Thioctic Acid in the Treatment of Poisoning with Alpha-Amanitin

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Summary

Between August 8, 1974, and November 1, 1978, calls reporting 100 cases of mushroom poisoning were received by the National Institutes of Health. Thioctic acid was sent (under IND #9957) for the treatment of seventy-five of these patients thought to have ingested mushrooms containing alpha-amanitin. Sixty-seven patients recovered, and eight died. The lapse of time between ingestion of mushrooms and the start of the protocol appears to be inversely related to the success of treatment. Serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase appear to be the best indices of the severity of poisoning. No toxicity attributable to thioctic acid was observed when thioctic acid was given from a container shielded from light, containing glucose, 5% and saline, 0.85%.

Introduction

Thioctic acid (alpha lipoic acid, 6,8 dithio-n-octanoic acid, 1,2 dithiolane-3-valeric acid) was first used in Italy for liver failure, especially "acute yellow atrophy." Its use for "Amanita phalloides-type" poisoning, wherein the major cause of death is "acute yellow atrophy" of the liver resulting primarily from alpha-amanitin [6], was soon begun in Czechoslovakia, where it was tested extensively, as reported by *Kubička* [4] and others.

Thioctic acid prepared for use in man was first available in the United States in 1972. In 1974 the Investigational New Drug (IND) permit of the Food and Drug Administration for its use was issued to *Frederic C. Bartter,* who later requested that the name of *Charles E. Becker* be added. Seventy-five patients have received thioctic acid for mushroom poisoning in the United States. The first twelve cases have been reported in a brief summary [1]. The remaining sixty-three cases are reported herein.

Methods

The thioctic acid used in the study at the outset was a gift of Richardson Merrell Co. through their subsidiary in Italy. After the closing of this subsidiary the drug was prepared through a contract with Elkins-Sinn Company, a subsidiary of *A. H. Robins,* from commercially-purchased thioctic acid. The drug was prepared in 25-mg lots, each ampoule containing 5 ml of solution with ethylenediamine and phenol as preservatives. The material was packaged in the Pharmacy Department of the Clinical Center into mailing boxes each containing ninety 25-mg ampoules, a protocol for use of the drug, and a form for the reporting of results. The boxes containing this amount – approximately that sufficient for a two-week period of treatment – were kept at room temperature, wrapped and ready for mailing.

Poison Centers in the United States were supplied with the telephone number of the National Institutes of Health and that of the principal investigator. A call to the NIH operator was relayed both to the principal investigator and to the pharmacy. The pharmacist in charge ascertained the telephone number and the address (and the nearest airport) of the calling physician or Poison Center nurse. When possible, he discussed the procedure with the principal investigator. In all cases, he proceeded to deliver a kit to the Admission Desk (open 24 hours a day), whence it was dispatched by taxi, by the next available plane, to the appropriate destination. When the principal investigator did not discuss the patient with the calling physician immediately, he did so in a follow-up call the next day; frequent follow-up communications by telephone constituted the immediate follow-up procedure in most cases.

The physician treating the patient was always urged to make positive identification, when possible, with the help of local mycologists. In all cases, the physician was urged to send specimens to Bethesda for identification, in which the mycology laboratory of the United States Department of Agriculture in Beltsville, Maryland *(Dr. Kent McKnight* and *Dr. David Farr),* was of considerable help. The kit delivered to physicians treating patients for amanitin poisoning included instructions for constant infusion of glucose and saline and for shielding of thioctic acid from light, a listing of the most important variables for laboratory monitoring (e.g., liver enzymes), and a suggestion that thioctic acid be given at a dosage of 100 mg a day the first day and 300 mg a day thereafter. (In later cases the dosage was often increased to 300 mg the first day as well, since no side effects have been noted, see also *Appendix.*)

Results

Six patients received thioctic acid between 1970 and 1973 (before the present protocol and IND were in effect) (Table I). Of these cases, as reported [1, 3, 5], the one who died received the thioctic acid only on day seven after ingestion of Amanita phalloides, after "cerebral death" (Table II, patient number 5); five recovered.

