High Prevalence of Potentially Hepatotoxic Herbal Supplement Use in Patients With Fulminant Hepatic Failure

Jason D. Estes, MD; David Stolpman, MD; Ali Olyaei, PharmD; Christopher L. Corless, MD, PhD; John M. Ham, MD; Jonathan M. Schwartz, MD; Susan L. Orloff, MD

Hypothesis: The use of potentially hepatotoxic herbal and dietary supplements is highly prevalent in the fulminant hepatic failure (FHF) patient population at our institution, and this subgroup of patients has a worse prognosis.

Design: Retrospective case series.

Settings: An adult tertiary care university hospital and a Veterans Affairs hospital in Oregon.

Patients: All patients referred to the liver transplantation service for FHF from January 2001 through October 2002 (N=20). We defined FHF as onset of encephalopathy within 8 weeks of onset of jaundice in the absence of preexisting liver disease. All patients underwent investigation for potential causes of liver injury. Potentially hepatotoxic supplements were defined as those with previously published reports of hepatic injury related to their use.

Results: Ten patients (50%) were recent or active users of potentially hepatotoxic supplements or herbs; 10 had no history of supplement use. In the supplement group, 7 patients (35%) had no other identified cause for hepatic failure. Six patients in the supplement group and 2 patients in the nonsupplement group underwent orthotopic liver transplantation. Five patients in each group died. There were no significant differences in transplantation rate (P=.07) or survival (P=.99) between groups. Supplement use alone accounted for the most cases of FHF during this period, exceeding acetaminophen toxicity and viral hepatitis.

Conclusions: Herbal and dietary supplements were potential hepatotoxins in a high proportion of patients with FHF at our institution. Enhanced public awareness of the potential hepatotoxicity of these commonly used agents and increased regulatory oversight of their use is strongly urged.

Arch Surg. 2003;138:852-858

Fulminant hepatic failure (FHF) is defined as the onset of jaundice followed by encephalopathy within 8 weeks in patients with no history of liver disease. This condition affects approximately 2000 patients annually in the United States. Worldwide, viral hepatitis is the most common cause of FHF, but in the United States and Europe acetaminophen toxicity and idiosyncratic drug reactions are more common. The mortality rate for patients with FHF ranges from 35% to 80%, and liver transplantation remains the only effective therapy for many patients. In as many as 30% of FHF cases, no cause can be identified. Dietary and herbal supplement use is highly prevalent in the United States and is consistently underreported by patients. Forty million Americans use at least 1 supplement per week, and Americans spend between $4 and $17 billion annually on supplements, even in the absence of data confirming safety or efficacy. It is estimated that fewer than 1% of the adverse events associated with dietary supplements are reported to the Food and Drug Administration (FDA). Of note, the hepatotoxicity of several common herbs and dietary supplements has been widely reported, varying from asymptomatic elevations in hepatic enzyme levels to FHF. Despite these longstanding reports, these supplements continue to be widely used.

The aim of this study was to establish the prevalence of use of supplements with known hepatotoxic potential among patients with FHF at our institution. We also sought to determine whether patients with FHF associated with potentially hepatotoxic supplements had different rates of orthotopic liver transplantation (OLT) or survival than their counterparts with other causes of FHF.

From the Division of Liver/Pancreas Transplantation, Oregon Health & Science University, and Portland Veterans Affairs Medical Center, Portland.
Of 20 patients referred for FHF during the study period, 10 (50%) had recently used a dietary supplement or herb with documented hepatotoxic potential (Table 1). In patients with multiple herb or supplement use, only those agents identified as potentially hepatotoxic are listed. In 7 patients (35%), no other cause of FHF could be identified. In 3 patients (15%), an additional cause of FHF was found. Duration of supplement use ranged from days to years. Histological analysis of liver specimens showed significant hepatic necrosis in all cases, with varying degrees of inflammatory changes. There was no single pattern of injury common to all supplement users.

