The efficacy and safety of comfrey

Felix Stickel[1,*] and Helmut K Seitz[2]

[1]Department of Medicine I, Division of Gastroenterology and Hepatology, University of Erlangen-Nuernberg, Krankenhausstrasse 12, 91054 Erlangen, Germany: [2]Laboratory of Alcohol Research, Salem Medical Center, University of Heidelberg, Germany

Abstract

Herbal medication has gathered increasing recognition in recent years with regard to both treatment options and health hazards. Pyrrolizidine alkaloids have been associated with substantial toxicity after their ingestion as tea and in the setting of contaminated cereals have led to endemic outbreaks in Jamaica, India and Afghanistan. In Western Europe, comfrey has been applied for inflammatory disorders such as arthritis, thrombophlebitis and gout and as a treatment for diarrhoea. Only recently was the use of comfrey leaves recognized as a substantial health hazard with hepatic toxicity in humans and carcinogenic potential in rodents. These effects are most likely due to various hepatotoxic pyrrolizidine alkaloids such as lasiocarpine and symphytine, and their related N-oxides. The mechanisms by which toxicity and mutagenicity are conveyed are still not fully understood, but seem to be mediated through a toxic mechanism related to the biotransformation of alkaloids by hepatic microsomal enzymes. This produces highly reactive pyrroles which act as powerful alkylating agents. The main liver injury caused by comfrey (*Symphytum officinale*) is veno-occlusive disease, a non-thrombotic obliteration of small hepatic veins leading to cirrhosis and eventually liver failure. Patients may present with either acute or chronic clinical signs with portal hypertension, hepatomegaly and abdominal pain as the main features.

Therapeutic approaches include avoiding intake and, if hepatic failure is imminent, liver transplantation. In view of the known serious hazards and the ban on distributing comfrey in Germany and Canada, it is difficult to understand why comfrey is still freely available in the United States.

Keywords
Comfrey
Veno-occlusive disease
Herbal medicine
Pyrrolizidine alkaloids

Over thousands of years, physicians and health practitioners have treated patients with innumerable different medicinal preparations with substantially different outcomes. In the last 250 years, efforts towards a scientific treatment approach have increased our understanding of diseases and their possible cures. Many diseases have remained incurable and even relief is often unsatisfactory. In particular, chronically ill individuals, such as those suffering from cancer, AIDS and chronic inflammatory disorders, seek 'a mental comfort from taking action' which often seems not provided by conventional medicine[1].

Recently, alternative medicine has gained increasing attention with regard to possible curative effects as well as potential health hazards. Alternative medicine comprises a wide array of approaches, of which herbal preparations are only one component aiming to give cure or improvement. The reasons for taking herbal drugs, apart from disappointment with conventional medicine, are variable and the majority of patients use herbs in a complementary fashion[2]. Often, patients with minor ailments, such as cold or headache, rely on herbal self-medication because professional treatment is not available or is inconvenient. Natural preparations are believed to be less toxic and may be conceived to be 'the less aggressive way' to handle uncomfortable but largely harmless complaints. In addition, cultural trends have made natural medicine highly fashionable, along with natural foods, physical exercise and other non-manufactured products. In medieval times, support for the use of herbs as medicines came from the Doctrine of Signatures, which proposed that God would not have created ills without plants to cure them[3]. More recently, the serious side effects of some conventional drugs have boosted a desire for treatments that complement nature rather than fight against it.

Herbal medicines represent a $1.8 billion market in the United States, with annual increase rates of around 20%, and studies show a use prevalence between 3% and 93% depending on the criteria applied[3,4]. Around 80% of the

*Corresponding author: Email felix.stickelamed1.med.uni-erlangen.de

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press

world's population rely primarily on herbal medicine, mainly because conventional medicine is so costly. This finding led to a recommendation for developing countries issued by the World Health Organization (WHO) to promote herbal medicine in order to 'fulfil a need unmet by modern systems'[5]. However, medicinal plants do contain powerful compounds, which may explain both their curative properties as well as their toxicity.

Over the last few decades, reports about severe health impairments have mounted and substances associated with various forms of toxicity have been found in herbs used in traditional Chinese medicine, germander (*Teucrium chamaedrys*), chaparral (*Larrea tridentata*), atractylosides (*Atractylis gummifera*) and various other plant species such as greater celandine (*Chelidonium majus*), scullcap (*Scutellaria* spp.) and plants containing pyrrolizidine alkaloids[6].

The aim of the present review is to summarize the most important facts to date about the efficacy and safety of the pyrrolizidine alkaloid containing herb *Symphytum officinale*, commonly named comfrey.