Table I Reported cases of amanitin poisoning in the United States

reported cases	before 1974	after 1974
number of calls	6	100
thioctic acid given	6	75
recovered	5	67
died	1	8
thioctic acid not given	—	25

Table II Deaths resulting from amanitin poisoning despite the treatment with thioctic acid. "Delay" indicates the time elapsed after the ingestion of the mushroom before thioctic acid was given

pt/age/sex	mushroom	TA rec'd	delay	notes
# 5/52/f	A. phalloides	?	7d	"cerebral" death
# 17/59/m	A. verna	200	?	coma on adm.
# 26/75/m	A. virosa	75	5d	arrested in E.R.
# 28/53/f	A. phalloides	1975	5d	coma on adm.
# 30/36/m	A. phalloides	3100	5d	coma before P_t
# 33/70/m	A. phalloides	125	3d	coma and renal failure
# 45/6/m	A. phalloides	50	3d	"cerebral" death on adm.
# 73/45/m	A. bisporigera	5800	2d	not "Amanita" death
# 96/12/m	A. phalloides	300?	5d	hepatic coma

The authors received one hundred reports of mushroom poisoning in the United States between August 8, 1974, and November 1, 1978. Twenty-five of these patients did not receive thioctic acid, and thus do not form part of this report; their histories will be reported separately.

Patients who died: Table II lists the ages and sex of the patients who died. Whereas all received thioctic acid, there is nothing to suggest either that thioctic acid had an adverse effect or that any case can be considered a "failure" of thioctic acid. Thus, cases No. 17, 28, 30, 33 and 45 had suffered "cerebral death" in the opinion of the attending physician *before* thioctic acid was given; case No. 33 had renal failure as well. Case No. 96, who did not receive thioctic acid until five days after ingestion of A. phalloides, suffered from hepatic encephalopathy with coma before treatment was begun. Case No. 73, who received thioctic acid and died is listed in Table II as "not Amanita death" because 1. the SGOT and SGPT, having risen to 3700 and 3100 mU/ml, decreased to values of 114 (SGOT, day 7) and 200 (SGPT, day 15) before death, and 2. autopsy showed massive cerebral hemorrhage, probably not a result of amanitin poisoning.

Evidence of hepatotoxicity: Seventy-five patients received thioctic acid between August 26, 1974, and November 1, 1978: of these cases, sixty-seven recovered and eight died (Table I).

Of the seventy-two patients (5 and 67) who received thioctic acid and survived (Table I), twenty-nine did not show elevation of SGOT or SGPT above 200 mU/ml; thus there is no good evidence for severe, or any, hepatic damage in these patients.

The remaining forty-two patients showed clear elevation of SGOT and SGPT, and thus presumably suffered from hepatic damage from which they recovered. The course of recovery of liver enzymes following instigation of thioctic acid therapy is shown for patient No. 25 (a 52-year-old woman) in Fig. 1, and for patient No. 47 (an 82-year-old woman) in Fig. 2. It is apparent that the enzyme concentration in serum decreases with a half-life of approximately two days. It should be noted (vide infra) that the role of thioctic acid in the result cannot be assessed without appropriate control data. Whereas the data are too few for valid statistical evaluation, it is clear that the mortality from Amanita phalloides-type poisoning is directly related to the initial SGOT and SGPT concentrations. Thus, with either SGOT or SGPT concentration at or above 2000 units/l (Fig. 3), the mortality rate was approximately 30% (5/18); with both enzymes below 500 units/l, the mortality rate was below 3%.

