Forensic Science International 241 (2014) 138–140

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Lethal hepatocellular necrosis associated with herbal polypharmacy in a patient with chronic hepatitis B infection

John D. Gilbert [a], Ian F. Musgrave [b], Claire Hoban [b], Roger W. Byard [a,b,*]

[a] Forensic Science SA, Adelaide, SA 5000, Australia
[b] School of Medical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia

ARTICLE INFO

Article history:
Received 9 April 2014
Received in revised form 20 May 2014
Accepted 22 May 2014
Available online 2 June 2014

Keywords:
Herbal medicine
Liver failure
Death
Polypharmacy
Polyherbacy
Hepatitis B

ABSTRACT

Following a short treatment for irritable bowel with the following herbs: *Astragalus propinquus*, *Codonopsis pilosula*, *Paeonia* sp., *Atractylodes macrocephala*, *Pueraria* sp., *Poria cocos*, *Dioscorea opposita*, *Patriniae*, *Psoralea corylifolia*, *Alpinia katsumadai*, *Glycyrrhiza uralensis* and *Dolomiaea souliei* sp. a 43-year-old woman developed acute severe liver failure requiring liver transplantation. Histopathological examination of the liver showed massive hepatic necrosis in keeping with drug/chemical toxicity. Surgery was followed by multiorgan failure and death. While numerous studies have evaluated the effect of polypharmacy, the study of multiple concurrent herb use is only just emerging, despite the popularity of herbal medicine use in the western world. As this case demonstrates that fulminant hepatic failure and death may be caused by the concomitant use of a number of herbal products, the possibility of untoward effects from herbal polypharmacy must be increasingly considered in the evaluation of medicolegal cases.

1. Introduction

Polypharmacy refers to the "use of multiple drugs, or more than are medically necessary" and is an increasing problem in the elderly and in those with chronic disease [1]. The additive and interactive effects of multiple prescribed medications increase the likelihood of drug reactions and associated morbidity and mortality [2]. Considerable attention has, therefore been devoted in recent years to determining the incidence of this problem, identifying its manifestations, and instituting preventive measures. These investigations have, however, focused on prescription medications rather than on herbal medicines.

The use of herbal medicines in Western countries has increased in recent times with adverse effects being reported due to a range of factors, often derived from a single preparation [3,4]. The popularity of herbal medicine use (and the inevitable associated adverse drug reactions) prompted Ness and co-workers [5] to coin the term "polyherbacy" to describe the use of multiple natural health products [5,6]. A case is reported to demonstrate that significant adverse effects may also arise from this "polyherbacy".

2. Case report

A 43-year-old Asian woman with a past medical history of irritable bowel syndrome had a normal colonoscopy six months earlier. She was taking no regular medications, despite an underlying chronic hepatitis B infection. Two and a half weeks prior to her death she consulted a traditional Chinese doctor for her irritable bowel and was prescribed treatment for 10 days with the raw forms of the following herbs: *Astragalus propinquus*, *Codonopsis pilosula*, *Paeonia* sp., *Atractylodes macrocephala*, *Pueraria* sp., *Poria cocos*, *Dioscorea opposita*, *Patriniae*, *Psoralea corylifolia*, *Alpinia katsumadai*, *Glycyrrhiza uralensis* and *Dolomiaea souliei* sp. Blood tests, including general biochemistry and a full blood count performed by her general practitioner some time before the fatal episode had all been normal except for a low vitamin D level. Specifically there were no biochemical indications of liver or kidney dysfunction.

Within hours of commencing the course of herbal treatment she became unwell with nausea, vomiting, lethargy, sweats, chills and myalgia. This was attributed to a flu-like illness and she was prescribed Panadeine (paracetamol and codeine). She subsequently took 1 g of paracetamol each day for two days. Her condition deteriorated and on hospital assessment she was noted to have a metabolic acidosis and evidence of both liver and renal failure. The diagnosis of severe drug-induced acute liver failure was made that required liver transplantation. Histopathological examination of

* Corresponding author at: Discipline of Anatomy & Pathology, Level 3 Medical School, North Building, The University of Adelaide, Frome Road, Adelaide 5005, Australia. Tel.: +618 8313 5441; fax: +618 8313 4408.
E-mail address: roger.byard@sa.gov.au (R.W. Byard).

http://dx.doi.org/10.1016/j.forsciint.2014.05.021
0379-0738/

the excised liver showed massive hepatic necrosis most in keeping with drug/chemical toxicity. Surgery was followed by multiorgan failure and death six days after the onset of the acute illness.

