

Initially purported hepatotoxicity by *Pelargonium sidoides*: the dilemma of pharmacovigilance and proposals for improvement

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ABSTRACT

Background. Spontaneous reports of herb induced liver injury (HILI) represent a major regulatory issue, and it is in the interest of pharmacovigilance to identify and quantify previously unrecognized adverse reactions and to confirm or refute false positive signals of safety concerns. In a total of 13 spontaneous cases, liver disease has initially been attributed to the use of *Pelargonium sidoides* (PS), a plant from the South African region. Water/ethanol extracts derived from its roots are available as registered herbal drugs for the treatment of upper respiratory tract infections including acute bronchitis. **Objectives.** The present study examines whether and to what extent treatment by PS was associated with the risk of liver injury in these spontaneous cases. **Study design:** Overall, 13 spontaneous cases with primarily suspected PS hepatotoxicity were included in the study. Their data were submitted to a thorough clinical evaluation that included the use of the original and updated scale of CIOMS (Council for International Organizations of Medical Sciences) to assess causality levels. These scales are liver specific, validated for liver toxicity, structured and quantitative. **Results.** None of the 13 spontaneous cases of liver disease generated a positive signal of safety concern, since causality for PS could not be established on the basis of the applied CIOMS scales in any of the assessed patients. Confounding variables included comedication with synthetic drugs, major comorbidities, low data quality, lack of appropriate consideration of differential diagnoses, and multiple alternative diagnoses. Among these were liver injury due to comedication, acute pancreatitis and cholangitis, acute cholecystitis, hepatic involvement following lung contusion, hepatitis in the course of virus and bacterial infections, ANA positive autoimmune hepatitis, and other preexisting liver diseases. In the course of the case assessments and under pharmacovigilance aspects, data and interpretation deficits became evident. Possible improvements include appropriate data quality of cases in spontaneous reports, case assessment by skilled specialists, use of a validated liver specific causality assessment method, and inclusion only of confirmed cases into the final regulatory case database. **Conclusions.** This study shows lack of hepatotoxicity by PS in all 13 spontaneous cases as opposed to initial judgment that suggested a toxic potential of PS. Major shortcomings emerged in the pharmacovigilance section that require urgent improvements.

Key words. Herbal hepatotoxicity. Herb induced liver injury. *Pelargonium sidoides*. *Pelargonium sidoides* questionable hepatotoxicity. Pharmacovigilance.

INTRODUCTION

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Among the most important aims of pharmacovigilance is the identification and quantification of previously unrecognized adverse reactions and the confirmation or refusal of false positive signals, whether in published case reports or from spontaneous reports.¹ To achieve these goals, specific qua-

lications in pharmacovigilance are desired,² and adherence to guidelines for submitting adverse reaction reports is recommended³ to meet the requirements for complete case data, which currently often are of low quality.⁴⁻⁶ Adverse reactions associated with the use of conventional drugs and herbs are not uncommon, and most of these may easily be recognized, but this does not necessarily apply to cases of rare drug induced liver injury (DILI) or herb induced liver injury (HILI). For cases of liver injury, a thorough causality assessment is more important^{7,8} than generating signals of safety concerns simply by counting spontaneous reports or published case reports.⁹

At present, pharmacovigilance and clinical considerations contribute to the discussion whether the use of PS (*Pelargonium sidoides* DC) may be hepatotoxic.¹⁰⁻¹² PS is a plant of southern African origin, and water/ethanol extracts from its roots are mainly used in European countries.¹⁰ In Germany, PS extracts are marketed since at least 1976 and are registered as a herbal medicinal product with the indication for symptomatic treatment of acute bronchitis; indications in other countries may be broader, but focus on respiratory tract infections including common cold.^{10,11} In 2011, EMA (European Medicines Agency) described a favorable benefit/risk ratio and a lack of unwanted hepatic effects in causal relationship to PS use in European countries.¹⁰ Surprisingly, in the same year 19 spontaneous reports on assumed PS hepatotoxicity collected since 2004 were published in Germany,¹¹ but causality for PS could not be substantiated upon further assessment.¹²

In the present study we assessed causality for PS in additional spontaneous cases of assumed PS hepatotoxicity in purported connection with PS use partially going back to 2004. These cases were presented in 2011 by European regulatory agencies, the WHO, and the manufacturer. None of these cases now presented has been thoroughly evaluated for causality before.

MATERIAL AND METHODS

Patients

Overall 13 patients were evaluated as study group that included cases of spontaneous reports with liver disease in primarily assumed temporal and causal association with *Pelargonium sidoides* (PS) treatment. The patients originated from Germany (n = 9), Switzerland (n = 2), Italy (n = 1),

and Singapore (n = 1). Case data were supplied by the German regulatory agency (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM, Bonn, Germany) for 6 cases without final assessment and/or presentation of causality levels, but with the understanding that the global introspection WHO scale has been used, a method which is not liver-specific and not validated for hepatotoxicity and thereby in no way an acceptable method for causality assessment of regulatory assumed HILI cases by PS; additional data of these 6 cases were presented by the manufacturer. Data of the remaining 7 cases were kindly provided upon request by the manufacturer (Dr. Schwabe, Karlsruhe, Germany) of one of the PS drugs; among these was one case initially presented to and now provided by the WHO database to the manufacturer upon its actual request. The case of a 46-year-old female patient with comedicated polytherapy and LTX was not further assessed due to various confounding variables such as comedication, poor data quality, and lack of an established temporal association, because short term PS treatment was initiated to treat flu like symptoms erroneously not considered as prodromi of the emerging liver disease at that time.