Discussion

Toxicity of thioctic acid: The protocol for IND # 9957 calls for constant intravenous drip of 5% dextrose in saline; this is the only route allowed for infusion of

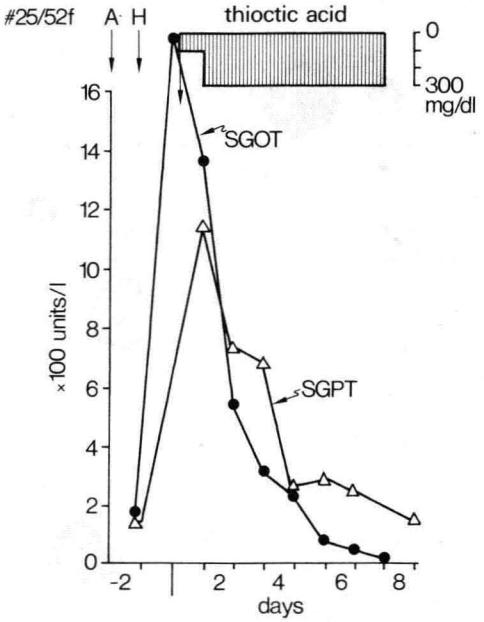

Fig. 1 SGOT and SGPT concentrations before and after the infusion of thioctic acid in a 52-year-old woman who had ingested Amanita phalloides. *A* indicates time of Amanita ingestion. *H* indicates day of hospitalization

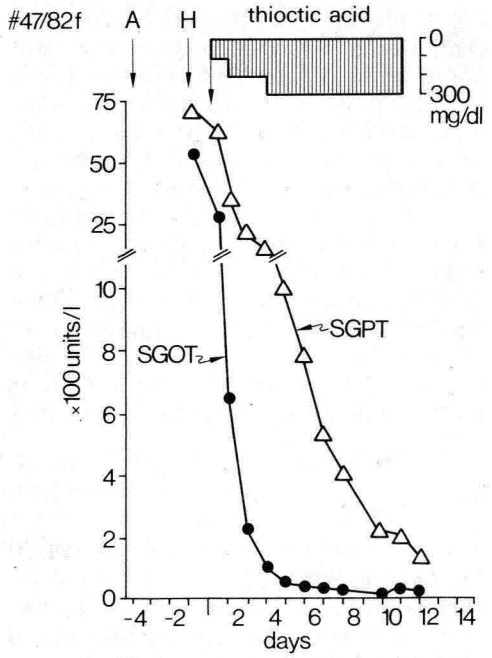

Fig. 2 SGOT and SGPT concentrations before and after the infusion of thioctic acid in an 82-year-old woman who had ingested amanita phalloides. *A* indicates time of Amanita ingestion. *H* indicates day of hospitalization

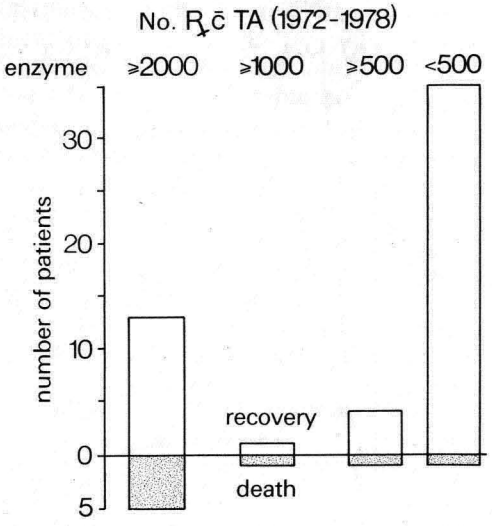

Fig. 3 The number of patients treated with thioctic acid who recovered (above the zero line) and who died (below the zero line), classified according to the liver enzyme concentrations

thioctic acid. Perhaps for this reason, no hypoglycemia was reported for this series. Indeed, no toxic effect was attributed to the thioctic acid itself – or, of course, to the ethylene diamine (2.1 mg per ampoule), the ethyl alcohol (0.1 ml per ampoule) or the phenol (4.0 mg per ampoule) – by any investigator who reported results.

Limitations of the study: The most important limitations of the study concern the lack of clear measure of the "dose" of toxin (primarily alpha-amanitin) ingested, and the standardized dose of thioctic acid used for almost all patients.

As regards the "dose" of toxin, the pharmacist or physician receiving the initial call generally cannot ascertain the type of mushroom (although it has often been possible to determine this in retrospect), or the amount actually eaten (generally given in household terms, such as "three tablespoonfuls" or "a plateful"). Often a mixture of species was cooked and eaten.