In the remaining 10 patients with no hepatotoxic supplement use, acetaminophen toxicity was the leading cause of FHF (n = 5, 25%) (Table 1). One patient had Budd-Chiari syndrome identified on postmortem examination. No cause for FHF could be identified in 2 patients (10%).

Etiologic data for both groups are shown in Figure 1.

The 2 groups did not have significant differences in age (P = .08) or sex (P = .65). Outcome data for the 2 groups are shown in Figure 2. There were no significant differences in overall survival (P > .99) or rate of liver transplantation (P = .17) between the supplement and nonsupplement groups. Subgroup analysis showed no significant differences between groups in recovery rate without OLT (P = .58), recovery rate with OLT (P = .63), mortality without transplantation (P = .65), or mortality after transplantation (P = .47).

Although there have been multiple case reports of hepatic injury associated with the use of dietary supplements during the last 15 years, to our knowledge this is the first description of the high prevalence of these agents in FHF. In our series we identified 4 major agents with well-described hepatotoxic potential: LipoKinetix (Syntrax Innovations Inc, Cape Girardeau, Mo), kava, chaparral, and ma huang.

LipoKinetix, which contains phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, and

---

### Table 1. Characteristics and Outcomes Among Patients With Fulminant Hepatic Failure (FHF) Who Used Supplements or Herbs

<table>
<thead>
<tr>
<th>Patient Age, y/Sex</th>
<th>Agent</th>
<th>Duration of Use</th>
<th>Cofactor</th>
<th>Hepatic Histological Analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/M</td>
<td>Bai-Fang herbs</td>
<td>Unknown</td>
<td></td>
<td>Subtotal necrosis</td>
<td>Death (herniation)</td>
</tr>
<tr>
<td>21/M</td>
<td>Ma huang; kava</td>
<td>Several months</td>
<td>None</td>
<td>Massive necrosis, inflammatory infiltrate</td>
<td>Recovery</td>
</tr>
<tr>
<td>40/F</td>
<td>Herbal diet prep</td>
<td>Weeks</td>
<td>None</td>
<td>Subtotal necrosis, noninflammatory, c/w toxin</td>
<td>Death (subarachnoid hemorrhage)</td>
</tr>
<tr>
<td>56/M</td>
<td>Chaparral; kava</td>
<td>15 years</td>
<td>None</td>
<td>Massive necrosis, lymphocytic infiltrate</td>
<td>OLT; death (herniation)</td>
</tr>
<tr>
<td>51/M</td>
<td>Ma huang</td>
<td>Unknown</td>
<td>Chronic HBV</td>
<td>Marked necrosis, chronic HBV</td>
<td>OLT; survival</td>
</tr>
<tr>
<td>23/F</td>
<td>Ma huang; kava</td>
<td>Several days</td>
<td>None</td>
<td>Subtotal necrosis, noninflammatory, c/w metabolic injury</td>
<td>Recovery</td>
</tr>
<tr>
<td>42/M</td>
<td>LipoKinetix*</td>
<td>1 year</td>
<td>None</td>
<td>Submassive necrosis, inflammatory infiltrate</td>
<td>Recovery</td>
</tr>
<tr>
<td>54/F</td>
<td>LipoKinetix*</td>
<td>Several months</td>
<td>None</td>
<td>Subtotal necrosis, noninflammatory, c/w toxin</td>
<td>Death (multigang failure)</td>
</tr>
<tr>
<td>30/F</td>
<td>Kava</td>
<td>Unknown</td>
<td></td>
<td>Massive necrosis</td>
<td>OLT; survival</td>
</tr>
<tr>
<td>56/F</td>
<td>LipoKinetix</td>
<td>25/F</td>
<td></td>
<td>Massive necrosis</td>
<td>OLT; death (herniation)</td>
</tr>
<tr>
<td>25/F</td>
<td>Skullcap</td>
<td>3 weeks</td>
<td>Disulfiram</td>
<td>Patchy necrosis, mild lymphoid infiltrate</td>
<td>OLT; survival</td>
</tr>
<tr>
<td>40/F</td>
<td>Herbal diet prep</td>
<td>Weeks</td>
<td>None</td>
<td>Massive necrosis, inflammatory infiltrate</td>
<td>OLT; survival</td>
</tr>
<tr>
<td>23/F</td>
<td>Herbal diet prep</td>
<td>Several months</td>
<td>None</td>
<td>Subtotal necrosis</td>
<td>OLT; survival</td>
</tr>
<tr>
<td>54/F</td>
<td>Bai-Fang herbs</td>
<td>Unknown</td>
<td>Acute HBV</td>
<td>Massive necrosis, c/w toxic or metabolic injury</td>
<td>OLT; survival</td>
</tr>
</tbody>
</table>