History

Human exposure to pyrrolizidines is worldwide since these alkaloids are contained in more than 300 different plant species[7]. Not all of these are used as herbal preparations and not all are toxic. Nevertheless, the toxicity of certain pyrrolizidine alkaloids has been recognized since 1920 after Wilmot and Robertson reported cases of 'Senecio disease' in South Africa, showing the development of liver cirrhosis after the ingestion of *Senecio longilobus*[8]. Subsequently, other investigators showed that the liver disease observed in *Senecio* poisoning is characterized by an occlusion of hepatic veins resembling Budd-Chiari syndrome[9]. Another pyrrolizidine alkaloid (*Crotalaria*) ingested as 'bush tea' led to numerous cases of veno-occlusive disease in Jamaica[10]. In the seventies, endemic outbreaks of veno-occlusive liver disease were observed in Afghanistan and India related to the intake of *Heliotropium*, another plant containing pyrrolizidine alkaloids[11,12]. In the latter epidemic a cereal named 'Gondli', representing a major nutritional source, had been contaminated by a local plant containing *Crotalaria* spp., which is known to be hepatotoxic. During that period, the first sporadic case reports of infants given herbal tea made with *Senecio* emerged in the United States[13,14].

Pyrrolizidines are the leading plant toxins associated with herb-related diseases and present a serious health hazard to humans through contamination of foodstuffs or when ingested as herbal medicines. In more recent years, toxicity of *Symphytum officinale* (comfrey) has been recognized. It is currently acknowledged that this particular pyrrolizidine-containing agent acts primarily as a hepatotoxin but can also be mutagenic, carcinogenic and a cause of pulmonary hypertension[15–18].

Therapeutic use

While the toxicity of *Heliotropium*, *Senecio* and *Crotalaria* became known as a result of accidental exposure of humans by contamination of foodstuff or by ingestion as teas, comfrey has been applied as a therapeutic product. *Symphytum* spp. can be found all over Europe, Siberia (*Symphytum uplandicum*), North America and Asia. Comfrey belongs to the family Boraginaceae and is an evergreen perennial. It can grow to a height of 50–150 cm, has long, hairy leaves with narrowing ends, and yellowish to red-violet flowers. The term *Radix consolidae* is applied synonymously and it is known as comfrey root or *Symphytum* root. Its German and French names are Beinwellwurzel and Racine de consoude, respectively. It grows as a weed, but other *Symphytum* species may be cultivated as feed for animals or fertilizers (*Symphytum asperum*, *S. uplandicum*). In addition, *Symphytum peregrinum* is grown as a vegetable.

Symphytum officinale has a long tradition as an external treatment for inflammatory disorders of joints, wounds, gout, bone fractures, distorsions, haematomas and thrombophlebitis. It is also applied as a decoction for oral and pharyngeal gargle. For internal application, comfrey is claimed to benefit gastritis and gastroduodenal ulcers, though its effects have never been demonstrated in controlled investigations. In addition, herb practitioners recommend comfrey capsules for the treatment of rheumatoid arthritis, bronchitis, various allergies and for diarrhoea, regardless of the pathogenic cause.

The wide variability of pyrrolizidine content in various comfrey preparations makes it difficult to judge their toxic potential and most physicians, health practitioners and patients are unaware of the total amount ingested, especially when consumed on a regular basis over a long period of time. Ridker and co-workers reported the case of a woman suffering from hepatic veno-occlusive disease, who had drunk ground comfrey tea in addition to taking six comfrey–pepsin capsules daily over a 6 month period[15]. Each comfrey pill contained 400 mg of a white powder which had a pyrrolizidine alkaloid content of 107 nmol g^{-1} and 757 nmol g^{-1} pyrrolizidine N-oxides. According to the patient's history, she drank 480 g of 'MU-16 herbal tea', subsequently found to have a pyrrolizidine concentration of 23.9 nmol g^{-1} tea. Taking all preparations together, she probably consumed a daily amount of 700–740 μg (15 μg kg^{-1} body weight) of pyrrolizidine alkaloids over a period of several months. By comparison, severe liver disease from *Heliotropium* alkaloids has been observed after a daily dose of 30–40 μg kg^{-1} (Ref. 11). Another report from Bach *et al.* estimated the amount of comfrey alkaloids ingested as tea in a 47-year-old female social worker as high as 26 mg per cup based on a pharmaceutical monograph[19], whereas other reports show only up to 8.5 mg alkaloids per cup[20]. The lady had consumed 10 cups a day over a period of 1 year following the

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press

recommendations of a homeopathic doctor in order to treat vague symptoms of fatigue and allergies[17]. Apparently, other preparations contain even higher concentrations[21].

The pharmacological mechanisms are based upon allantoin, which is responsible for the stimulation of connective tissue proliferation and regeneration. Anti-inflammatory properties are probably mediated through rosemarinic acid, which is also likely to account for the analgesic and astringent effects[22]. These anti-phlogistic properties are not conveyed through inhibition of the arachidonic acid metabolism, but seem to be the result of inhibitory actions of plant extracts upon the classical and alternative pathway of complement activation. High molecular glycoproteins so far uncharacterized have been isolated which seem to interact with the complement factors C_3 and C_4 in a dose-dependent fashion but do not affect factors C_1 and C_2. Other constituents of *Symphytum officinale*, such as triterpenoid saponins, have antibacterial properties[23] and the bidesmosidic triterpene glycoside Symphytoxide A was shown to lower blood pressure in rats through anti-cholinergic effects[24].

According to the above reference, indications for external use are traumatic and inflammatory lesions of bones, muscles and joints as well as infected skin lesions such as furunculosis, mastitis and phlebitis. The recommended mode of application is as a paste under a bandage. In this context, comfrey has anti-inflammatory and slight analgesic properties. Owing to side effects, its external use is restricted in Germany and the daily dose is limited to a maximum of 100 μg per day, since a considerable fraction of externally applied pyrrolizidine alkaloids is absorbed through the skin and between 0.1 and 0.4% can be detected in urine[35].

