 3 days (de Tollenaer et al., 2006). Several workers with long-term exposure to the chemical have developed parkinsonism, possibly as a result of manganese accumulation (Ferraz et al., 1988; Meco et al., 1994). The metabolite ethylenethiourea is suspected to be goitrogenic, carcinogenic and teratogenic in humans (Kurttio and Savolainen, 1990).

Analysis. Ethylenethiourea has been determined in biological fluids by gas chromatography-mass spectrometry (Fustinoni et al., 2005) and by liquid chromatography with ultraviolet (Kurttio et al., 1988; Debbarh and Moore, 2002) or mass spectrometric detection (Montesano et al., 2007). Methods for manganese analysis are described in the section on manganese.

Ethylenethiourea was stable in urine for 3 months at room temperature or 4 °C (Montesano et al., 2007) and 6 months at -20 °C (Fustinoni et al., 2005).

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Manganese

Mn

$t_{1/2}$: 12–36 days
Vd: ?
Fb: ?
b/p: 12–20

Occurrence and Usage. Manganese is widely used industrially in the manufacture of steel, welding rods, batteries, ceramics and refractory materials. It is also an essential trace element and is supplied in daily amounts of 3–7 mg by dietary intake. Dietary supplements are available in the form of capsules, tablets or liquids that provide 0.25–10 mg of manganese per daily oral dose for adults, usually as an aspartate-citrate-glycine complex with manganese carbonate (containing 20% manganese by weight). Occupational exposure usually occurs by inhalation or ingestion of fumes and dusts produced during the refining of manganese ores or the treatment

of manganese alloys. Certain organic derivatives of manganese are currently being used as octane-improving additives in unleaded gasoline. The current threshold limit value is 0.2 mg/m³ for manganese and its inorganic compounds (both expressed as Mn). Substances that contain manganese, such as mancozeb, maneb and permanganate, are discussed in separate sections.

Blood Concentrations. Whole blood manganese, most of which is bound to hemoglobin in the erythrocytes, averages 9 µg/L (range, 3.9–15) in normal adults when measured by atomic absorption spectrometry. Serum manganese in normal adults averages 0.6 µg/L, ranging from 0.2–1.1 µg/L (Neve and Leclercq, 1991). Other authors, using either similar techniques, colorimetry or neutron activation analysis, are in general agreement with this data (Cotzias et al., 1966, 1968; Pleban and Pearson, 1979; Roels et al., 1992; Heitland and Koster, 2006a). However, many discrepancies exist in the literature on endogenous manganese concentrations, probably as a result of methodological difficulties and problems with contamination, with some authors claiming normal blood or serum levels 5–40 times higher than those cited above (Nilubol et al., 1968; Mahoney et al., 1969; Jonderko et al., 1971). Workers in a ferroalloy plant exposed to an average air manganese level of >0.25 mg/m³ had post-shift blood manganese concentrations averaging 11 µg/L, versus an average of 6.0 µg/L in a control group of unexposed adults (Apostoli et al., 2000). Asymptomatic workers exposed to an average air manganese concentration of 0.39 mg/m³ had blood manganese levels averaging 14 µg/L (range, 6.1–23), compared to unexposed control subjects whose levels averaged 7.5 µg/L (range, 2.6–15) (Bader et al., 1999). The current German BAT (biological tolerance value) for occupational exposure to manganese and its inorganic compounds is 20 µg/L manganese in an end-of-exposure blood specimen (DFG, 2007).

Metabolism and Excretion. Most inhaled manganese is mobilized up the trachea and swallowed. The efficiency of gastrointestinal absorption of the element is low, usually less than 10%, but is quite variable and appears to correlate inversely to the amount available for absorption (Mena et al., 1969). The absorbed manganese leaves the blood quickly and is stored in parenchymatous tissues; the half-time for excretion of manganese from the body in normal subjects is about 40 days. Elimination of injected manganese is largely via the feces, which contain from 14–54% of a single dose after 15 days, and to a very minor extent in urine (Mena et al., 1967; Mahoney and Small, 1968).

Urine manganese concentrations in 87 German adults averaged 0.09 µg/L (range, 0.02–0.71) (Heitland and Koster, 2006b). Urinary manganese concentrations in unexposed persons have been reported to range from less than 1–10 µg/L (Nilubol et al., 1968; Ajemian and Whitman, 1969; Weissman and Pileggi, 1974; Buchet et al., 1976; Paschal et al., 1998). Urine concentrations in asymptomatic manganese workers have ranged from 25–124 µg/L (Nilubol et al., 1968), although it has been found that urine levels do not usually exceed 8 µg/L when occupational manganese exposure is limited to 5 mg/m³ (Tanaka and Lieben, 1969). Post-shift urinary manganese concentrations in asymptomatic workers exposed to an average air manganese concentration of >0.25 mg/m³ averaged 7.0 µg/L, compared to an average value of 1.2 µg/L for unexposed control subjects (Apostoli et al., 2000).

The following average manganese concentrations were present in the tissues of Japanese citizens (Sumino et al., 1975):

Manganese Concentrations in Normal Human Tissues (mg/kg)

Brain	Lung	Liver	Kidney	Bone	Fat
0.25	0.22	1.2	0.56	0.07	0.05

Toxicity. Typical metal fume fever may develop after acute exposure to manganese oxide fumes, with symptoms of fever, muscle pains, chills, and dryness of the mouth and throat. However, chronic overexposure to manganese is more frequently encountered. This may require a year or more of exposure prior to the manifestation of CNS symptoms such as headache, restlessness, irritability, personality change, hallucinations and hearing impairment. Severe toxicity results in muscle weakness and rigidity, tremor and other extrapyramidal symptoms. Administration of levodopa has been successfully employed in the treatment of manganism (Hine and Pasi, 1975). Repeated intravenous infusion of p-aminosalicylic acid was effective in resolving the symptoms of chronic manganism in one patient (Jiang et al., 2006).