PS is available in the form of film-coated tablets and oral liquid.¹⁰ For adult patients, the recommended dose in Germany is 3 x 30 drops daily which corresponds to 3 x 1 tablet 20 mg each daily. According to the patient leaflet, treatment should not exceed 3 weeks.

Methods

All data of the patients were supplied in anonymous form. The information commonly consisted of a condensed form presented to or generated by BfArM. A condensed form as well as narrative information was also provided by the drug manufacturer. In a few cases only, the data also included a medical report of the treating physician, a discharge report, and an adverse drug reaction report.

The data of all 13 cases were submitted to a causality algorithm that consisted of 4 steps: assessment of key items related to a temporal association (step 1), criteria of PS hepatotoxicity and definition of the pattern of liver injury (step 2), application of an appropriate causality assessment method (step 3), and exclusion of alternative diagnoses (step 4).¹³⁻¹⁵ Evaluations also included synthetic drugs and other herbs.

In the first step, clear information is required for timetables with respect to start and end of PS use as

well as to the appearance of symptoms and/or increased liver values. For the second step, values of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are essential as clear criteria for liver injury and for the differentiation between the hepatocellular, cholestatic or mixed hepatocellular-cholestatic pattern.^{13,15} The third step of the diagnostic algorithm requires the application of the liver specific, for hepatotoxicity validated, structured, quantitative and updated scale of CIOMS (Council for International Organizations of Medical Sciences);¹⁵⁻¹⁷ for reasons of comparison the original CIOMS scale was also used.¹³ In the fourth step, all case data were analyzed regarding various other differential diagnoses not yet evaluated with the updated CIOMS scale.¹⁵

RESULTS

Basic data of the study group

In the study group of 13 patients, the ratio of males:females was 7:6, and in 12 of these the ages were known with a range from 31 to 81 years and an average of 56.7 years (Table 1). The indication for PS treatment was described for 11 of the 13 patients and included unspecific infection, flu like symptoms, sinusitis, sinubronchitis, nasopharyngitis, pharyngitis, and infections of the upper respiratory tract including bronchitis. The brand name and the manufacturer of the used herbal PS drug were available in all 13 cases (Tables 1 and 2). PS was used as a clearly identifiable monopreparation in all cases; no patient took a herbal mixture preparation (Table 2). In 9 patients comedication was reported that consisted of up to 9 chemical drugs, suggesting multimorbidities. Apart from PS, in none of the cases was there any additional use of a herbal drug or a dietary supplement except for one who used a gel with arnica contained in a herbal drug (Tables 1 and 2).

The daily dose of the used PS drug was known in only 9 out of 13 cases: of these 4 patients adhered to the recommended daily dose of 3 x 30 drops (n = 3) or 3 x 1 tablet with 20 mg extract (n = 1); with 3 x 50 drops daily PS overdose was reported for 1 patient; underdosed PS treatment was described for the remaining 4 patients who daily used 1 x 20 drops (n = 1), 1 x 30 drops (n = 1), or 3 x 20 drops (n = 2) (Tables 1 and 2). In four cases corresponding to almost one third of the patients the daily dose of PS remained unclear.

Incomplete data were also obtained for other items such as beginning and end of PS use and ap-

pearance of symptoms, total time on PS, time to onset to assess the latency period, and verification of a temporal association (Tables 1 and 2). The exact dates of PS start and end were presented for 7 and 9 patients, respectively. As a consequence, time on PS signifying overall treatment duration was known only in 7 cases (Table 2); with 5 patients who used PS between 2 and 11 days with an average of 5.8 days and with 2 other patients who were treated for 30 and 180 days. This reflects overlong treatment because drug information limits PS use to a maximum of 21 days (Table 1). Whereas the exact date of symptoms or increased liver values were described in 10 of 13 patients, the time to onset considered as latency period was known only in 6 cases with an established temporal association in 5 cases (Table 2).

Clinical and laboratory data

Symptoms were reported by the physicians only rarely, as were considerations of differential diagnoses that were usually required to assess the causes of increased liver values (Table 1). Outcome was favourable in 12 patients and fatal in 1 patient with preexisting liver cirrhosis due to a chronic active hepatitis on the basis of an ANA positive AIH that required steroid treatment and finally led to a terminal aspergillus sepsis.

Among the 13 study patients, values of ALT, AST AST (aspartate aminotransferase), and ALP were available in 8, 6, and 5 cases, respectively (Tables 1 and 2). ALT was on average 1,041 U/L with a range of 101 to around 2,500 U/L; with AST, the average was 1,288 U/L and a range from 49 to around 4,000 U/L; and ALP showed an average value of 140 U/L with a range of 63 to 178 U/L (Table 1). ALT values following PS cessation were reported in 6 cases and found decreased, but in none of the overall 13 patients ALT normalization has been reported (Tables 1 and 2). Therefore, in none of these cases the diagnosis of an acute and resolving liver disease is warranted. In some of the remaining cases, any form of chronic liver disease may be present, including AIH that has only rarely been excluded in the overall 13 patients (Table 1).