There are no justified indications for internal use and the German Federal Institute for Drugs and Medicinal Products (BfArM) has banned the use of comfrey alkaloids for the treatment of gastritis, gastroduodenal ulcers and diarrhoea and there are no tea brands available containing comfrey. Nevertheless, sometimes the leaves are harvested and ingested as tea, albeit to a much lesser extent in Germany than in North America.

In summary, the therapeutic effects of *Symphytum officinale* are exerted through plant components other than pyrrolizidine alkaloids, whereas the latter are responsible for the sometimes fatal side effects.

Biochemistry and metabolism

More than 350 different pyrrolizidine alkaloids have been identified so far in over 6000 different plants of the Boraginaceae, Compositae and Leguminosae families[25]. Pyrrolizidine-containing plants are distributed worldwide and about half of the identified pyrrolizidines are toxic. *Symphytum officinale* contains a number of chemically heterogeneous compounds (Table 1). Pyrrolizidine alkaloids and their corresponding N-oxides are of particular interest since these compounds are associated with toxicity. The parent molecule of pyrrolizidine alkaloids is shown in Fig. 1.

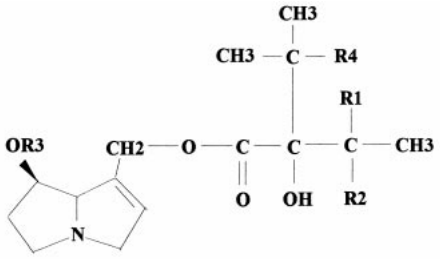
Even within comfrey alone, the pyrrolizidine content of this particular species may vary throughout the year and according to the age of the plant. In comfrey, there are also considerable differences in alkaloid content between the roots and aerial parts with higher contents in the former[26]. Reports show a range between 0.003 and 0.115% (dry weight) while other *Symphytum* species, such as *S. asperum*, contain concentrations up to 0.4%[27].

After ingestion and uptake in the gastrointestinal tract, pyrrolizidine alkaloids undergo metabolic transformation in the liver via the action of microsomal enzymes. The main enzymatic system responsible for the detoxification of

Table 1 Chemical constituents of *Symphytum officinale*

Compound	Content (%)
Allantoin	0.6–0.8
Pyrrolizidine alkaloids (and N-oxides)	0.04–0.6 (depending on plant part)
Intermedine	
Acetylintermedine	
Lycopsamine	
Acetyllycopsamine	
Symphytine	
Echimidine	
Symviridine	
Tannins	4–6
Fructanes (mucopolysaccharides)	15–30
Starch	25
Triterpenes (Isobauerenole)	
Triterpenoid saponins (monodesmosidic and bidesmosidic)	
Hederagenin hexasaccharide	
Oleanolic acid	
Sitosterole	
Lithospermic acid	
Asparagine	1–3
Amino acids	Variable

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press



Pyrrolizidine	R1	R2	R3	R4
Intermedine	OH	H	H	H
Acetylintermedine	OH	H	Acetyl	H
Lycopsamine	H	OH	H	H
Acetyllycopsamine	H	OH	Acetyl	H
Symphytine	H	OH	Tiglyol	H
Echimidine	H	OH	Angeloyl	OH
Symviridine	OH	H	Senecioyl	H

Fig. 1 Molecular structure of pyrrolizidine alkaloids contained in comfrey

foreign compounds is the cytochrome P450 enzyme family, which may also form toxic compounds from previously innocuous substances[28]. Pyrrolizidine alkaloids are metabolized by cytochrome P450 enzymes to either dehydroretronecine, a highly toxic pyrrole metabolite with alkylating properties that damages the endothelium of the liver and other organs, or into alkaloid-N-oxides (Fig. 2). The enzymatic formation of toxic necines from alkaloid-N-oxides is also possible[29,30]. Enzymatically converted alkaloid metabolites may be highly reactive electrophilic compounds capable of reacting with cellular structures, forming adducts which may cause acute or chronic toxicity. Some of these adducts may be persistent in tissues and may re-induce damage long after the initial time point of ingestion[18]. Support for the cytochrome P450-mediated activation of pyrrolizidines into their corresponding toxins comes from the observation that potent microsomal enzyme inducers, such as the anticonvulsant phenobarbital, can enhance the toxicity of pyrrolizidines[31]. There are three essential conditions that can be held responsible for the hepatotoxicity of the pyrrrolizidine alkaloid molecule: the double bond of the 1,2-unsaturated necine base, esterification of the hydroxy group in positions 9 and 7 and a branched carbon chain in at least one of the ester side chains[32].