A 44 year old man who had been taking a dietary supplement containing 4 mg manganese once daily for 2 weeks developed insomnia, mental depression, delusions and disorganized speech; his serum manganese level was 1.3 µg/L when meaured 5 weeks after discontinuation of intake (Leikin and Mottram, 2008). Three adults accidentally given 60–80 g of manganese sulfate orally experienced emesis, diarrhea and elevation of hepatic enzymes; serum and urine manganese concentrations of 14–47 and 5–110 µg/L, respectively, were present (Munne

et al., 2009). Two elderly adults who had been maintained on total parenteral nutrition (20 µmol Mn daily) for 3–4 months developed confusion, parkinsonism and serum manganese levels of 42–51 µg/L (Nagatomo et al., 1999). Manganese concentrations in a 23 year old man with chronic occupational poisoning were elevated in blood (75 µg/L) but normal in urine (Rosenstock et al., 1971); another such young man demonstrated a blood concentration of 36 µg/L and a urine concentration of 160 µg/L (Hine and Pasi, 1975). Blood manganese levels in 4 men with chronic industrial poisoning ranged from 102–405 µg/L (Huang et al., 1989). Urine manganese concentrations in other manganism patients have ranged from less than 10 to as high as 260 µg/L (Nilubol et al., 1968; Tanaka and Lieben, 1969; Smyth et al., 1973; Chandra et al., 1981). A man who survived the acute oral ingestion of 155 mg manganese in a liquid fertilizer developed hyperkalemia, metabolic acidosis, renal failure and blood and urine manganese levels of 195 and 80 µg/L, respectively; he responded to hemodialysis and was discharged after 1 week (Huang and Lin, 2004).

A 50 year old man who orally ingested 60–80 g of manganese sulfate (mistakenly labeled as magnesium sulfate) presented with emesis, diarrhea, severe hopotension, hepatorenal failure and a serum manganese level of 1980 µg/L; he died 3 days post-admission (Munne et al., 2009). His postmortem manganese concentrations were as follows (Sanchez et al., 2009):

Manganese Concentrations in a Fatal Case (mg/L or mg/kg)

Blood	Lung	Liver	Kidney	Fat
6.7	7.5	63	26	1.7

Analysis. Manganese may be analyzed in biofluids by electrothermal atomic absorption spectrometry (Tsalev et al., 1977; Watanabe et al., 1978; Pleban and Pearson, 1979; Casey et al., 1987; Hams and Fabri, 1988; Neve and Leclercq, 1991; Guillard et al., 2007; Olmedo et al., 2010). Neutron activation analysis (Cotzias et al., 1966; Versieck et al., 1974) and inductively-coupled plasma emission spectrometry (Rahil-Khazen et al., 2002; Zougagh et al., 2003; Bornhorst et al., 2005) have also been employed.

Manganese was stable in urine for 2 months at room temperature, 5 or -5 °C (Bornhorst et al., 2005).

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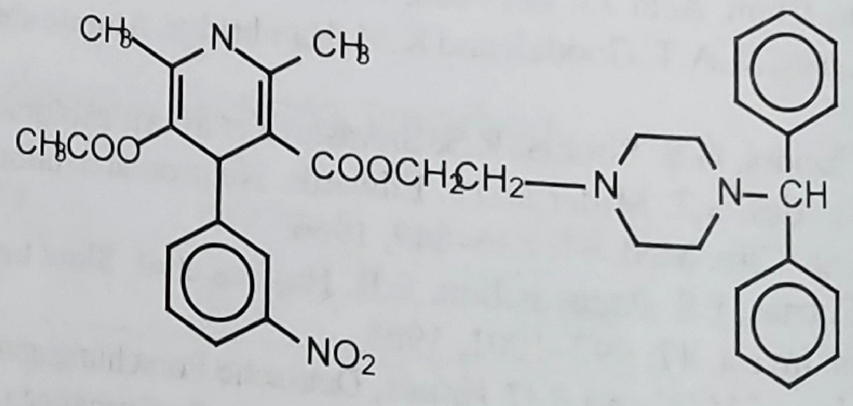
Manidipine



$t_{1/2}$: 2–5 h
Vd: ?
Fb: 0.99
pKa: ?
b/p: ?

Occurrence and Usage. Manidipine (franidipine, Calslot, Manidolot) is a dihydropyridine derivative and calcium channel blocking agent that has been used clinically since 1990 as an antihypertensive drug. It is supplied as the dihydrochloride salt in 10–20 mg tablets for oral administration. Adult doses are normally 10–20 mg once daily.

Blood Concentrations. Eighteen healthy younger men given a single 10 mg oral dose developed peak plasma manidipine concentrations averaging 3.5 µg/L at 1.0 hour, declining with an average elimination half-life of 3.3 hours (Stockis et al., 2003). A single oral 20 mg dose given to 12 healthy men produced peak plasma manidipine levels that averaged 8.6 µg/L at 1.5 hours and declined with an average half-life of 3.9 hours (Deroubaix et al., 1998). Administration of the drug on a full stomach increased the average peak plasma level by 26% and the area-under-the-curve by 50% without significantly affecting the elimination half-life (Rosillon et al., 1998). Patients with moderate to severe hepatic impairment demonstrated increases of 36, 158 and 115% in average peak plasma level, area-under-the-curve and elimination half-life versus healthy control subjects (Deroubaix et al., 1998).