Abbreviations: c/w, consistent with; HBV, hepatitis B virus infection; OLT, orthotopic liver transplantation; prep, preparation.

*Syntrax Innovations Inc, Cape Girardeau, Mo.

---

### METHODS

#### PATIENT SELECTION

The medical records of all patients referred to the liver transplantation service at Oregon Health & Science University, Portland, and the Portland Veterans Affairs Medical Center from January 2001 through October 2002 were reviewed. Patients with FHF were selected for additional review (N = 20). The patient’s age, sex, and cause of FHF (when identifiable) were recorded. This study was approved by the Internal Review Board of Oregon Health & Science University.

#### PATIENT EVALUATION

All patients referred for FHF had undergone a standardized evaluation to determine the cause of liver injury. This evaluation included (1) a detailed history and physical examination, including review of prescription medication or supplement use and toxin exposure, (2) assays for hepatitis B surface antigen, anti–hepatitis B core antibody (lgM), anti–hepatitis A (lgM), anti–hepatitis C, human immunodeficiency virus, cytomegalovirus, and herpes simplex virus antibodies, (3) autoimmune antibody assays, and (4) serum ceruloplasmin and 24-hour urine copper quantification.

In addition, histological specimens obtained via core biopsy, liver explantation, or autopsy were reviewed by an experienced hepatopathologist (C.L.C.) to further characterize the type of liver injury.

The identity and duration of medication or supplement use were determined. A MEDLINE search was then performed for each agent (or each component of multiagent supplements), cross-referencing with the keywords hepatotoxic, hepatoxicity, and liver injury. Those substances associated with multiple reports of liver injury were classified as potentially hepatotoxic. The mechanism of hepatic injury for each substance was determined if possible. All cases of FHF thought to be related to supplement use were reported to the county health department and the FDA.

### STATISTICAL METHODS

The primary outcomes were recovery with or without transplantation and death with or without transplantation. Transplantation and mortality rates and patient demographic characteristics were then compared between the supplement and nonsupplement groups using the Fisher exact test (2 sided) and the 2-sided t test. P < .05 was considered significant.
Caffeine, was marketed as a dietary supplement for weight loss. Following reports of 7 cases of severe hepatotoxicity associated with its use, the FDA moved to remove it from the market in November 2001. Hepatic injury appears to be due to an idiosyncratic reaction, perhaps related to phenylpropanolamine.

Kava (kava kava, awa, or kew), derived from the dried root and rhizome of \textit{Piper methysticum}, is used traditionally in the South Pacific and has more recently been marketed in the West as an anxiolytic and mood enhancer. Recent series from Europe have described more than 30 cases of kava-associated hepatic injury, including 5 cases leading to OLT. The mechanism of hepatic injury appears to be immune-mediated, with cytochrome P4502D6 deficiency perhaps being a risk factor. The FDA issued a consumer advisory in March 2002 regarding the potential risk of liver injury associated with kava use.

Chaparral (creosote bush, greasewood, or \textit{Larrea tridentata}) is a desert shrub traditionally used by Native Americans for treatment of several ailments. More recently, preparations of chaparral leaves have been marketed for use as liver tonics, blood purifiers, and weight loss agents. Reports of chaparral hepatotoxicity were first seen in 1992, and the FDA issued a health warning at that time. The mechanism of chaparral toxicity is unclear but may involve phytoestrogen-induced changes in liver function or toxic effects of its active ingredient, n diglycoside.