Overall hepatitis serology and imaging data was poorly documented in most of the 13 cases (Tables 1 and 2). In only 5 or less cases was there any information on biliary tract imaging, hepatitis A, hepatitis B, or hepatitis C, and in only 2 cases hepatitis E was assessed. Data of infections by cytomegalovirus, Epstein Barr virus, or herpes

Table 1. Clinical data of all patients (n = 13) with primarily suspected liver disease in assumed association with the treatment by *Pelargonium sidoides* (PS).

Patient	Identification	Individual information for each patient
01	BfArM 08074646 52 years Female Germany	<ul style="list-style-type: none"> Details: Report from a hospital physician. PS used for treatment of an infection with 3 x 30 drops daily for February 17 to 22, 2008. Increased liver values reported only 15 days after PS cessation on March 7, 2008: ALT 1213 U/L, AST 533 U/L, ALP 169 U/L. Subsequent decrease of the liver values, ALT 388 U/L on March 13, 2008, the day the patient was hospitalized. During hospitalization, no further details of aminotransferases available. Appropriate exclusion of hepatitis A-C, but HCV-PCR not done. Negative titers of not further specified autoantibodies. Lack of data for HEV, CMV, EBV, HSV, VZV. No imaging data presented. For cervicobrachial syndrome, intermittent use of Diclofenac, for instance starting December 2007 to January 2008 and from March 7 to March 11, 2008. Regular use of norgestrel and Dolo Arthrosenex Gel which contains among others 2-hydroxyethylsalicylate as a non-steroidal anti-inflammatory drug (NSAID), heparin, and arnica. Final diagnoses: Hepatitis associated with virus or bacterial infection; NSAID hepatotoxicity; unassessed hepatobiliary disease. Causality: Unlikely causality with respect to PS according to CIOMS criteria. Comment: Poorly documented case. Lack of exclusion of infections by HEV, CMV, EBV, HSV, and VZV. Partial exclusion of hepatitis C. Missing exclusion of biliary diseases, since hepatobiliary imaging not done. Overall unclear case.
02	BfArM 11133488 68 years Male Germany	<ul style="list-style-type: none"> Details: Report to the drug company primarily by a pharmacist who provided the initial information and a medical report of a pulmonologist. The client told the pharmacist that he used PS for treatment of a severe bronchitis over a period of 6 months, and his liver values were normal before initiation of the treatment. Additional information by an internist revealed the use of 3 x 30 drops of PS daily between October 2004 and April 2005. On April 14, 2005 the patient visited the pulmonologist who diagnosed a chronic sinubronchitis, found elevations of ALT (101 U/L) and of AST (49 U/L), and recommended to stop the use of the antibiotic. There was lack of laboratory data to assess the cause of the increased liver values, and there were no imaging results of the hepatobiliary system although recommended. Final diagnosis: Liver injury by antibiotic drug; not further classified liver disease. Causality: Unlikely causality with respect to PS according to CIOMS criteria. Comment: Poorly documented case. Prolonged PS treatment.
03	BfArM 11133514 67 years Female Germany	<ul style="list-style-type: none"> Details: Report from a hospital physician. PS used for unknown indication with 30 drops daily short-term without further specification until November 30, 2007 when right upper abdominal pains and scleral jaundice led to hospitalization after vomiting, nausea and pyrexia 2 days before. At admission, ALT 505 U/L, AST 471 U/L, amylase 374 U/L. After 5 days, ALT 140 U/L, AST 129 U/L, and amylase 29 U/L. At discharge, ALT value not reported, but AST normalized. During hospitalization, maximum values for γ-glutamyltranspeptidase 586 U/L, ALP 178 U/L, bilirubin 5.6 mg%, lipase 175 U/L, and CRP 22.3 mg/L. Hepatitis serology was reported as without pathological changes, but details not communicated. The report of the hepatobiliary sonography describes that there is no passage of a biliary stone, but there is lack of details regarding gall bladder, bile ducts within and outside the liver, and pancreas. Comedication with paracetamol (1,000 mg/d), but no details presented. Known penicillin allergy and multiple other allergies, arterial hypertension without specified treatment, and type II diabetes mellitus without specified treatment. The hospital diagnosis is drug induced jaundice or calculus passage. Final diagnoses: Acute pancreatitis and cholangitis, possibly related to transient choledocholithiasis; paracetamol hepatotoxicity. Causality: Possible causality with respect to PS only on formal grounds according to CIOMS criteria, but this particular judgement is actually a false positive signal in face of the established alternative and final diagnosis. Comment: Considering the clinical course with upper abdominal pains, nausea, vomiting, and increased values of amylase and lipase, there is no question regarding the diagnosis of acute pancreatitis. Fever and increased CRP values are in line with this diagnosis, but also with the diagnosis of cholangitis. The diagnosis of cholangitis is supported by increased liver values. The two diseases are most probably caused by a transient choledocholithiasis, but there is lack of