Autopsy examination confirmed multiorgan failure with diffuse edema and congestion of both lungs with patchy pneumonic consolidation, focal hemorrhage in the interventricular septum of the heart and elsewhere, in keeping with terminal coagulopathy, a recent liver transplant with intact anastomoses, cortical pallor of both kidneys and mild cerebral edema. The liver transplant was histologically normal with no features of hyperacute rejection.

Post mortem microbiology performed on a specimen of lung tissue yielded a pure growth of *Klebsiella pneumoniae*. PCR testing for respiratory viruses, herpes simplex virus, varicella zoster virus, cytomegalovirus, enteroviruses and *Bordetella pertussis* was negative and no acid fast bacilli were detected. Analysis of blood taken on the day of admission to hospital revealed therapeutic levels of paracetamol and codeine (paracetamol 11–16.6 mg/L, codeine 0.02 mg/L), with no alcohol or other significant common drugs. In 2005 antenatal serology screen had been negative for hepatitis B surface antigen. The full hepatitis serology on the second day of admission to hospital detected hepatitis B surface antibody (102 mIU/mL) and hepatitis B core total antibody, but not hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B core IgM antibody or hepatitis C antibody. Her hepatitis C virus RNA was negative and PCR for hepatitis B viral load in blood was 203 IU/mL. Analysis of the prescribed herbal medicines revealed no common drugs, organophosphorus or organochlorine compounds, heavy metals or aflatoxins, although unfortunately it was not possible to test for other potential contaminants such as nitrosamines. Death was due to multi-organ failure and bronchopneumonia complicating acute liver failure. Although paracetamol overdose is one of the most common causes of hepatic necrosis, based on the decedent's account of her limited use of Panadol and Panadeine only after her illness commenced, and the corroborative toxicology results, paracetamol toxicity appears unlikely to be the cause in this case.

3. Discussion

Traditional herbal medicines have been associated with a number of adverse reactions due to a variety of factors which have resulted from either the deliberate or accidental substitution of herbs, inadequate processing, or the addition of prescription pharmaceutical drugs [3,7,8]. Although this may result in serious side effects and even death, the exact role played by herbal products in medicolegal cases is usually unclear as documentation of herbal medicines at death scenes is often neglected by investigating police officers, product labels may not accurately reflect content, and toxicological identification of organic compounds in traditional forensic laboratories is difficult [3,9,10]. For this reason a newer metabolomics approach using DNA sequencing may provide a more effective approach [11].

Herbal preparations may also contain toxic substance that are either deliberate additives, such as heavy metals, or accidental contaminants such as pesticides and herbicides [8]. None of these were identified in the reported case. A study of 251 Asian herbal products being sold in California, USA, found that 36 contained arsenic, 35 had mercury and 24 lead [12]. Acute lead and mercury poisoning have been reported. Organic toxins including highly poisonous substances such as aconite root may also be added [13]. *Chan su* is a traditional medicine used for treating sore throats, boils and palpitations that contains the venomous secretions of Chinese toads (*Bufo melanostictus Schneider* or *Bufo bufo gargarizans Cantor*). The bufadienolides have a digoxin-like effect and may cause cardiac arrhythmias, seizures or coma [14]. Sudden death has occurred if *Chan su* is injected [15].

In the reported case serious and fulminant liver necrosis followed the concurrent ingestion of a series of different herbal preparations. The list of causes for fulminant hepatic failure is long and includes various viruses, toxins, idiosyncratic reactions to various drugs, vascular causes and certain metabolic conditions. It has also been reported to result from idiosyncratic hypersensitivity reactions to certain herbal medicines, the effects of which can range from transiently high liver enzyme levels to lethal hepatic failure [16]. While most cases are caused by hepatotoxins integral to the preparations, interactions with prescription medications may also occur [17]. Hepatitis may follow consumption of a variety of herbs including germander (*Teucrium chamaedrys*) and those of the *Aristolochia* species. Hepatic veno-occlusive disease may be caused by comfrey (*Symphytum officinale*) and skullcap (*Scutellaria laterflora*) ingestion. As in the reported case fulminant liver failure requiring transplant (or resulting in death) may occur. This has also occurred with pennyroyal (*Mentha pulegium*), kava (*Piper methysticum*), *Jin bu huan*, *Syo saiko to*, and *Ma huang* [18,19].