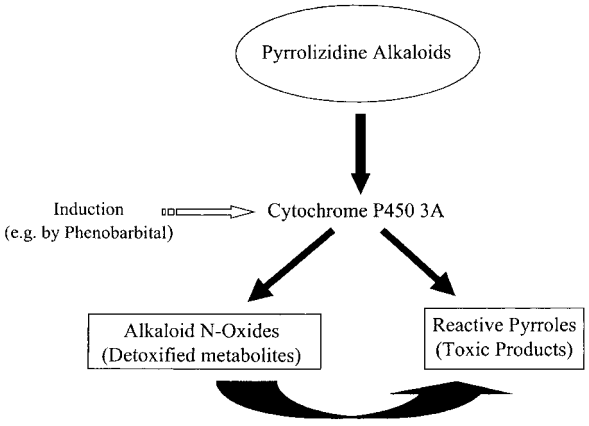


Fig. 2 Enzymatic toxification of pyrrolizidine alkaloids contained in comfrey by cytochrome P450 3A. Induction may enhance the amount of toxic metabolites generated. Alternatively, N-oxides may also be transformed to expoxides

Until recently, there were considerable problems in detecting pyrrolizidine alkaloids in human blood or tissue samples, whereas a method for the identification of alkaloids in plants and herbal products was developed several years ago. As early as the 1960s, pyrrolizidines were identified using spectrophotometry[33] and subsequent improvements were possible through thin-layer chromatography and gas chromatography–mass spectrometry[34]. Betz *et al.* reported the development of a capillary gas chromatography technique and subsequent identification of different alkaloids via thin-layer chromatography[26]. More recently, a simple bioassay using a human cell line was developed to enable investigators to evaluate the mutagenic potential of various alkaloids[35]. Lin *et al.* have established the first analytical method to detect pyrrolizidine alkaloids in blood samples using high performance liquid chromatography (HPLC) which now provides the first tool for a definite diagnosis of pyrrolizidine alkaloid poisoning and for the identification of alkaloids in plants or herbal products[36].

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press

Toxicity

Pyrrolizidine alkaloid related toxicity may be directed against different target organs. The most frequently observed toxicity is against the liver. The main liver injury caused by comfrey and related pyrrolizidines is that of veno-occlusive disease (VOD) also termed 'Stuart-Bras syndrome'[10]. Pyrrolizidine-related VOD in Western countries has been recognized primarily in infants, who seem to be particularly susceptible[13,14,16,37,38]. Other known aetiologies for VOD are cytostatic drugs[39], bone marrow transplantation[40], oral contraceptives[41], systemic lupus erythematosus[42] and alcoholic hepatitis[43].

The histologic picture is essential for the diagnosis although false negative results may occur due to sample errors. Pathologically, a thrombotic form can be distinguished from a non-thrombotic variety and both entities can be observed in pyrrolizidine-induced VOD[44,45]. The toxic effects of enzymatically generated pyrroles lead to defects of sinusoidal endothelia with increased permeability and red blood cell extravasation into the space of Dissé. Subsequently, reticulin fibres are generated within the lumen of central and sublobular veins eventually followed by the obstruction of the vessels. Eventually the thickening of the venous vessel walls leads to a functional outflow obstruction and to a massive organ congestion (Fig. 3). As a result, necrosis of hepatocytes and mesenchymal cells follows[46]. Functional cells are replaced by fibrotic tissue which shows the pattern of 'reversed lobulation' (fibrotic septa extending from perivenular areas rather than from the portal tracts). Signs of inflammation are usually lacking[15]. Ultrastructural investigations revealed the occurrence of hepatocyte blebs in sinusoidal borders leading to an obstruction of sinusoids[47]. The storage of hepatocyte blebs together with cellular debris in the perisinusoidal areas may serve as an explanation for the fact that portal hypertension becomes evident long before venous outflow obstruction has developed[48]. The detection of hepatocyte blebs can be seen in other liver pathologies such as cholestasis, alcoholic hepatitis, transplant rejections as well as in acute *Amanita phalloides* intoxication[49]. The phenomenon is commonly referred to as clasmatosis and may indicate imminent cell death as a result of either lipid peroxidation or disturbances of the extramitochondrial calcium homeostasis[50]. In acute VOD, light-microscopical lobular architecture may be preserved but cellular plates are severely distorted by massive haemorrhagic congestion affecting predominantly zones II and III. However, reticulin accumulation or even fibrosis is not detectable in these cases and a clear-cut vascular obstruction cannot be shown[37].

In addition to hepatotoxicity, pyrrolizidine alkaloids have also been shown to damage the lungs[51]. As with VOD, endothelial defects are the cause of blood cell extravasation, venous vascular occlusion and the subsequent development of pulmonary hypertension. Lung toxicity of pyrrolizidine alkaloids has only been described in experimental rodents exposed to monocrotaline, a pyrrolizidine related to comfrey[52]. In fact, monocrotaline is used in an experimental animal model of *cor pulmonale*[53]. Other potential organ toxicities include lesions to the glomeruli of the kidneys, the pancreas and the gastrointestinal tract, although all of these pathologies have so far only been seen in experimental animals[29].