		a detailed description of the hepatobiliary sonography results including the gall bladder. Short-term use of PS with only 30 drops daily, hardly to be considered as cause for the presented disease entities.
04	BfArM 11133521 31 years Female Germany	<ul style="list-style-type: none"> Details: Report from a physician. PS used for flu like symptoms, but daily dose and actual dates of treatment not reported. On December 18, 2007 ALT 150 U/L and AST 984 U/L. Later values without actual dates were for ALT 52 U/L and for AST 35 U/L. Not further detailed improvements of ALT and AST within the following 3 weeks. Comedication with acetylsalicylic acid for the flu like symptoms, but no details presented. One month before the present onset, contact via skin with a patient with hepatitis B and C. Present analysis regarding hepatitis B and C was reported to be without pathological findings, but actual parameters not communicated. No data presented to exclude hepatitis A and E, CMV, HSV, and VZV. Laboratory confirmation of previous EBV infection, but details not presented. Oedematous wall of the gallbladder and minor hepatomegaly. Final diagnoses: Unassessed acute virus hepatitis, acute cholecystitis, and aspirin induced liver injury. Causality: Unlikely causality with respect to PS according to CIOMS criteria. Comment: Unusual and poorly documented case. The initial assessments of the aminotransferases show much higher values for AST compared to ALT, which results in a De-Ritis quotient of > 6. This may be found in alcoholic liver disease, cardiac and muscle diseases, but due to lack of additional laboratory values a final diagnosis is not feasible. Considering the flu like symptoms as prodromi, the present illness may well be attributed to a virus hepatitis. There was contact with a patient with hepatitis B and C, and this diagnosis might have been missed through insufficient parameters and due to missing surveillance with respective parameters in the further course. Overall, hepatitis A-C and E as well as the other forms of hepatitis should have been clearly ruled out.
05	BfArM 11174502 56 years Male Germany	<ul style="list-style-type: none"> Details: Report from the wife of a patient (pharmacist) and hospital physicians. PS used for a respiratory infection at a daily dose of 3 x 50 drops from August 2 to August 13, 2011. Few days after PS start dark urine, but PS continuation. On August 18, 2011 symptoms of nausea, reduced appetite, and jaundice. Hospitalization on August 22, 2011. Aminotransferases reported as around 2,500 U/L initially, under prednisone ALT 287 U/L and AST 254 U/L on September 16, 2011 and ALP 297 U/L on September 19, 2011. Reported exclusion of hepatitis A-C, hepatitis E, CMV, EBV, HSV, and autoimmune liver disease except ANA 1:160. Ultrasonography with slight hepatosplenomegaly. Solitary lesion (1.7 cm) in liver segment IV/VIII by imaging assessment, questionable hepatocellular carcinoma. Liver histology with chronic active hepatitis and cirrhosis. Reported arterial hypertension, comedication with Olmetec® and Rasilez® for a longer duration and with an unknown daily dose and not further specified duration. Intermediate listing for LTX, death on October 13, 2011 due to aspergillus sepsis. Final diagnoses: ANA positive AIH with chronic active hepatitis and preexisting, liver cirrhosis; liver injury by comedication (Olmetec®). Causality: Excluded causality with respect to PS according to CIOMS criteria. Comment: Dark urine as first symptom of liver disease was noticed few days after PS start, incompatible with PS hepatotoxicity. PS overdose: 3 x 50 drops used instead as recommended 3 x 30 drops per day. AIH, responding to prednisone therapy.
06	BfArM 11174689 51 years Female Germany	<ul style="list-style-type: none"> Details: Report via the Drug Commission of the German Pharmacists from a pharmacist. PS used for treatment of pharyngitis with 3 x 20 drops on August 8 and 9, 2011. Increased liver values without actual data reported on August 28, 2011. Known increased cholesterol values. Lack of any other details. Final diagnosis: Increased liver values of unknown etiology, unrelated to PS. Causality: Unlikely causality with respect to PS according to CIOMS criteria. Comment: Insufficiently documented case. PS use of only 2 days with increased liver values only 19 days hereafter.
07	WHO 10401380 SwissMed 2008-03269	<ul style="list-style-type: none"> Details: Report from a physician. PS used to treat acute nasopharyngitis. Daily dose of PS not reported. According to databases, start of PS use 4/2008 and end 4/2008 with documented 0 day(s) as undefined duration of use. Ankylosing spondylitis since 1955. Infliximab from 01/2008 until March 19, 2008 with 300 mg 1 x per 6 weeks parenterally. Hepatitis reported on May 6, 2008, described as emerged within one month after PS treatment, thereby lack of temporal

