MUSHROOM POISONING:

CORTINARIUS SPECIOSISSIMUS NEPHROTOXICITY

AKADEMISK AVHANDLING

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av

JOHAN HOLMDAHL

leg. läkare

Avhandlingen baseras på följande delarbeten:

- I. Holmdahl J, Ahlmen J, Svalander C, Eriksson J and Bucht H (1980). **Renal** damage after intoxication with *Cortinarius* mushrooms. In: *Toxicological Aspects*, p. 155-163 (*Kovatsis*, A., Ed.) Thessaloniki, Greece: Technika Studio.
- II. Holmdahl J, Ahlmén J, Bergek S, Lundberg S and Persson S-Å (1987). Isolation and nephrotoxic studies of orellanine from the mushroom *Cortinarius speciosissimus*. *Toxicon* 25 (2):195-199.
- III. Holmdahl J and Blohmé I (1995). Renal transplantation after Cortinarius speciosissimus poisoning. Nephrol Dial Transplant 10:1920-1922.
- IV. Holmdahl J. The *Cortinarius* NephroToxicity (CNT) index: a method for the evaluation of treatment and outcome in *Cortinarius* mushroom poisoning. Manuscript.
- V. Holmdahl J. Cortinarius mushroom nephrotoxicity in Sweden 1979-1999: treatment, short and long-term outcome. Manuscript.
- VI. Holmdahl J and Bohlin A (2001). *Cortinarius speciosissimus* intoxications in Sweden 1979-1999: epidemiological aspects. *Windahlia*, journal of mycology. In press.

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Abstract

Cortinarius mushroom nephrotoxicity causes acute and/or end-stage renal failure. Although on average only 1-2 cases yearly require qualified medical treatment for *Cortinarius* intoxication in Sweden, the poor long-term outcome after the acute renal failure in 30-50% of the patients makes this mushroom poisoning one of the most feared.

The overall purpose of the study was to investigate *Cortinarius* intoxications in mice and man with the aim of preventing and/or treating acute renal failure and/or end-stage renal disease.

To achieve this, the LD_{50} in mice of freeze-dried *Cortinarius speciosissimus* and *Cortinarius orellanus* was determined and shown to be 2.0 g/kg and 3.2 g/kg respectively.

A nephrotoxic substance in *Cortinarius speciosissimus* was isolated and the 3,3′,4,4′-tetrahydroxy-2,2′-bipyridine-N,N′-dioxide structure was confirmed by the mass spectrum and the NMR spectra.

The LD₅₀ in mice of the nephrotoxic molecule isolated from *Cortinarius speciosissimus* was calculated to be approximately 20 mg/kg.

The short and long-term results in five patients transplanted after *Cortinarius specio*sissimus intoxication showed that renal transplantation 6-36 months after the intoxication does not carry any additional short or long-term risks in comparison with other renal transplant patients.

The *Cortinarius* NephroToxicity (CNT) prognostic index was constructed to evaluate the treatment and outcome in *Cortinarius* poisoning and made it possible to classify the patients in three risk-groups: CNT index < 1.1, = 1.1 - 2.1 or > 2.1, indicating a good, an intermediate or a poor prognosis. The CNT index was based on the serum creatinine value (µmol/l) before treatment (y) and the number of days after the mushroom meal (x) according to the formula: CNT index $= (y+316)/(x \times 10^2)$.

The short and long-term results in 30 patients treated for *Cortinarius* intoxications in Sweden between 1979 and 1999 showed that treatment with haemoperfusion and/or haemodialysis 3-8 days after the ingestion of mushrooms does not influence the clinical course of *Cortinarius* intoxications. The geographical distribution of 31 cases of *Cortinarius speciosissimus* intoxication in Sweden between 1979 and 1999 did not exclude the possiblity of a causal connection related to the acidification. The chronological distribution of the 31 cases indicates that the incidence is not increasing. The reason is suggested to be that mushroom-pickers nowadays are more aware of the existence of the dangerous fungus.

Keywords: *Cortinarius speciosissimus*, acute renal failure, nephrotoxicity, end-stage renal failure, renal transplantation, mushroom intoxication, orellanine, haemodialysis, haemoperfusion, prognostic index.