Ma huang (from \textit{Ephedra sinica} and other \textit{Ephedra} species) is a traditional Chinese extract used for treatment of asthma, nasal congestion, and fever. Recent Western marketing has focused on the stimulatory effects of ma huang, which contains 0.15% to 2% of ephedrine-like alkaloids by weight. Although most adverse ef-

### Table 2. Characteristics and Outcomes Among Fulminant Hepatic Failure (FHF) Patients Without Supplement or Herb Use

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex</th>
<th>Cause</th>
<th>Hepatic Histological Analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/F</td>
<td>Acetaminophen</td>
<td>NA</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>21/F</td>
<td>Acetaminophen</td>
<td>NA</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>22/F</td>
<td>Acetaminophen</td>
<td>NA</td>
<td></td>
<td>Death (herniation)</td>
</tr>
<tr>
<td>27/M</td>
<td>Acetaminophen</td>
<td>NA</td>
<td></td>
<td>Death (herniation)</td>
</tr>
<tr>
<td>18/F</td>
<td>Acetaminophen</td>
<td>NA</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>26/F</td>
<td>Budd-Chiari syndrome</td>
<td>Hepatic vein thrombosis, extensive necrosis, extramedullary hematopoiesis</td>
<td>Death (cardiac arrest)</td>
<td></td>
</tr>
<tr>
<td>32/M</td>
<td>Acute HBV</td>
<td>NA</td>
<td></td>
<td>Death (multiorgan failure)</td>
</tr>
<tr>
<td>25/F</td>
<td>Disulfiram</td>
<td>Massive necrosis, cholestatic hepatitis</td>
<td>OLT; survival</td>
<td></td>
</tr>
<tr>
<td>39/F</td>
<td>Unknown</td>
<td>Acute hepatitis/necrosis</td>
<td>Death (herniation)</td>
<td></td>
</tr>
<tr>
<td>52/F</td>
<td>Unknown</td>
<td>Massive necrosis</td>
<td>OLT; survival</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus infection; NA, not available; OLT, orthotopic liver transplantation.

### Figure 1. Cause of fulminant hepatic failure in 20 patients, January 2001 through October 2002. No comparisons were statistically significant.

### Figure 2. Outcomes among 20 patients with fulminant hepatic failure, January 2001 through October 2002. OLT indicates orthotopic liver transplantation.
fects of ma huang are cardiovascular or neurologial (e.g., tremor, hypertension, myocardial infarction, seizures, stroke, and psychosis), 4% of reports mentioned overt hepatitis. 34,35 Ma huang contains phytochemicals other than ephedriline alkaloids which are thought to modify its toxic activity. 21,33

In addition to the above supplements, liver injury has been attributed to other botanical agents. The pyrrolizidine alkaloids found in comfrey leaves and Heliotropium, Senecio, and Crotalaria species are known to cause veno-occlusive disease of the liver via a toxic effect. 36,37 The FDA advised manufacturers to remove comfrey-containing products from the market as of July 2001. Germander (Teucrium chamaedrys) extracts, used widely in Europe in the 1980s as a weight loss agent, cause liver injury mediated by furano neoclerodane diterpenoids. 23 Mixtures of valerian and skullcap (Valeriana officinalis and Scutellaria lateriflora) have induced hepatitis via alkylating agents. 25

In this series, the prevalence of potentially hepatotoxic dietary supplement use was surprisingly high. Thirty-five percent of these patients had no other identifiable risk factor for FHF, whereas acetaminophen toxicity was seen in 25% and viral hepatitis in 15%. Although it is not possible to draw a direct causal relationship between the use of these agents and the patients’ subsequent liver failure, other investigators have reported compelling evidence that these agents do have the potential to cause significant liver injury. 31,33,36-38 This evidence includes biochemical models of hepatic injury, evidence of recurrent hepatic injury with rechallenge, and histological findings consistent with immune-mediated or toxin-related hepatic injury.