The striking feature in the reported case was that the decedent had been relatively well with normal laboratory parameters immediately prior to commencing the course of herbal medicines. In examining the 12 herbal agents taken by the decedent, there are a number that have been associated with hepatotoxicity [20]. For example, studies point to possible hepatotoxic effects of *Glycyrrhiza* roots [21–23] and another report that examined the incidence of acute hepatitis in Chinese herb users identified an increased risk in those taking formulae containing Radix *Paeoniae* and Radix *Glycyrrhizae* [24]. The risks of traditional Chinese medicine-induced hepatotoxicity may also be exacerbated in patients with chronic hepatitis B, which may be relevant in this case [21]. However, the two most likely candidates in this case are *Atractylodes macrocephala* and *Psoralea corylifolia.* Rhizomes of *Atractylodes macrocephala* have been reported to be associated with hepatotoxicity [22,23]. These rhizomes contain the hepatotoxin atractyloside [25]. Herbal medicines containing other atractyloside producing plants are also associated with hepatotoxicity [26].

Psoralea corylifolia also has an association with significant hepatotoxicity [20]. A case of acute cholestatic hepatitis in a patient taking an excessive dosage of *P. corylifolia* seeds prescribed for osteoporosis has been reported [27] and a further three cases of hepatotoxicity from consumption of dried seeds of *P. corylifolia* at the prescribed doses have also been reported [28]. Furthermore, 158 cases of adverse reactions characterized by cholestatic liver damage were reported from herbal preparations whose main component was dried seeds of *P. corylifolia* [29].

Extracts of *P. corylifolia* are hepatoxic in rats [29], more commonly in females. *P. corylifolia* extracts contain numerous phytochemicals, but of most significance are the furocoumarins (psoralen, isopsoralen, psoralenoside and isopsoralenoside) and the meroterpene bakuchiol. The furocoumarins and bakuchiol have been shown to be cytotoxic [30,31]. Of relevance to this report is that some coumarin metabolites are also hepatotoxic. Coumarin is metabolised by a variety of cytochrome P450s: CYP2A6, CYP3A4, CYP1A and CYP2E1 [32]. The hepatotoxic metabolite *o*-hydroxyphenylacetaldehyde is produced by CYP1A and CYP2E1 [32]. Inhibition of CYP3A4 is likely to push metabolism through the CYP1A and CYP2E1 pathways, increasing the concentration of hepatotoxic metabolites. Significantly, several of the herbal agents consumed by the decedent inhibit CYP3A4.

Astragalus propinquus and *Codonopsis pilosula* ssp. *tangshen* extracts both inhibit CYP3A4 [33]. As well, extracts of *Atractylodes macrocephala* increase the concentrations of *Astragalus* glycosides by an as yet undetermined mechanism [34]. Thus, this herbal mixture, with potentially toxic furocoumarins and inhibitors of CYP3A4 could direct the metabolism of these furocoumarins into a

more toxic pathway; combined with an at-risk subject (female with hepatitis), this may have produced an unfortunate synergism resulting in severe hepatotoxicity.

It is, however, recognized that sparse information is available on the presumed hepatotoxicity of several of these agents; for example, extracts from *Glycyrrhiza glabra* (from which liquorice is derived) is used extensively in TCM as a demulcent and expectorant and rarely results in an overdose.

Clinical and diagnostic complications arising from polypharmacy with herbal medicines include the inability to determine causative active compound(s), and difficulty in diagnosing the type of drug interaction. Treating polypharmacy due to herbal medicines may also present more challenges than polypharmacy with conventional medicines, due to inaccuracies between reported and actual ingredients of herbal products [9,35]. The decedent's multiple herb use meant that the crucial identification of active ingredient(s) in order to treat and counteract the toxicity was not possible. Consequently, critical information regarding the type of drug interaction could also not be classified at the time. When the type of interaction is known, it may be possible to treat and manage adverse effects [36]. The type of interaction may be additive (the sum of the effect of the drugs/agents taken exclusively), synergistic (greater than the sum of effect of either drugs/agents taken exclusively) or antagonistic (the sum of the interaction is less than the effect of the drugs/agents taken exclusively) [35–37]. Unfortunately without knowing the active ingredients of herbal medicines treatment is restricted to simply symptomatic management [36,38].

In summary, these studies indicate a possibility that the decedent's fulminant hepatic failure could have been mediated by one or more of the 12 ingredients of her herbal medicine prescription. The most likely scenario is of coumarin-induced hepatotoxicity from *Psoralea corylifolia*, possibly exacerbated by pharmacokinetic interactions with *Astragalus propinquus, Codonopsis pilosula* and *Atractylodes macrocephala*. There may also have been a direct toxic effect from *Atractylodes macrocephala* itself. Linking the observed hepatotoxicity to *Psoralea corylifolia* was made difficult by alternate names for the medicine, and that the most extensive reports of hepatotoxicity from *Psoralea corylifolia* containing medicines are not easily available outside China. There also exists a possibility that the underlying chronic hepatitis B infection may have predisposed the decedent to such a reaction. Whether the addition of modest doses of paracetamol could have further compounded the situation is open to question, although CYP3A4 inhibition by the components of the herbal medicine is likely to be protective. Toxic reactions to *Glycyrrhiza uralensis or Paeoniae* or an idiosyncratic reaction to one of the other constituents or to an undetected contaminant also cannot be excluded.