Apart from acute and chronic organ damage, pyrrolizidine alkaloids can induce tumorigenesis, particularly in the liver. Symphytine, a major constituent of comfrey, has been associated with hepatocellular carcinoma in rats[54]. The assumption is that the alkylating effects of the highly reactive pyrrole metabolites lead to the cancerous transformation of hepatocytes[55]. Metabolites of several pyrrolizidine alkaloids are mutagenic in the *Salmonella typhimurium*/mammalian microsome system and alkaloid extracts of *Symphytum officinale* induce sister chromatid exchanges as well as chromosome aberrations. This effect was even more pronounced when microsomes were induced prior to pyrrolizidine dosing[18,56]. Other investigators have recently shown that pyrrolizidines enhance the proliferation of neoplastic cells while an anti-mitotic effect was observed in human T lymphocytes[57].

However, an association between pyrrolizidine alkaloids and cancer in humans has so far not been found. Considering the possible exposure of humans to pyrrolizidines due to their worldwide occurrence, which is comparable to what experimental animals have been dosed with, it seems unlikely that humans face a relevant threat from these chemical compounds with regard to carcinogenesis. The long-term observation of individuals who have been chronically exposed to pyrrolizidines will clarify this uncertainty[58].

Clinical presentation

The clinical picture of VOD is often difficult to distinguish from other liver pathologies and sometimes remains unrecognized. The first reports describe Jamaican children with 'bush tea disease' due to *Senecio longilobus* complaining about sudden abdominal right upper quadrant pain, hepatosplenomegaly and a rapid occurrence of ascites[10]. From these observations, a classification has been established separating acute and subacute from chronic signs, the latter being characterized by a subclinical appearance. In general, the symptoms resemble those of Budd-Chiari syndrome but 10% may be asymptomatic. In acute forms, a rapid progression to cirrhosis, complicated by portal hypertension, and finally death from liver failure results in 20% of patients due to extensive hepatocyte necrosis[59]. Chronic cases develop slowly and may only present with asthenia, fatigue, mild diarrhoea and signs of portal hypertension[60]. In advanced liver disease, ascites, bleeding from oesophageal varices, portosystemic encephalopathy

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press

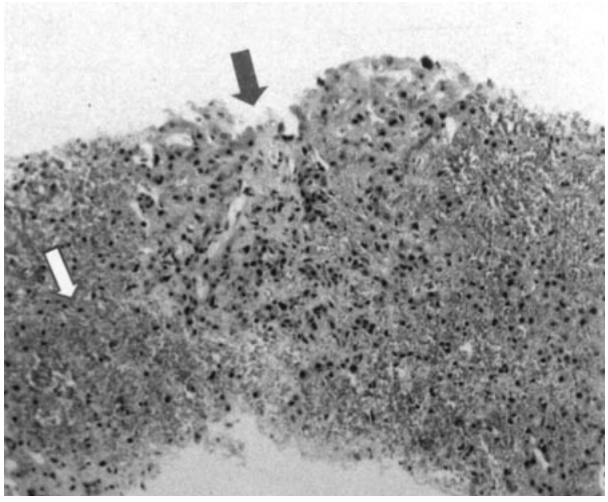


Fig. 3 Liver biopsy of a 18-month-old child following the ingestion of Seneciophylline, a pyrrolizidine also contained in comfrey (haematoxylin–eosin preparation). The histologic features include massive congestion (white arrow), thickening of venous vessel walls (black arrow) and perivenular necrosis. Fibrosis or signs of inflammation are not evident in this case (courtesy O. Dietze, Salzburg, Austria)

and signs of impaired hepatic synthetic function may become intractable.

Laboratory findings show variable elevation of serum levels of transferases, alkaline phosphatase and γ-glutamyltranspeptidase. Jaundice is usually mild and shows raised indirect bilirubine levels. Thrombocytopenia develops due to splenomegaly and anaemia occurs because of intrahepatic haemolysis. Progression of fibrosis may be monitored by serum levels of procollagen-III-N-propeptide, a surrogate marker of fibrogenesis[61]. Hepatic vein wedge pressure is moderately to highly elevated according to a post-sinusoidal block[15]. Ultrasound, computer tomograms and magnetic resonance scans are not particularly helpful since the vascular lesions are sized below the discriminatory level, although changes in portal blood flow can be detected and guide diagnosis[62]. However, histology is mandatory for a diagnosis.

The natural course of pyrrolizidine poisoning varies as mentioned above. Spontaneous remissions have been reported but, nevertheless, mortality is approximately 50%[38,63].

Treatment

A specific treatment is not available except for avoiding the intake of pyrrolizidines. In the Jamaican studies, more than 50% of the affected children recovered completely after sodium and fluid restriction[10]. Similar results have been achieved in adults[15]. As with other causes of VOD, treatment should target portal hypertension and associated clinical problems such as ascites, variceal bleeding and the risk of developing spontaneous bacterial peritonitis. Hence, lowering portal blood pressure, removing ascitic fluid and ligation of varices are prophylactic means to reduce potentially life-threatening complications and offer time for possible remission of the underlying VOD. Efforts to slow down or even stop the occlusive process using anticoagulant drugs have unfortunately not met the high expectations[44]. More invasive treatment options for severe cases of portal hypertension may be the implantation of a transjugular intrahepatic portosystemic stent shunt (TIPS) or a surgically applied Denver shunt[17,64]. Lastly, as soon as liver failure is inevitable, orthotopic liver transplantation may offer a therapeutic option but data about the outcome are still sparse. Detailed therapeutic options are displayed in Table 2.