	40 years Male Switzerland	association; and with ALT 760 U/L, AST 382 U/L, and ALP 119 U/L. On May 16, 2008 ALT 1289 U/L, AST 553 U/L, and ALP 152 U/L Aminotransferases marginally increased on July 15, 2008. Exclusion of hepatitis B, hepatitis C, and CMV infection without reported details. Previous hepatitis A, hepatitis E, and EBV infection described but again no specific data. No data for HSV and VZV. Negative titers for ANA, anti-dsDNA, ANCA, anti-SS-A/B, AMA, SMA, anti-LKM. Normal imaging data. Liver histology with portal inflammation and eosinophils. Primary hyperparathyroidism as comorbidity, but unclear whether acute illness or treated by surgery. Daily one glass wine.
		<ul style="list-style-type: none"> • Final diagnosis: Infliximab hepatitis. • Causality: Excluded causality with respect to PS according to CIOMS criteria. • Comment: Hepatitis due to Infliximab that started with acute nasopharyngitis as prodromi. As a slowly metabolized drug with elimination of up to 6 months, Infliximab runs the risk of cumulation. Alternative hepatitis E with rapid IgM disappearance not excluded with certainty. Lack of temporal association with respect to PS.
08	Schwabe 2004022516 56 years Female Germany	<ul style="list-style-type: none"> • Details: Report by a general practitioner. Treatment for a not further assessed virus infection, respiratory tract infection, and chronic sinusitis. Daily 3 times 20 drops of PS during 11/2002-12/2002, but lack of exact dates of exposure. Increased aminotransferases reported, with lack of individual values and missing exact date of assessment. Significant improvement reported at a control on March 6, 2003, but again without actual values at this time and in the period before. Normalization of aminotransferases not reported. Exclusion of hepatitis of other causes mentioned by the practitioner, with lack of any details regarding the used laboratory parameters and technical procedures. In a note later on the practitioner reported actually an increase of the aminotransferases at two different occasions: at first, there was comedication with a potentially hepatotoxic antibiotic drug of not declared product identity or manufacturer, and at second, there was no comedication, a threefold increase of aminotransferases (not specified in detail) and a reduction of the values in the further course after drug cessation without any details with respect to the time frame. Bronchial asthma and multiple allergies were reported as underlying diseases. The practitioner assumes a possible causality for PS. • Final diagnoses: None, due to poor documentation. • Causality: Excluded causality with respect to PS according to CIOMS criteria. • Comment: Poorly documented case. Whether there is a temporal association at all, is doubtful or at least not clearly documented. There are no data that exclude alternative causes of the observed liver disease, a possible reexposure test is invalid due to insufficient data, and a chronic liver disease has not been excluded, since normal values of aminotransferases before and after PS use have not been presented. Prolonged treatment duration.
09	Schwabe 2008041801 70 years Male Switzerland	<ul style="list-style-type: none"> • Details: Report by an internist. PS used to treat cough, dosage 3 x 30 drops daily for the period of March 1 to 31, 2008. Elevated liver enzymes of ALT, AST, and γ-glutamyltranspeptidase reported as assessed on March 14, 2008, but actual values and further time course not clearly reported. There is, however, the notification that liver values failed to decrease despite PS cessation. Comedication with Amlodipin, Acetylsalicylic acid, Candesartan, and Glimepirid. No attempt to exclude any of the other potential liver diseases, in particular hepatitis A-C and E, CMV, EBV, HSV, VZV. Lack of imaging data. • Final diagnoses: Preexisting liver disease; liver injury by comedicated drugs. • Causality: Unlikely causality with respect to PS according to CIOMS criteria. • Comment: Poorly documented, basically not assessable case. Since liver values are not presented, the criteria for hepatotoxicity may not have been fulfilled. According to medication, multimorbid patient with arterial hypertension, diabetes mellitus, and COPD. Increased liver values are best explained either by preexisting disease or by comedication by some drugs with potential hepatotoxic side effects.
10	Schwabe 2009030901 Unknown age Female Germany	<ul style="list-style-type: none"> • Details: Report via pharmacy from a female patient. PS used for unknown indication and unknown duration with unknown daily dose. Lack of any medical record, no other information available except that liver values are reported increased, but lack of actual values. • Final diagnosis: None due to lack of any data. • Causality: Excluded causality with respect to PS according to CIOMS criteria. • Comment: Unassessable case.

