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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Margosa Oil. [Updated 2020 Feb 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Margosa Oil

Updated: February 5, 2020.

OVERVIEW

Introduction

Margosa or neem oil is a yellow oil with a disagreeable smell and bitter taste that has been used as a medical remedy in India and Southeast Asia for several centuries. In recent years, there have been rare reports of acute onset of severe metabolic acidosis, hepatic and multiorgan failure and death following ingestion of margosa oil.

Background

Margosa oil is an extract of the seeds of Azadirachta indica, commonly known as the neem tree native to India and Sri Lanka. In low doses, margosa oil has been a traditional remedy for centuries in India and Southeast Asia used in treating asthma, intestinal parasites, arthritis and leprosy. It is also an insecticide. The oil has a disagreeable smell and bitter taste attributable to volatile sulphur compounds and fatty acids. Free fatty acids account for 20% of its weight and bitters (nimbin, nimbinin, nimbidin and nibidol) for about 2%. The bitters are secondary products formed during storage of the oil or the seeds and concentrations can vary in different commercial samples.

Hepatotoxicity

Several case reports have suggested that margosa oil can cause severe metabolic acidosis and death, particularly in young children. Symptoms of nausea, vomiting and progressive stupor develop within hours of consumption, followed by severe metabolic acidosis, coma, and progressive hepatic dysfunction, similar to Reye syndrome. Serum aminotransferase levels are generally normal or minimally elevated initially, but then rise to high levels accompanied by increases in LDH and CPK levels. Progressive hepatic encephalopathy and cerebral edema develop within days. Unexplained is why neem oil has been safely used for centuries in traditional Ayurvedic medicine. Outbreaks of this toxic syndrome have been described in India and South East Asia, suggesting that the toxicity may have been due to contamination of the ordinarily tolerated oil by seeds of plants that resemble Azadirachta indica. DNA from Azadirachta indica has been found as a contaminant in commercial herbal supplements in at least one toxicological screening report.

Likelihood score: C (known cytotoxic agent and probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of hepatotoxicity of margosa oil appears to be related to mitochondrial dysfunction and poisoning of the electron transport pathway by a component of margosa oil or a contaminant. A similar syndrome has been induced in laboratory animals with samples of the implicated oil.

Outcome and Management

Hepatotoxicity attributed margosa oil has been reported from India and Malaysia. The clinical syndrome is similar to Reye syndrome and should be managed accordingly with electrolyte, nutritional, ventilatory and hepatic support.

Other Names: Neem oil

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Margosa Oil – Generic

DRUG CLASS

Herbal and Dietary Supplements

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Margosa Oil	8002-65-1	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 05 February 2020

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; mentions that margosa oil has been linked to cases of liver injury resembling Reye syndrome).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; margosa oil is a fatty-rich extract of the seeds of the neem tree and the oil is used in treating asthma, parasites, arthritis and leprosy; in children margosa oil can cause a Reye-like syndrome).

Neem. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 599-600.

(Compilation of short monographs on herbal medications and dietary supplements).

Sinniah D, Baskaran G. Margosa oil as a cause of Reye's syndrome. Lancet. 1981;1:487–9. PubMed PMID: 6110100.

(13 Malaysian children with margosa oil poisoning, with onset of vomiting within a few minutes of taking the herbal medicine, presented with drowsiness and metabolic acidosis, liver tests being usually normal but liver biopsy showing steatosis of liver and renal tubules with mitochondrial damage suggestive of Reye's syndrome).

Sinniah D, Baskaran G, Looi LM, Leong KL. Reye-like syndrome due to margosa oil poisoning: report of a case with postmortem findings. Am J Gastroenterol. 1982;77:158–61. PubMed PMID: 7081175.

(4 month old Indian female developed vomiting 1 hour after second ingestion of margosa oil [for cough], with drowsiness and acidosis [pH 6.8, bilirubin 0.2 mg/dL, AST 170 U/L, ALT 44 U/L, CPK 3180 U/L, prothrombin 16%], liver biopsy on day 5 showing microvesicular fat and mitochondrial abnormalities, died of cerebral edema on day 10).

Koga Y, Yoshida I, Kimura A, Yoshino M, Yamashita F, Sinniah D. Inhibition of mitochondrial functions by margosa oil: possible implications in the pathogenesis of Reye's syndrome. Pediatr Res. 1987;22:184–7. PubMed PMID: 3658544.

(Studies of isolated rat mitochondria demonstrated that margosa oil is a mitochondrial toxin, uncoupling respiratory chain enzymes and depleting ATP).

Sinniah R, Sinniah D, Chia LS, Baskaran G. Animal model of margosa oil ingestion with Reye-like syndrome. Pathogenesis of microvesicular fatty liver. J Pathol. 1989;159:255–64. PubMed PMID: 2593049.

(In mice, margosa oil causes rapid onset of mitochondrial injury, steatosis and glycogen depletion).

Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. Curr Med Chem Anticancer Agents. 2005;5:149–56. PubMed PMID: 15777222.

(More than 140 compounds have been isolated from different parts of the neem tree and extracts of leaves, flowers, seeds, fruits, roots and bark have been used in traditional medicine for many medical conditions with little evidence of toxicity).

Senanayake MP, Rupasinghe S, Dissanayake PV. Margosa (Kohomba) oil induced toxic encephalopathy following home remedy for intestinal worms. Ceylon Med J. 2009;54:140. PubMed PMID: 20052860.

(14 month old boy developed vomiting, seizures and respiratory arrest hours after oral ingestion of a spoonful of margosa oil, presenting with hepatomegaly, no jaundice [ALT 120 U/L], and rapid and complete recovery).

Deng YX, Cao M, Shi DX, Yin ZQ, Jia RY, Xu J, Wang C, et al. Toxicological evaluation of neem (Azadirachta indica) oil: Acute and subacute toxicity. Environ Toxicol Pharmacol. 2013;35:240–6. PubMed PMID: 23353547.

(A four week course of neem oil in doses as high as 1.6 g/kg daily produced no acute or chronic toxicity in mice with no change in serum ALT levels and only mild congestion and fatty change in hepatocytes).

Giuggioli D, Lumetti F, Spinella A, Cocchiara E, Sighinolfi G, Citriniti G, Colaci M, et al. Use of Neem oil and Hypericum perforatum for treatment of calcinosis-related skin ulcers in systemic sclerosis. J Int Med Res 2019: Dec 25:300060519882176.

(Application of a Neem oil containing topical solution to cutaneous ulcers in 21 patients with systemic sclerosis resulted in more rapid healing compared to a non-treated historical control group of 20 patients and was well tolerated without systemic adverse events).

Crighton E, Coghlan ML, Farrington R, Hoban CL, Power MWP, Nash C, Mullaney I, et al. Toxicological screening and DNA sequencing detects contamination and adulteration in regulated herbal medicines and supplements for diet, weight loss and cardiovascular health. J Pharm Biomed Anal. 2019 Nov 30;176:112834. PubMed PMID: 31472365.

(Among 137 samples of herbal medications and supplements available in Australia that underwent toxicological and genetic analysis [DNA barcoding], 51% had additional plant DNA, one of which was Neem tree DNA, which was not declared on the product label).