Table 2 Management of veno-occlusive disease

Management of hepatic veno-occlusive disease
Conservative
Avoiding further exposure to toxin
Sodium restriction
Fluid restriction
Aldosterone-antagonists (Spironolactone)
Reduction of portal pressure with Nitrates, Molsidomine, Propranolol, Nadolol, Losartan (?)
Avoidance of prostaglandin inhibitors (Diclofenac, Ibuprofen)
Avoidance of sedatives (especially benzodiazepines)
Nutritional support (sufficient protein supply and carbohydrates)
Interventional
Removal of ascites via paracentesis (effective and safe)
Endoscopic treatment of bleeding complications
Transjugular intrahepatic portosystemic shunt (TIPS)
Surgical shunts (Denver shunt)
Orthotopic liver transplantation

Conclusion

Hepatotoxicity following the intake of pyrrolizidine alkaloids including comfrey is established. However, the dose–effect relationship remains unclear and differences in inter-individual susceptibility are high. The frequency with which comfrey alkaloids and other plant medicines cause organ damage still remains unclear. Hepatotoxicity in particular may easily be misinterpreted as the result of other aetiologic factors, e.g. alcoholic liver disease, a tendency frequently noticed in physicians when standard causes of liver disease cannot be identified. However, controlled trials addressing diseases for which herbal drugs are acclaimed to be effective are mostly lacking and dose-finding studies are not available. To date, the effectiveness of comfrey has not been studied but the proven hazardous effects are far more numerous than those showing a benefit.

Hepatotoxic effects of conventional drugs are widely acknowledged and most physicians are well aware of them, but the side effects of herbal preparations have not always reached public awareness. As with conventional drugs, interactions with other prescribed medication cannot be ruled out. Lack of awareness is even more

https://doi.org/10.1017/S1368980000000586 Published online by Cambridge University Press

profound in patients who take herbs mostly for self-medication, with obvious dangers. First, the assumed diagnosis, for which the patient takes herbs, might be wrong. Second, the chosen medication might not be optimal, possibly delaying appropriate treatment. Toxicity symptoms and side effects may occur, but some people even increase the dose of the herbal product as a response to the onset of symptoms.

These concerns may not hold for many herbal products that are distributed on the market but comfrey definitely belongs to a potentially dangerous kind. One should follow the simple but effective rules offered by Ryan Huxtable: do not use herbal drugs in infants and children; avoid medication with herbs during pregnancy and while nursing; do not take herbs on a regular basis and in large quantities; and lastly, beware of taking comfrey[65].

Acknowledgements

We would like to thank Otto Dietze, M.D., Professor of Pathology, Salzburg Hospital, for his kind help regarding the histologic preparations.