11	Schwabe 2009083101 62 years Male Singapore	<ul style="list-style-type: none"> Details: Report from a hospital physician. PS 20 mg was used as 3 x 1 tablets per day from August 11 to 18, 2009 to treat cough and phlegm following pneumothorax contusion on August 11, 2009. On August 11, 2009 ALT was increased with 59 U/L (normal range 0-40). On August 18, 2009 ALT was 182 U/L, and PS use was stopped. ALT declined to 151 U/L on August 21, 2009, to 77 U/L on August 24, 2009, and to 51 U/L on August 28, 2009. On August 11, 2009 AST was 39 U/L (normal range 3-40), and ALP 63 U/L (normal range 35-120), with increases of both enzymes in the further course. During August 11 to 18, 2009 comedication consisted of etrocoxib and ranitidine. Preexisting morbidity consisted of hypercholesterolemia, hypertension, and diabetes mellitus, comedication with Lipitor, Atenolol, Aspirin, Concor, and Doxazosin; treatment was stopped on August 21, 2009. Lack of exclusion of all forms of virus hepatitis. Normal hepatobiliary sonography. Final diagnosis: Hepatic involvement following pneumothorax contusion. Causality: Unlikely causality with respect to PS according to CIOMS criteria. Comment: Due to lack of a temporal association, there is no causality for PS. On the day PS treatment was initiated. ALT was already increased. Consequently, any medication initiated at August 11, 2009 has to be excluded as cause, not only PS but also the potentially hepatotoxic etrocoxib and ranitidine. Any other comedication used for various comorbidities has to be considered, since some are potentially hepatotoxic. But these comedications have been used for a long period, possibly without major hepatic adverse effects. Increased liver values are best explained with the consequences of traumatic pneumothorax contusion with liver involvement.
12	Schwabe 2011031603 IT-MINISAL 02-136235 46 years Male Italy	<ul style="list-style-type: none"> Details: Report from a pharmacist via a regional pharmacovigilance centre. PS used to treat a virus infection with 1 x 20 drops daily from February 26 to March 1, 2011 when high liver values (ALT 712 U/L, AST 700 U/L) were found. There was a massive peak on March 2, 2011 (ALT 2385 U/L, AST 4072 U/L) with decreased values on March 4, 2011 (ALT 1,813 U/L, AST 1,251 U/L). There is lack of the further course of ALT and lack of ALP values). Comedication consisted of Olanzapine, Valproic acid, Carbamazepine, Cardioaspirin, Lansoprazole, Potassium Canrenone, Euthyrox, Furosemid, and Allopurinol, and most of these drugs are considered potentially hepatotoxic. Comorbidity included congenital heart disease, oligophrenia, and epilepsy. There was no exclusion of any form of hepatitis, genetic and autoimmune liver diseases. Final diagnoses: Preexisting liver disease; hepatotoxicity by comedicated drug(s), cardiac hepatopathy. Causality: Excluded causality with respect to PS according to CIOMS criteria. Comment: Poorly documented, basically not assessable case. Lack of exclusion of hepatitis A-C and E, CMV, EBV, HSV, VZV, and autoimmune liver diseases. Biliary diseases not excluded by hepatobiliary sonography. Short-term use of PS for 4 days with one third of the recommended daily dose.
13	Schwabe 2011090801 81 years Male Germany	<ul style="list-style-type: none"> Details: Report via database of arznei-telegramm. No details apart from brand name reported with respect to PS use. Upper respiratory infection. C-reactive protein 6.5 x the upper normal value, ALT and γ-GT slightly increased without actual values. No other details available. Final diagnosis: Bacterial infection of the upper respiratory tract with liver involvement. Causality: Excluded causality with respect to PS according to CIOMS criteria. Comment: Basically unassessable case.

Individual data were presented for each patient (n = 13) with primarily suspected liver injury by the use of the herb *Pelargonium sidoides* (PS). For details see the headings of Material and methods. Causality for PS was evaluated by the use of the original and updated CIOMS scale with identical results. The cases 01-06 refer to BfArM, case 07 to WHO, and cases 08-13 to the manufacturer Dr. Schwabe. AIH: autoimmune hepatitis. ALP: alkaline phosphatase. ALT: alanine aminotransferase. AMA: anti mitochondrial antibodies. ANA: anti nuclear antibodies. ANCA: antineutrophil cytoplasm antibodies. AST: aspartate aminotransferase. BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (German regulatory agency). CIOMS: Council for International Organizations of Medical Sciences. CMV: cytomegalovirus. COPD: chronic obstructive pulmonary disease. CRP: C-reactive protein. EBV: Epstein Barr virus. γ -GT: γ -glutamyltranspeptidase. HCV: hepatitis C virus. HEV: hepatitis E virus. HSV: herpes simplex virus. LKM: liver kidney microsomes. NSAID: non-steroidal anti-inflammatory drug. PCR: polymerase chain reaction. PS: *Pelargonium sidoides*. SMA: smooth muscle antibodies. VZV: varicella zoster virus. WHO: World Health Organization.

Table 2. Overview of known information regarding all 13 cases with primarily suspected *Pelargonium sidoides* (PS) hepatotoxicity.

Presented information	Cases	Individual cases
Brand name	13/13	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
Manufacturer	13/13	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PS as a drug	13/13	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PS as an undetermined product	0/13	-
PS as a polyherbal product	0/13	-
Daily dose	09/13	1, 2, 3, 5, 6, 8, 9, 11, 12
Exact date of PS start	07/13	1, 2, 5, 6, 9, 11, 12
Exact date of PS end	09/13	1, 2, 3, 4, 5, 6, 9, 11, 12
Exact date of symptoms	10/13	1, 2, 3, 4, 5, 6, 7, 9, 11, 12
Time on PS	07/13	1, 2, 5, 6, 9, 11, 12
Time to onset	06/13	1, 2, 5, 6, 9, 12
Temporal association	05/13	1, 2, 3, 9, 12
ALT value	07/13	1, 2, 3, 4, 5, 7, 11, 12
ALT dechallenge	06/13	1, 3, 4, 7, 11, 12
ALT normalization	0/13	-
ALP value	05/13	1, 3, 5, 7, 11
Laboratory criteria for hepatotoxicity	08/13	1, 2, 3, 4, 5, 7, 11, 12
Laboratory hepatotoxicity pattern	05/13	1, 3, 5, 7, 11
Biliary tract imaging	05/13	3, 4, 5, 7, 11
HAV	04/13	1, 3, 5, 7
HBV	05/13	1, 3, 4, 5, 7
HCV	05/13	1, 3, 4, 5, 7
HEV	02/13	5, 7
CMV	02/13	5, 7
EBV	03/13	4, 5, 7
HSV	01/13	5
VZV	0/13	-
Comedicated synthetic drug(s)	09/13	1, 2, 3, 4, 5, 8, 9, 11, 12
Comedicated herbal drugs	1/13	1
Comedicated herbal supplements	0/13	-
Comedicated dietary supplements	0/13	-

Analysis of 13 cases with primarily assumed hepatotoxicity with additional data as described in table 1. Time to onset indicates time to symptoms, alternatively to abnormal liver tests.