As regards the dose of thioctic acid, we employed the standardized figure (100 mg the first day or part day, and 300 mg a day thereafter) because of the practical value in adherence to a single protocol, and because the first limitation rendered virtually meaningless any attempt to individualize dosage.

A third limitation in this study concerns what might be called "physician compliance." Few physicians have submitted specimens of mushrooms (which were, of course, often not available) for final identification, and many have not submitted a completed synopsis of the day-to-day progress of each case. Close follow-up of each patient by the principal investigator requesting laboratory values, is clearly a *sine qua non* of a study such as this, requiring the cooperation of a host of investigators.

The optimal study: The first requirement for an ideal study is a measure of alpha-amanitin "dosage". We hope to approach this by measurement of plasma concentrations of alpha-amanitin, for which a method has been published [2].

The second requirement for an ideal study is an individualization of dosage of thioctic acid. The dosage could be adjusted for "dosage" of alpha-amanitin if the plasma concentration and its variation with "dosage" and time after ingestion can be calibrated with the help of animal studies. Alternatively, the dosage of thioctic acid could be adjusted for body weight (used to get an estimate of liver weight) or for the concentration of SGOT and SGPT (used as an estimate of the extent of liver damage). Until the methods for measurement of plasma alpha-amanitin and an appropriate "calibration" to allow extrapolation for dose initially ingested, it appears justified to apply a sliding scale of dosage for thioctic acid, based roughly on the serum values for SGOT and SGPT. In this way, some measure of adjustment for "dosage" of alpha-amanitin is achieved: there is nothing in our past experience to suggest any undesirable side effects from the thioctic acid itself, *providing it is always given with glucose.* A request for such adjustment of dosage is pending before the Food and Drug Administration.

Appendix

Poisoning from Alpha-Amanitin Taken with Amanita or Galerina

There is a latency after ingestion of 10 to 24 h (reported range, 2 to 48 h). Symptoms begin with nausea, vomiting and diarrhea. Diarrhea may become bloody. There is often abdominal pain. There may be mild fever. There is often the early onset of jaundice. The subsequent signs may reflect hypovolemia on the one hand, and liver damage on the other. These may include hypotension, and nitrogen retention, delirium and convulsions, with hepatic encephalopathy and dilated, unreactive pupils. SGOT and SGPT show marked elevation. The SGPT is often much higher than the SGOT. Hepatic coma may appear early. Characteristically, however, symptoms may disappear after 3 to 4 days, but SGPT and SGOT may remain high. When this occurs, the enzymes should be the guide to treatment, and not the clinical condition. After the transient improvement, which may last a few days, the signs of hepatic necrosis with hepatic coma may ensue.

Protocol for Users of Thioctic Acid

Thioctic acid has been effective in preventing death from poisoning by Amanita phalloides, A. virosa, A. verna (these mushrooms have cup, ring and volva, and white spores), and by Galerina autumnalis, G. marginata and G. veneneta (these mushrooms have no cup, a transient ring and brown spores).

The effectiveness of thioctic acid appears to decrease with lapsed time after ingestion.

Please follow this protocol for use of thioctic acid:

1. Obtain stomach washings or remnants of mushrooms if possible. These will be sent to Dr. *Frederic C. Bartter.*

2. Obtain informed consent from patient or responsible agent (a copy of this must be submitted with your report).

3. Start i.v. glucose and saline drip. (If cardiac failure appears to be present or imminent, this may be replaced by glucose alone.) Glucose is *very important:* both amanitin and thioctic acid may lower blood sugar.

4. Get blood for serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic acid dehydrogenase (LDH), creatine phosphokinase (CPK), bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), and prothrombin time. Get urinalysis if possible. (At least SGOT, SGPT, and BUN should be obtained; these should be done daily-)

5. Start treatment with one day of thioctic acid, 25 mg q.i.d. (100 mg a day) given i.v. into the glucose drip. Because the drug is light-sensitive, the infusion bottles should be protected from exposure to light.

6. Dosage may be increased to 75 mg q.i.d. (300 mg a day) thereafter, as rapidly as deemed necessary.

7. Further increase of dosage should not be instituted without consultation with *Dr. Bartter.*

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