References

1 Brown JS, Marcy SA. The use of botanicals for health purposes by members of a prepaid health plan. *Res. Nurs. Health* 1991; **14**: 339–50.
2 Moore J, Phipps K, Marcer D, Lewith G. Why do people seek treatment by alternative medicine? *Br. Med. J.* 1985; **290**: 28–9.
3 Winslow LC, Kroll DJ. Herbs as medicine. *Arch. Intern. Med.* 1998; **158**: 2192–9.
4 Schuppan D, Jia JD, Brinkhaus B, Hahn EG. Herbal products for liver disease: a therapeutic challenge for the new millennium. *Hepatology* 1999; **30**: 1099–104.
5 Trevelyan J. Herbal medicine. *Nurs. Times* 1993; **89**: 36–8.
6 Schiano T. Liver injury from herbs and other botanicals. In: Gitlin N, ed. *Clinics in Liver Disease*, vol. 2. Chicago: W.B. Saunders, 1998: 607–30.
7 Smith LW, Culvenor CCJ. Plant sources of hepatotoxic pyrrolizidine alkaloids. *J. Nat. Prod.* 1981; **44**: 129–52.
8 Wilmot FC, Robertson GW. *Senecio* disease or cirrhosis of the liver due to senecio poisoning. *Lancet* 1920; **II**: 828–828.
9 Selzer G, Parker RGF. *Senecio* poisoning exhibiting as Chiari's syndrome. *Am. J. Pathol.* 1951; **27**: 885–907.
10 Bras G, Jeliffe DB, Stuart KL. Veno-occlusive disease of the liver with non-portal type of cirrhosis, occurring in Jamaica. *AMA Arch. Pathol.* 1954; **57**: 285–300.
11 Mohabat O, Srivastava RN, Younos MS, Gholam Gsediq GG, Merzad AA, Aram GN. An outbreak of hepatic veno-occlusive disease in north-western Afghanistan. *Lancet* 1976; **2**: 269–71.
12 Tandon BN, Tandon RK, Tandon HD, Narndranathan M. An epidemic of veno-occlusive disease of liver in central India. *Lancet* 1976; **2**: 271–2.
13 Stillman AS, Huxtable RJ, Consroe P, Kohnen P, Smith S. Hepatic veno-occlusive disease due to pyrrolizidine (*Senecio*) poisoning in Arizona. *Gastroenterology* 1977; **73**: 349–52.
14 Fox DW, Hart MC, Bergeson PS, Jarrett PB, Stillman AE, Huxtable RJ. Pyrrolizidine (*Senecio*) intoxication mimicking Reye's syndrome. *J. Paediatr.* 1978; **93**: 980–2.
15 Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venoocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology* 1985; **88**: 1050–4.
16 Weston CFM, Cooper BT, Davies JD. Veno-occlusive disease of the liver secondary to ingestion of comfrey. *Br. Med. J.* 1987; **295**: 183.
17 Bach N, Thung SN, Schaffner F. Comfrey herb tea-induced hepatic veno-occlusive disease. *Am. J. Med.* 1989; **87**: 97–9.
18 Prakash AS, Pereira TN, Reilly PE, Seawright AA. Pyrrolizidine alkaloids in human diet. *Mutat. Res.* 1999; **15**: (443) 53–67.
19 Comfrey. In: *The Lawrence Review of Natural Products Monograph System*. Pharmaceutical Information Associates, 1987
20 Roitman JN. Comfrey and liver damage. *Lancet* 1981; **1**: 944.
21 Huxtable RJ, Lüthy J, Zweifel U. Toxicity of comfrey-pepsin preparations. *N. Engl. J. Med.* 1986; **315**: 1095.
22 Ahmad VU, Noorwala M, Mohammad FV, Sener B. A new triterpene glycoside from the roots of *Symphytum officinale*. *J. Nat. Prod.* 1993; **56**: 329–34.
23 Ahmad VU, Noorwala M, Mohammad FV, Sener B, Gilani AH, Aftab K. Symphytoxide A, a triterpenoid saponin from the roots of *Symphytum officinale*. *Phytochemistry* 1993; **32**: 1003–6.
24 Stegelmeier BL, Edgar JA, Colegate SM, Gardner DR, Schoch TK, Coulombe RA, *et al.* Pyrrolizidine alkaloid plants, metabolism and toxicity. *J. Nat. Toxins* 1999; **8**: 95–116.
25 Betz JM, Eppley RM, Taylor WC, Andrzejewski D. Determination of pyrrolizidine alkaloids in commercial comfrey products (*Symphytum* sp.). *J. Pharm. Sci.* 1994; **83**: 649–53.
26 Mattocks AR. Toxic pyrrolizidine alkaloids in comfrey. *Lancet* 1980; **2**: 1136.
27 Nebert DW, Nelson DR, Coon MJ, Estabrook RW, Feyereisen R, Fuji-Kuriyama Y, *et al.* The P450 superfamily: update on new sequences, gene mapping, and recommended nomenclature. *DNA Cell Biol.* 1991; **10**: 1–14.
28 Huxtable RJ. New aspects of the toxicology and pharmacology of pyrrolizidine alkaloids. *Gen. Pharmacol.* 1979; **10**: 159–67.
29 Couet CE, Hopley J, Hanley AB. Metabolic activation of pyrrolizidine alkaloids by human, rat and avocado microsomes. *Toxicon* 1996; **34**: 1058–61.
30 Mattocks AR. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*, London: Academic Press, 1986: 1.
31 McLean EK. Senecio and other plants as liver poisons. *Isr. J. Med. Sci.* 1974; **10**: 436–40.
32 Mattocks AR. Spectrophotometric determination of pyrrolizidine alkaloids – some improvements. *Anal. Chem.* 1968; **40**: 1749–50.
33 Brauchli J, Lüthy J, Zweifel U, Schlatter C. Pyrrolizidine alkaloids from *Symphytum officinale* L. and their percutaneous absorbtion in rats. *Experientia* 1982; **38**: 1085–7.
34 Couet CE, Crews C, Hanley AB. Analysis, separation, and bioassay of pyrrolizidine alkaloids from comfrey (*Symphytum officinale*). *Nat. Toxins* 1996; **4**: 163–7.
35 Lin G, Zhou KY, Zhao XG, Wang ZT, But PP. Determination of hepatotoxic pyrrolizidine alkaloids by on-line high performance liquid chromatography mass spectrometry with an electrospray interphase. *Rapid Commun. Mass Spectrom.* 1998; **12**: 1445–56.
36 Roulet M, Laurini R, Rivier L, Calame A. Hepatic veno-occlusive disease in a newborn infant of a woman drinking herbal tea. *J. Pediatr.* 1988; **2**: 481–500.
37 Sperl W, Stuppner H, Gassner J, Judmaier W, Dietze O, Vogel W. Reversible hepatic veno-occlusive disease in an infant after consumption of pyrrolizidine-containing herbal tea. *Eur. J. Pediatr.* 1995; **154**: 112–16.
38 Essell JH, Thomson JM, Harman GS, Halvorson RD, Snyder MJ, Johnson RA, *et al.* Marked increase in veno-occlusive disease of the liver associated with methotrexate use for Graft-Versus-Host disease prophylaxis in patients receiving busulfan/cyclophosphamide. *Blood* 1992; **79**: 2784–8.
39 Fried MW, Connaghan DG, Sharma S, Martin LG, Devine S, Holland K, *et al.* Tranjugular intrahepatic portosystemic shunt