As it has been reported that individuals in Western countries are more likely to use herbal treatments with multiple ingredients than people in third-world countries, who tend to use single-ingredient herbal preparations to treat disease [39], the possibility of untoward effects from herbal polypharmacy must be increasingly considered in the evaluation of medicolegal cases.

References

[1] R.L. Maher, J. Hanlon, E.R. Hajjar, Clinical consequences of polypharmacy in elderly, Expert Opinion on Drug Safety 13 (2014) 57–65.
[2] R.L. Bushardt, E.B. Massey, T.W. Simpson, J.C. Ariail, K.N. Simpson, Polypharmacy: misleading, but manageable, Clin. Interv. Aging 3 (2008) 383–389.
[3] R.W. Byard, I. Musgrave, Herbal medicines and forensic investigations, Forensic Sci. Med. Pathol. 6 (2010) 81–82.
[4] E. Ernst, Risks of herbal medicinal products, Pharmacoepidemiol. Drug Saf. 13 (2004) 767–771.
[5] J. Ness, D. Johnson, N. Nisly, "Polyherbacy": herbal supplements as a form of polypharmacy in older adults, J. Gerontol. A Biol. Sci. Med. Sci. 58 (2003) M478.
[6] K. Votova, R. Blais, M.J. Penning, M.K. Maclure, Polypharmacy meets polyherbacy: pharmaceutical, over-the-counter, and natural health product use among Canadian adults, Can. J. Public Health 104 (2013) e222–e228.
[7] P. Posadzki, L. Watson, E. Ernst, Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews, Eur. J. Clin. Pharmacol. 69 (2013) 295–307.
[8] E. Ernst, Toxic heavy metals and undeclared drugs in Asian herbal medicines, Trends Pharmacol. Sci. 23 (2002) 136–139.
[9] L. Blacksell, R.W. Byard, I.F. Musgrave, Forensic problems with the composition and content of herbal medicines, J. Forensic Leg. Med. 23 (2014) 19–21.
[10] R.W. Byard, R.A. James, P. Felgate, Detecting organic toxins in possible fatal poisonings – a diagnostic problem, J. Clin. Forensic Med. 9 (2002) 85–88.
[11] R.W. Byard, I. Musgrave, C. Hoban, M. Bunce, DNA sequencing and metabolomics: new approaches to the forensic assessment of herbal therapeutic agents, Forensic Sci. Med. Pathol. (2014), doi:http://dx.doi.org/10.1007/s12024-014-9537-8.
[12] R.J. Ko, Adulterants in Asian patent medicines, N. Engl. J. Med. 339 (1998) 847.
[13] T.Y. Chan, J.C. Chan, B. Tomlinson, J.A. Critchley, Chinese herbal medicines revisited: a Hong Kong perspective, Lancet 342 (1993) 1532–1534.
[14] T.L. Barry, G. Petzinger, S.W. Zito, GC/MS comparison of the West Indian aphrodisiac "Love Stone" to the Chinese medication "chan su": bufotenine and related bufadienolides, J. Forensic Sci. 41 (1996) 1068–1073.
[15] C. Kostakis, R.W. Byard, Sudden death associated with intravenous injection of toad extract, Forensic Sci. Int. 188 (2009) e1–e5.
[16] F. Stickel, E. Patsenker, D. Schuppan, Herbal hepatotoxicity, J. Hepatol. 43 (2005) 901–910.
[17] M.H. Pittler, E. Ernst, Systematic review: hepatotoxic events associated with herbal medicinal products, Aliment. Pharmacol. Ther. 18 (2003) 451–471.
[18] A.N. Webb, W. Hardikar, N.E. Cranswick, G.R. Somers, Probable herbal medication induced fulminant hepatic failure, J. Paediatr. Child Health 41 (2005) 530–531.
[19] F. Skoulidis, G.J. Alexander, S.E. Davies, Ma huang associated acute liver failure requiring liver transplantation, Eur. J. Gastroenterol. Hepatol. 17 (2005) 581–584.
[20] R. Teschke, R. Bahre, Severe hepatotoxicity by Indian Ayurvedic herbal products a structured causality assessment, Ann. Hepatol. 8 (2009) 258–266.