ALP: alkaline phosphatase. ALT: alanine aminotransferase. CMV: cytomegalovirus. EBV: Epstein Barr virus. HAV: hepatitis A virus. HBV: hepatitis B virus. HCV: hepatitis C virus. HEV: hepatitis E virus. HSV: herpes simplex virus. PS: *Pelargonium sidoides*. VZV: varicella zoster virus.

simplex virus was provided for 3 or less patients and was lacking in the remaining cases. In none of the cases infections by varicella zoster virus have been ruled out. Because common forms of hepatitis have not been ruled out in 8 or more cases, data quality is considered low.

Disease classification and pattern

Criteria for hepatotoxicity as a disease requiring ALT and/or ALP values of at least $2 \times N$ were fulfilled in 8 out of 13 patients but not in the remaining 5 patients (Table 2). In these 5 cases uncertainty prevails whether hepatotoxicity as a well defined liver disease really exists.

Both ALT and ALP as required criteria for assessing the hepatotoxicity pattern were provided in 5 cases (Table 2). Since these criteria were only rare-

ly available (Tables 1 and 2), clear laboratory differentiation to assess the pattern of liver injury was not feasible. Criteria for the pattern of liver injury in these 5 patients showed a hepatocellular pattern of injury; it was assumed, on grounds of practicability, that this form prevailed in all other cases to facilitate causality assessment.

Causality assessment

With the updated CIOMS scale applicable to the hepatocellular type of liver injury, none of the 13 cases with liver disease had a highly probable or probable causality level for PS (Table 3). In 6 cases causality was excluded and in another 6 cases unlikely. Causality for PS was possible on the basis of the CIOMS items in 1 patient (case 3), but this judgement likely represents a false positive signal in

Table 3. Causality assessment of all 13 patients with primarily suspected *Pelargonium sidoides* (PS) hepatotoxicity.

Less than 4 causes of group I ruled out	-2						-2			-2	-2		
Non drug cause highly probable	-3	-3	-3	-3	-3	-3		-3	-3	-3	-3	-3	
8. Previous information on hepatotoxicity of the drug													
Reaction labelled in the product characteristics	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	
Reaction published but unlabelled	+1												
Reaction unknown	0												
9. Response to readministration													
Doubling of ALT with the drug alone	+3												
Doubling of ALT with the drugs already given at the time of first reaction	+1												
Increase of ALT but less than N in the same conditions as for the first administration	-2												
Other situations	0												
Total points for patient	+02	+01	+04	+02	0	+01	-03	0	+02	0	+02	-01	0

In all 13 patients with primarily suspected *Pelargonium sidoides* (PS) hepatotoxicity, causality assessment for PS was performed with the updated scale of CIOMS (Council for International Organizations of Medical Sciences), considering the items for the hepatocellular type of liver injury as defined previously.^{7,13,15} In the section 6 of concomitant drug(s), the following products were considered: synthetic drugs, dietary supplements including herbal ones, and polyherbal products. In the section 7 (search for non drug causes), the symbol of - denotes that the obtained result was negative and that of + was positive, whereas lack of a symbol indicates that assessment was not performed. All data were also submitted to the original CIOMS scale¹³ and identical results (individual data not shown) were obtained as with the updated CIOMS scale shown in the table above. Details of the cases are also presented in tables 1 and 2, and additional information is provided under the section Material and methods. ALT: alanine aminotransferase. AST: aspartate aminotransferase. HAV: hepatitis A virus. HBc: hepatitis B core. HBV: hepatitis B virus. HCV: hepatitis C virus. CMV: cytomegalovirus. EBV: Epstein Barr virus. HSV: herpes simplex virus. PCR: polymerase chain reaction. VZV: varicella zoster virus. Total points/causality: ≤ 0 = excluded; 1-2 = unlikely; 3-5 = possible; 6-8 = probable; ≥ 9 = highly probable.

face of the established alternative diagnoses of acute pancreatitis and cholangitis. Identical results were obtained for all cases when the original CIOMS scale was applied; this approach established and confirmed the updated CIOMS as a validated scale in comparison to the original CIOMS scale.

Final diagnoses

Despite the low data quality found in most cases and on the basis of clinical judgements, there were numerous diagnoses causally unrelated to the use of PS in the 13 patients analyzed in this study (Table 1). Final alternative diagnoses include a wide variety of diseases including hepatitis associated with virus or bacterial infections, DILI, acute pancreatitis and cholangitis, acute cholecystitis, ANA positive autoimmune hepatitis (AIH) with chronic active hepatitis and preexisting liver cirrhosis, other preexisting liver diseases, and hepatic involvement following lung contusion.

