K44 "Slim 10" - Slim Chance

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This is a fatal case of fulminant hepatic failure, probably induced by N-nitrosofenfluramine, present as an adulterant in a weight-reducing, herbal product, sold as complementary medicine. It illustrates the difficulties and medico-legal issues encountered in the evaluation of the role of a specific nitrosamine in the causation of death, in the absence of published reports on its hepatotoxicity in humans.

It is hoped that knowledge of the avoidably tragic consequences of this case might alert users of sliming agents, including herbal preparations (generally regarded by the lay public as being safe), to exercise vigilance and discernment in their choice of these products. From a forensic perspective, it also indicates the need for more extensive, multidisciplinary research into the human hepatotoxic potential of the nitrosamines, especially in the case of N-nitrosofenfluramine.

Case History**:** A 42-year-old lady developed acute hepatitis, which rapidly progressed to fulminant hepatic failure and eventual multi-organ failure, after having ingested an unknown quantity of a herbal product over a period of some 4 months prior to the onset of her illness. The product contained the following ingredients: *Herba Gynostemmae, Folium Camelliae Sinensis, Succus Aloes Folii Siccatus, Semen Raphani* and *Fructus Crataegi.* It was officially listed as a form of Chinese Proprietary Medicine (CPM) and marketed as weight-reducing capsules, under the trade name "Slim 10." The probable cause of liver failure was clinically assessed to be drug-induced and she eventually underwent total hepatectomy, with porto-caval shunting, in anticipation of an allogenic (living unrelated) liver transplant. Unfortunately, her condition deteriorated and she died <48 hours post-operatively, some 3 weeks post-admission.

Post-mortem Findings**:** The subject was deeply jaundiced and severely obese (BMI: 47.1 kgm^{-2}), with evidence of diffuse hemorrhage, including the presence of nearly 1.5 l of blood in the peritoneal cavity (which was likely to be iatrogenic in nature). The liver had been removed and was later recovered as a formalin-fixed specimen, which was markedly contracted, comprising multiple micronodules interspersed with extensive areas of dense fibrotic tissue. Histologically, there was massive necrosis of the hepatic parenchyma, such that the residual hepatocytes were disposed as nodules displaying variable cellular regeneration and ballooning degeneration, attended by florid ductal proliferation and mixed inflammatory infiltrates (CD3+, CD20-). Infective, autoimmune, metabolic, vascular, neoplastic and most other natural causes of massive hepatocellular necrosis were effectively excluded.

Forensic Toxicology**:** Analysis of the post-mortem blood samples yielded (µg/ml) fluconazole (1.8), frusemide (3.1), lignocaine (0.59) and tramadol (0.11), which would have been therapeutic agents administered to the patient during her last illness. Subsequent analysis of a sample of residual "Slim 10" capsules (purchased by the patient) revealed that it was contaminated by fenfluramine, N-nitrosofenfluramine (1.3-1.6 g per capsule), nicotinamide (13.3 - 15.6 g per capsule) and thyroid extract.

Conclusion**:** None of the herbal ingredients is currently known to be hepatoxic (indeed, *Succus Aloes Folii Siccatus* is apparently liverprotective) and much the same applies to fenfluramine, nicotinamide (except in exceptionally high doses, exceeding 3 g per day) and thyroid extract. However, as nitrosamines are known to be variably hepatotoxic, it would be reasonable to surmise that, in the absence of a more plausible cause of liver damage, N-nitrosofenfluramine was the likely cause of massive hepatocellular necrosis in this instance. The importer of the herbal product was later convicted of contravening the Medicines Act and was subsequently found by a Coroner's inquiry to be responsible for having caused death through an act of criminal negligence.

N-nitrosofenfluramine, Massive Hepatocellular Necrosis, Sliming Agent

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