Although the etiologic association may be inclusive, it is possible that supplement and herbal agents may account for a significant proportion of cases of FHF that were previously considered to be of indeterminate cause. The small number of patients in our FHF population may have been the cause of our inability to detect significant differences in outcome between groups.

Under current law (the Dietary Supplement Health and Education Act of 1994), manufacturers and distributors of dietary supplements are not required to record, investigate, or forward to the FDA any reports of injuries or illnesses that may be related to the use of their products. The general population and health care providers are often unaware of the potential adverse health effects, including FHF, of certain dietary and herbal supplements despite long-standing warnings from national health agencies. Future damage from these agents may be thwarted by enhanced public education regarding this potential.

Based on the results of this study, we now routinely question patients and relatives regarding supplement and herb use during the pretransplantation evaluation. In addition, we recommend that physicians review patient intake of such agents as part of patient medication lists and caution patients against the use of any of these potentially hepatotoxic agents. Finally, we recommend aggressive reporting of any suspected adverse events related to supplement use to the FDA’s MedWatch program (http://www.fda.gov/medwatch/), with the goal of developing more stringent regulatory oversight of these agents in the future.

Accepted for publication April 18, 2003.

This study was presented at the 74th Annual Meeting of the Pacific Coast Surgical Association; February 17, 2003; Monterey, Calif; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

Corresponding author and reprints: Susan Orloff, MD, Division of Liver/Pancreas Transplantation, Oregon Health & Science University, L590, 3181 SW Sam Jackson Park Rd, Portland, OR 97201 (e-mail: orloffs@ohsu.edu).

REFERENCES

Peter G. Stock, MD, San Francisco, Calif: Thank you for the opportunity to review the preliminary draft of this very topical and relevant paper concerning the incidence of FHF associated with the ingestion of a variety of herbal supplements. In fact, FHF secondary to herbal ingestion was the most common etiology in your series during the study period. So my comments and questions relate to both the clinical course of FHF following the ingestion of these supplements, the potential susceptibility to the toxic effects based on pharmacogenetics, and finally some general questions regarding the management of patients with FHF.

It was interesting, in your fairly large series of patients with FHF, that there were no cases secondary to mushroom poisoning, particularly in the moist Pacific Northwest. It is something that we see at least once a year. In fact, I remember one very busy weekend where we were transferred 5 patients with FHF from Southern Oregon, when a whole family had indulged in some toxic mushrooms.

In your series, 6 of 10 patients underwent liver transplant in the herbal supplement group, but only 2 of 10 in the nonherbal group. Although this wasn’t statistically significant because of the low numbers, I was wondering if there was some hesitancy to transplant some of the patients in the acetaminophen group? Although this wasn’t statistically significant based on pharmacogenetics, I am wondering if you are working with pharmacologists to determine the pleomorphisms of the genes for these metabolic enzymes. I realize your numbers are small, but were there any ethnic susceptibilities in terms of the toxicity of the herbs?

In terms of the clinical course of patients with fulminant failure secondary to their herbal supplements, were there any predictors for progression vs recovery, analogous to what you see with acetaminophen overdose such as INR [international normalized ratio] progression, age, metabolic acidosis, and the development of renal insufficiency.

Part of your management strategy includes placement of an intracranial bolt, and that procedure is complicated with a significant morbidity and mortality. How helpful was that to you in terms of management? Were you using it principally as an indicator to determine whether the intracranial perfusion pressure was sufficient to justify proceeding with transplant, or did you in some way use it for management? Also, do you use large-volume fresh-frozen plasma to correct coagulopathy, and, in conjunction with that, did you have to put patients on CVVH [continuous venovenous hemofiltration], or did you use factor VII which is expensive but much less volume?

An obvious factor in outcome following FHF is simply luck, that is, getting a donor liver in time. In order to buy time, does your group have any experience with the liver assist device, either loaded with pig hepatocytes, or immortalized human hepatocyte lines? There are also several reports in the literature saying that living-donor liver transplants, adult-to-adult right lobe to an adult, have poor outcomes when performed in patients with high MELD scores, the system we use to classify urgency for transplantation. Do you think there is any role at all for living donor transplants in this acute setting? Have you considered this as a last resort in the absence of a cadaveric donor?