DISCUSSION

Adverse herb reactions are major challenges, both in the clinical and regulatory field,¹⁸⁻²² particularly when suspected cases of HILI are to be consi-

dered.²³⁻²⁶ The present analysis evaluated spontaneous cases of primarily assumed PS hepatotoxicity; in none of the 13 cases evidence was found for an overt hepatotoxic potential causally related with PS use (Tables 1 and 3). These results are in line with conclusions from previous reports on PS in 15 cases¹² and in another case presented by EMA.¹⁰

In the past, lack of hepatotoxicity has also been shown for other herbs such as black cohosh (BC),^{27,28} whereas rare cases of liver injury were reported in connection with the use of kava^{29,30} or Greater Celandine (GC).^{31,32} In all primarily suspected cases associated with the use of PS, BC, kava, and GC, identical methods have been employed, namely the original and updated CIOMS scale. This confirms that different results obtained for all 4 herbs reflect differences in the individual herbal product to potentially cause liver injury rather than differences in the evaluating methods. For other herbs such as Ayurvedic herbs, Chaparral, Chinese herbal mixture, Chinese Jin Bu Huan, Chinese Ma-huang, Chinese Syo-saikoto, Herbalife®, Mistletoe, and Senna, hepatotoxicity has previously been established in most cases by positive reexposure tests.²⁸ Thus, hepatotoxicity may be ascribed to various herbal medications but not to PS.

Pharmacovigilance is confronted not only with common underreporting but also with frequent overreporting, as shown by overt other primary diagnoses and by lack of causality in cases of misattributed DILI^{14,15,27,33-38} and HILI.^{12,16,17,27-32,39,40} Initial positive signals of safety concerns generated at the pharmacovigilance level routinely led to over-reporting of HILI cases, regulatory assessment has often converted these cases into false positive signals;^{27-32,39,40} this conversion likely also applies to the present study with PS, where alternative diagnoses (Table 1) and lack of causality (Tables 1 and 3) have been found for all cases. It is obvious, therefore, that important issues of pharmacovigilance, i.e. confirmation or refusal of false positive signals from spontaneous reports¹ have been neglected both in previous studies and in the present report, calling for advanced strategies to resolve this problem.

Overreporting of HILI cases as a problem of pharmacovigilance may easily be counteracted by three lines of improvements at different levels of the overall assessment approach. Suggestions include first improvements of data quality of cases presented as spontaneous reports and elimination of cases with poor data quality and lack of causality at an early stage of assessment, second professional case assessment by skilled hepatologists with appropriate clinical evaluation and causality attribution methods, and third inclusion of cases into the final database only when causality for the respective herb has clearly been established.

At first, pharmacovigilance will be improved by a close contact with the physician or health care provider reporting a case of HILI. At this initial stage all necessary data have to be acquired, especially essential parameters which have been described in detail for HILI^{7,15,28,41,42} and herb related ADRs in general.⁶ To achieve this, the reporting physician and the pharmacovigilance assessor should have an item check list at hands. Cases with insufficient documentation regarding the herbal product used, the temporal association, and alternative diagnoses thus may be deleted from the regular database but may be collected in a sort of "black box".

Secondly, HILI cases in the data base are to be submitted to a careful causality assessment by expert hepatologists. These specialists evaluate cases item by item, especially with regard to alternative diseases or preexisting liver disease; keeping in mind that alternative diagnoses are frequently found and overlooked^{12,27-32} (Table 1). Incorrect diagnoses may eventually harm the patient if the appropriate therapy is not provided, including possible legal conse-

quences. This evaluating step must involve a validated causality assessment^{15,42} such as the scale of CIOMS in its original form¹³ or its updated variety.¹⁵ These two CIOMS scales represent structured and quantitative causality assessments for hepatotoxicity validated to assess suspected HILI and DILI.¹³⁻¹⁵ They were successfully applied to various settings like epidemiological studies, clinical trials, case reports, case series, regulatory analyses, and genotyping studies.⁴³ Overall, the CIOMS scales represent reliable and reproducible tools, providing objective assessment of complex cases and complete evaluation of the parameters that need to be addressed in cases of suspected HILI.^{13,15,43} By this approach, data analysis will be improved and made more consistent. Not recommended under any circumstances, but strongly refuted for causality assessment are methods^{16,17,43} such as the global introspection WHO scale⁴⁴ and the Naranjo scale⁴⁵ which are not liver specific and thereby not validated for hepatotoxicity assessment. External peer review by expert hepatologists should be installed for all regulatory reports dealing with spontaneous cases of assumed HILI before submission for publication. All these measures will ensure that HILI cases can reliably be reassessed by outside experts.

Finally, only verified HILI cases for a specific herb should remain in any pharmacovigilance database, not –as currently may be the case– reports with initially suspected HILI including those without proven causality. For reasons of transparency, individual data of all cases in a database should be available to both physicians and scientists. Using this data management, emphasis is put on quality criteria of causality assessment which may yield fewer but well validated cases, rather than on quantity criteria independent of causality level. Under these aspects, quality is more important than quantity, not vice versa.

In conclusion, this study showed lack of hepatotoxicity by PS in an additional 13 spontaneous cases as opposed to the initial suggestion of a toxic potency of PS. Common confounding variables were alternative diagnoses, inaccuracies in data acquisition, and low quality case data. These shortcomings reflect problems related to the pharmacovigilance section, and proposals are made for improvements.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

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