[21] M.F. Yuen, S. Tam, J. Fung, D.K. Wong, B.C. Wong, C.L. Lai, Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study, Aliment. Pharmacol. Ther. 24 (2006) 1179–1186.
[22] D. Melchart, K. Linde, W. Weidenhammer, S. Hager, D.R. Shaw Bauer, Liver enzyme elevations in patients treated with traditional Chinese medicine, JAMA 282 (1999) 28–29.
[23] D. Melchart, K. Linde, S. Hager, J. Kaesmayr, D. Shaw, R. Bauer, W. Weidenhammer, Monitoring of liver enzymes in patients treated with traditional Chinese drugs, Complement. Ther. Med. 7 (1999) 208–216.
[24] C.H. Lee, J.D. Wang, P.C. Chen, Case-crossover study of hospitalization for acute hepatitis in Chinese herb users, J. Gastroenterol. Hepatol. 23 (2008) 1549–1555.
[25] L.Y. Chen, A. Hu, C.J. Chang, The degradation mechanism of toxic atractyloside in herbal medicines by decoction, Molecules 18 (2013) 2018–2028.
[26] J. Yin, D. Li, W. Hu, Q. Meng, Effects of glycyrrhizic acid on cocklebur-induced hepatotoxicity in rat and human hepatocytes, Phytother. Res. 22 (2008) 395–400.
[27] S.W. Nam, J.T. Baek, D.S. Lee, S.B. Kang, B.M. Ahn, K.W. Chung, A case of acute cholestatic hepatitis associated with the seeds of *Psoralea corylifolia* (Boh-Gol-Zhee), Clin. Toxicol. 43 (2005) 589–591.
[28] W. Cheung I, M.L. Tse, T. Ngan, J. Lin, W.K. Lee, W.T. Poon, T.W. Mak, V.K. Leung, T.N. Chau, Liver injury associated with the use of Fructus Psoraleae (Bol-gol-zhee or Bu-gu-zhi) and its related proprietary medicine, Clin. Toxicol. 47 (2009) 683–685.
[29] J. Wang, Z. Jiang, J. Ji, Y. Li, M. Chen, Y. Wang, Y. Zhang, T. Tai, T. Wang, L. Zhang, Evaluation of hepatotoxicity and cholestasis in rats treated with EtOH extract of Fructus Psoraleae, J. Ethnopharmacol. 144 (2012) 73–81.
[30] Y. Wang, C. Hong, C. Zhou, D. Xu, H.B. Qu, Screening Antitumor Compounds Psoralen and Isopsoralen from *Psoralea corylifolia* L. Seeds, Evid. Based Complement. Alternat. Med. 2011 (2011) 363052.
[31] J. Iwamura, T. Dohi, H. Tanaka, T. Odani, M. Kubo, Cytotoxicity of corylifoliae fructus. II Cytotoxicity of bakuchiol and the analogues, J. Pharm. Soc. Jpn. 109 (1989) 962–965.
[32] D.F. Lewis, Y. Ito, B.G. Lake, Metabolism of coumarin by human P450s: a molecular modelling study, Toxicol. In Vitro 20 (2006) 256–264.
[33] C. Lau, K.D. Mooiman, R.F. Maas-Bakker, J.H. Beijnen, J.H. Schellens, I. Meijerman, Effect of Chinese herbs on CYP3A4 activity and expression in vitro, J. Ethnopharmacol. 149 (2013) 543–549.
[34] J. Song, S.R. Zheng, Y. Jin, J. Li, Pharmacokinetic interaction of astragaloside IV with atractylenolide i and prim-*O*-glucosylcimifugin in male Sprague Dawley rats, Planta Med. 80 (2014) 187–192.
[35] K. Cvijovic, H. Boon, W. Jaeger, S. Vohra, Group S, Polypharmacy, multiple natural health products and hepatotoxicity, Canadian Med. Assoc. J. 183 (2011) E1085–E1089.
[36] M.A. Riedl, A.M. Casillas, Adverse drug reactions types and treatment options, Am. Fam. Physician 68 (2003) 1781–1790.
[37] J. Strandell, S. Wahlin, Pharmacodynamic and pharmacokinetic drug interactions reported to VigiBase, the WHO global individual case safety report database, Eur. J. Clin. Pharmacol. 67 (2011) 633–641.
[38] R.W. Byard, The potential forensic significance of traditional herbal medicines, J. Forensic Sci. 55 (2010) 89–92.
[39] V.J. Navarro, L.B. Seeff, Liver injury induced by herbal complementary and alternative medicine, Clin. Liver Dis. 17 (2013) 715–735.