In your discussion of the paper, you referred to a European study that described 30 cases of kava-induced liver injury. Interestingly, the toxicity was correlated with a deficiency in the cytochrome P450 system. It’s notable that these herbs have been ingested in Asia for years, and I suspect that if a lot of people turned yellow and died, it wouldn’t have caught on as a good mood stimulant. Since the P450 enzyme system is one of the better-studied systems in the up-and-coming field of pharmacogenetics, I am wondering if you are working with pharmacologists to determine the pleomorphisms of the genes for these metabolic enzymes. I realize your numbers are small, but were there any ethnic susceptibilities in terms of the toxicity of the herbs?

Finally, in reviewing your manuscript, I was amazed to learn that 40 million Americans use at least 1 supplement per week, spending upwards of $17 billion on supplements in the absence of any data confirming safety and efficacy. Furthermore, only 1% of the adverse reactions to dietary supplements are reported to the FDA. It is hard to imagine that someone would go to a health food store and be told that they were getting a mood stimulant and then wake up several days later with a huge scratch on their belly and the requirement for a lifetime of immunosuppression. In this litigious society where there are numerous lawsuits for idiosyncratic drug reactions to FDA-approved drugs, I was curious if you are aware of successful lawsuits for adverse reactions to non-FDA-approved drugs, and what is being done to prevent the widespread use of these potentially very toxic substances?

Lawrence A. Danto, MD, Truckey, Calif: I would like to compliment the authors on an important study and Dr Estes on an excellent presentation. To echo Dr Russell, I think you deserve the prize just for listening to your wife.

Caring for patients taking herbal supplements, also known as complimentary alternative medications or CAMs, is an evolving challenge, largely ignored by surgeons. Even so, up to two thirds of our patients may be taking these supplements and about half of them won’t admit to it. To my knowledge this paper documents the clearest link between CAMs and serious surgical sequelae.

My questions are these: (1) How should we alter our practice related to CAM ingestion by our patients? Is simply telling them to stop 2 weeks before an elective operation enough? (2) Should we be giving patients information about the potential complications? (3) Are there absolute contraindications to elective surgery in such patients?

Kaj H. Johansen, MD, Seattle, Wash: Since you have emphasized this issue about incidence and prevalence, I want to explore this a little bit. This is a paper about FHF, and I am interested in knowing whether these supplements simply stimulate this accelerated process of hepatic necrosis, or if this is seen in that much larger set of patients that you contemplate for transplantation who do not have FHF but simply have end-stage liver disease?
Also, do we have some sense about what the use is of these various supplements in a non-liver-failure controlled population?

Christopher R. Shackleton, MD, Los Angeles, Calif: I will make my comments brief. If I interpreted your data correctly, the overall mortality in this series was 30%, irrespective of whether or not patients received a transplant or whether or not they used the herbal supplements. If this was indeed the case, it is a mortality rate which is considerably higher than averages one would currently expect for patients with FHF. Perhaps the authors could comment on possible reasons for this. Was it due to delays in patient referral, clinical deterioration while awaiting a donor organ offer, and/or other factors?

I would also like to comment about a statement that Dr Stock made regarding the use of intracranial pressure (ICP) monitoring in these patients and the potential morbidity and/or mortality associated with its use in these individuals with severe coagulopathy. Neurosurgeons are often hesitant to place an ICP monitor in these cases for fear of inducing refractory intracranial bleeding. However, FHF is notorious for the lag which often exists in the development of clinical or imaging manifestations of elevated ICP. Compromise of cerebral perfusion pressure (CPP) can be evolving without CT evidence of cerebral edema in these patients. Since decisions regarding candidacy for liver transplantation as well as intraoperative management are influenced by ICP and CPP parameters, we routinely insert an ICP monitor in patients with FHF as soon as they progress to stage 3 encephalopathy. In our experience, this often yields data that mandate therapeutic adjustments to maintain CPP.