for the management of severe venoocclusive disease following bone marrow transplantation. *Hepatology* 1996; **24**: 588–91.
40 Alpert LI. Veno-occlusive disease of the liver associated with oral contraceptives: case report and review of the literature. *Hum. Pathol.* 1976; **7**: 709–18.
41 Pappas SC, Malone DG, Rabin L, Hoofnagel YH, Jones EA. Hepatic veno-occlusive disease in a patient with systemic lupus erythematosus. *Arthritis Rheum.* 1984; **27**: 104–8.
42 Goodman ZD, Ishak KG. Occlusive venous lesions in alcoholic liver disease. *Gastroenterology* 1982; **83**: 786–96.
43 Rollins BJ. Hepatic veno-occlusive disease. *Am. J. Med.* 1990; **81**: 297–306.
44 Shulman HM, Fisher LB, Schoch HG, Henne KW, McDonald GB. Venooclusive disease of the liver after marrow transplantation: histological correlates of clinical sign and symptoms. *Hepatology* 1994; **19**: 1171–80.
45 Sherlock S. Noncirrhotic extrahepatic and intrahepatic portal hypertension. *Semin. Liver Dis.* 1982; **2**: 202–10.
46 Yeong ML, Wakefield St J, Ford HC. Hepatocyte membrane injury and bleb formation following low dose comfrey toxicity in rats. *Int. J. Exp. Pathol.* 1993; **74**: 211–17.
47 Brooks SEH, Miller CG, McKenzie K, Audretsch JJ, Bras G. Acute veno-occlusive disease of the liver. *Arch. Pathol.* 1970; **89**: 507–20.
48 Franke H. Substructural alterations of liver parenchymal cells induced by xenobiotics. *Exp. Pathol.* 1990; **39**: 139–55.
49 Jewell S, Bellomo G, Thor H, Orrenius S. Bleb formation in hepatocytes during drug metabolism is caused by disturbances in thiol and calcium ion homeostasis. *Science* 1982; **217**: 1257–8.
50 Miskelly FG, Goodyer LI. Hepatic and pulmonary complications of herbal medicines. *Postgrad. Med. J.* 1992; **68**: 935–6.
51 Shubat PJ, Banner W, Huxtable RJ. Pulmonary vascular response induced by the pyrrolizidine alkaloid monocrotaline in rats. *Toxicon* 1987; **25**: 995–1002.
52 Guzowski DE, Solgado ED. Changes in main pulmonary artery of rats with monocrotaline induced pulmonary hypertension. *Arch. Pathol. Lab. Med.* 1987; **111**: 741–5.
53 Hirono I, Haga M, Fujii M, Mori H. Induction of hepatic tumors in rats by senkirkine and symphytine. *J. Natl. Cancer Inst.* 1979; **63**: 469–72.
54 Petry TW, Bowden GT, Huxtable RJ, Sipes IG. Characterization of hepatic DNA damage induced in rats by the pyrrolizidine alkaloid monocrotaline. *Cancer Res.* 1984; **44**: 1505–9.
55 Behninger C, Abel G, Roder E, Neuberger V, Goggelmann W. Studies on the effect of an alkaloid extract of *Symphytum officinale* on human lymphocyte cultures. *Planta Med.* 1989; **55**: 518–22.
56 Olinescu A, Manda G, Neagu M, Hristescu M, Dasanu C. Action of some proteic and carbohydrate components of *Symphytum officinale* upon normal and neoplastic cells. *Roum. Arch. Microbiol. Immunol.* 1993; **52**: 73–80.
57 Culvenor CC. Estimated intakes of pyrrolizidine alkaloids by humans. A comparison with dose rates causing tumors in rats. *J. Toxicol. Environ. Health* 1983; **11**: 625–35.
58 Zimmermann HJ, Lewis JH. Chemical and toxin-induced liver disease. *Gastroenterol. Clin. N. Am.* 1995; **24**: 739.
59 Larrey D. Hepatotoxicity of herbal remedies. *J. Hepatol.* 1997; **26**: 47–54.
60 Eltumi M, Trivedi P, Hobbs JR, Portman B, Cheeseman P, Downie C, *et al.* Monitoring of venoocclusive disease after bone marrow transplantation by serum aminopropeptide of type III procollagen. *Lancet* 1993; **342**: 518–21.
61 Lassau N, Leclére J, Auperin A, Bourhis JH, Hartman O, Valteau-Couanet D, *et al.* Hepatic veno-occlusive disease after myoablative treatment and bone marrow transplantation: value of Gray-scale and Doppler US in 100 patients. *Radiology* 1997; **204**: 545–52.
62 Mowat AP. Biliary disorders in childhood. *Semin. Liver Dis.* 1982; **2**: 271–81.
63 Fried MW, Connaghan DG, Sharma S, Martin LG, Devine S, Holland K, *et al.* Transjugular intrahepatic portosystemic shunt for the management of severe venoocclusive disease following bone marrow transplantation. *Hepatology* 1996; **24**: 588–91.
64 Norris S, Crosbie O, McEntee G, Traynor O, Molan N, McCann S, *et al.* Orthotopic liver transplantation for veno-occlusive disease complicating autologous bone marrow transplantation. *Ransplantation* 1997; **63**: 1521–4.
65 Huxtable RJ, The myth of beneficient nature: the risks of herbal preparations. *Ann. Int. Med.* 1992; **117**: 165–6.