J. Craig Collins, MD, Los Angeles: In my own city of Los Angeles, we are not unaccustomed to seeing the use of FDA-unapproved substances. In particular, we have had issues with coagulopathy from *Ginkgo biloba*. Have the authors identified other deleterious effects associated with some of these supplements, and have these affected their surgical outcomes?

William H. Marks, MD, Seattle: This is an area of tremendous interest and a number of my questions were already anticipated. I am actually an old phytopharmacochemist, so I find this particularly fascinating. I am also a transplantan. As clinicians we have a great influence on our patient population, so outcomes can depend on many different things. In particular, one of the things that can affect the potency of natural products is how they are manufactured and who the manufacturers are. I wonder if you found that there was a prevalence of one type of manufacturer or claims made by a manufacturer for any of these products, in particular for kava, which is becoming increasingly used.

My other question relates again to the use of these substances in countries other than our own, in particular, countries doing liver transplantation such as in Germany where herbal chemistry is just considered a part of the system.

Michael Hart, MD, Seattle: A similar question: This paper points out for all of us who are not transplant surgeons the importance of attempting to discuss these supplements with our patients preoperatively and the potential adverse coagulation effects brought on by some of these herbs. I ask the authors: are there similar series from other countries where herbs are used extensively? Do the authors feel that the publications by our “colleague” Dr Andrew Weil, has contributed to this? And finally, if this hasn’t happened in other areas of the world, is this something peculiar to the Oregon population?

Dr Orloff: I want to thank Dr Stock for his insightful discussion as well as a number of other questions from the audience. I will attempt to answer them. Please let me know if I have left something out.

Peter, the first question you asked about mushroom poisoning and whether we had seen any mushroom poisoning recently: it is interesting that that group of 5 in which 4 were sent down to San Francisco and 1 was transplanted in Oregon actually was the last family that we have seen significant mushroom poisoning in. We have seen one other woman who came from Russia who had ingested mushrooms, and she actually recovered, and that was about 3 years ago. I think the public awareness of the dangers of *Amanita* is very great in the Northwest because of the moist climate and the tendency for people to pick mushrooms.

Then you asked the question about acetaminophen toxicity and the fact that Vicodin had been a problem with your program. In fact, in a number of our patients, the acetaminophen toxicity was due to Vicodin overdose, and a couple of those patients were taking the Vicodin for pain relief in addition to other pain medications. The reason why they potentially did not get transplanted were: one was because of potential suicide attempts, using Tylenol as a suicide gesture; the second was substance abuse. As you know, we don’t transplant patients who are active substance abusers. The third was that the Tylenol patients tend to recover; if you look in the table of patients with nonsupplement use, there were 3 Tylenol patients who actually recovered and for that reason they did not get transplanted. There was definitely a tendency, although not statistically significant, for the patients using supplements to go to transplant vs those that were nonsupplement patients.

Then you asked the question about prognosticators in the clinical course for patients using supplements. The symptoms and signs of FHF were really all over the board. However, the patients who had renal failure develop in their course tended to do more poorly. You asked about the use of an intracranial bolt. Dr Shackleton also commented on that, and we in fact do use ICP monitoring preoperatively (1) to let us know what the ICP is and whether this patient should be transplanted and (2) the anesthesiologist very much appreciates having the ICP monitor so that they can bolus thiopental during the case as well as appropriately manage fluids intraoperatively. Our neurosurgeons will not put in an ICP monitor unless the INR is 1.3 or less. This strict criteria for ICP monitor placement is one way that we have eliminated some of the bleeding problems with their placement.

Then you also asked about whether we used the liver assist device with or without porcine hepatocytes. We were involved in the randomized prospective trial using the porcine hepatocyte assist device, and thus far trial has actually been placed on hold because the results have now been borne out that there is any improved efficacy. We have used that as well as the liver dialysis machine in a few patients, but, again, the results have not been shown to have any effect.

You asked me if we were working with some pharmacologists on pharmacogenetics; this is a very interesting concept. We have not done that; however, in terms of the ethnicity of our patient population, there were a number of Asians as well as one woman from the South Pacific. These patients may have some of the cytochrome P450 gene deficiencies that may predispose these patients to developing fulminant failure when taking these herbs. You also asked about litigious involvement in these cases. We have a couple of patients whose attorneys have asked me to participate in some of the informational aspects regarding these agents because the families are suing the manufacturers of these agents related to the death of a family member. In addition, there is a class action suit currently ongoing with LipoKinetix which Dr Estes just informed us is on the Web site, and you can actually access pertinent information. In addition, reporting is encouraged with respect to adverse effects from LipoKinetix.

There were some questions from the audience, and I will try to cover those. Dr Danto asked me about CAMs and how...
we can modify our practice in terms of preoperative question-
ing and whether these medications affect patients during sur-
gery and postoperatively. We didn’t really look at this. We just
looked at patients who were taking herbs and developed FHF.
It is interesting that a number of the family members, when
their relative is comatose and you ask them what medications
the family member takes, it wasn’t until we got the family to
bring in what the patient was actually drinking or eating could
we find out what herbs were involved in some of these con-
coctions that they were drinking or eating. There are many sub-
stances that have a number of products, which are potentially
hepatotoxic, but the family members really aren’t aware. You
need to query your patients in detail about what sorts of other
agents they are ingesting. They may not consider them as medi-
cations or even supplements.

Dr Johansen asked about the incidence and prevalence and
do these supplements accelerate existing liver disease. In fact, we
haven’t seen this supplement use in our chronic liver patients.
They tend to take milk thistle and other agents that are helpful,
supposedly, for liver regeneration. However, we haven’t seen much
supplement use in our chronic liver disease patients and if we do
see patients who are taking supplements or herbs, we immedi-
ately caution them to stop taking these agents to hopefully pre-
vent any further liver disease in these patients. We do not know
our denominator because we don’t know how many patients are
admitted to the hospital who are taking supplements. However,
as Dr Estes mentioned, there are 4 million patients who are tak-
ing supplements per week, so there exists a larger population than
any of us realize.

Dr Shackleton queried our high mortality rates and poor
outcomes and why was this so. I think that as you know the
number of patients in our study is small, and there are times
when there is a donor organ shortage, and in fact a number of
these patients died waiting for an organ. They were referred
late; that was another problem. The community may not be
aware of the presentation of FHF as an entity, and in fact, some
of these patients were referred very late. In addition, we trans-
planted 2 patients who were very young and actually herni-
atated postoperatively. They both had ICP monitoring; they had
evidence of cerebral edema developing in an accelerated fash-
ion just before transplant, but we decided to pursue transplan-
tation with them to give them a chance. As it turned out, these
2 patients herniated posttransplant. As you mentioned about
ICP monitoring, that is something that we do routinely, al-
though we wait for placement until the INR is 1.3 or less.

Peter, I forgot to mention, you asked about in this situation
can living donor liver transplant be used. It is a difficult ethical
question because there is time pressure and not enough chance
to really assess the family’s psychological situation and whether
living donation is something that they fully understand in a pres-
sured situation. They may reflexively want to, and so I think it is
ethically a difficult question. However, it has been used in a num-
ber of centers to actually salvage patients that otherwise would
die waiting for an organ, especially in children.

Dr Collins asked about other deleterious effects of these
agents. Again, we just focused on the patients who presented
with FHF and found out that they were taking these herbs and
did not really look at some of the other effects because the pa-
tient was already at a state of FHF.

Dr Marks asked about whether there were specific manu-
facturers that we can target as suppliers of these herbal prepa-
rations. There are certain dietary supplements that are manu-
factured with a conglomeration of agents considered herbal. I
am not aware of the specific manufacturers.

Dr Hart asked about whether there were similar series in other
countries. In fact, Germany reported on kava and FHF in a num-
ber of patients who required transplantation. I don’t think this is
particular to the Northwest. However, it may just be that we have
a preponderance of patients who take supplements and herbs.
However, if you start asking your patients that have an indeter-
minate etiology of FHF, you may find that they are also taking
herbs.