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Review of Suspected Herb-Drug Interactions from Case Reports

by Michelle Morgan

Key Points at a Glance

- Case reports are generally rated as a relatively low level of evidence. The quality of reporting is often not high (e.g. insufficient information provided) for adverse effects and interactions caused by drugs, and this applies to herb-drug interactions (HDIs) as well.
- Assessment is often not standardised and validated tools can assist.
  - DIPS: for drug-drug interactions; developed as an improvement of the Naranjo scale
  - RUCAM: assesses causality where drug- or herb-induced liver injury is suspected
- Published HDIs (2001–August 2017): 49 case reports and two observational studies were reviewed
- Using DIPS to assess HDIs, of the 49 case reports:
  - 8.2% (4) were rated as highly probable (e.g. St John's wort and cyclosporin)
  - 55.1% (27), probable (e.g. Korean ginseng and imatinib, St John's wort and clozapine, green tea and simvastatin)
  - 34.7% (17), possible (e.g. St John's wort and rosuvastatin)
  - 2% (1) doubtful
- Worth remembering that published conclusions of HDIs do not always consider normal herbal practice
  - e.g. in the case involving Ginkgo and sodium aescinate which was rated as probable interaction, Ginkgo was administered by injection
  - plant part and dosage should also be considered
- Cross-sectional study (Israel, medical centre): 458 inpatients used supplements, 7 patients reported adverse effects from herbs/essential oil; assessment of these using DIPS:
  - 4 were rated as probable; 6 were rated as possible
  - experts using a simpler assessment rated these 10 interactions differently: agreed with DIPS assessment for 7 of them
- Prospective study (Korea, hospitals): 313 inpatients: 57 were treated with herbs, 256 were treated with herbs and drugs; liver injury defined by CIOMS laboratory criteria: slight elevations in liver function parameters
  - incidence of induced liver injury: 0% in the herbal group; 2.3% (6) in the herb + drug group
  - RUCAM scores suggest probable causality in 3 patients
  - liver function returned to normal 1 week after modification or cessation of medications

Case reports are generally regarded as low in the hierarchy of evidence for assigning drug interactions. Historically there has been a high degree of variability in the quality of reporting of cases involving adverse events, including drug interactions, partly because there has been no standardised method for reporting.[1] A 2003 descriptive analysis of reports involving highly significant adverse drug events (ADEs) published in English over a 20-year period, found that less than 1% of reporters objectively assessed the probability of the adverse event. All but one journal publishing the most ADE reports did not require such assessment.[2] Assessment of causality using validated tools was usually not done.[1,2] Evaluations in 2013 and 2015 found that although progress had been made in the quality of reporting, more improvement is needed to facilitate better assessment of causality to ensure the information is understandable and relevant to patient care.[3] The same concerns apply to the reporting of suspected herb-drug interactions.

A review conducted in 2018 aimed to assess the causality of published herb-drug interactions (HDIs), using validated tools: Horn's DIPS for general herb-drug interactions and RUCAM for suspected herb-induced liver injury.[4]

In 2007, Horn and colleagues proposed a specific tool for causality assessment of drug-drug interactions by adopting the Naranjo scale as a guide. (The Naranjo tool is not regarded as useful for categorising reactions linked to herb-drug interactions. For example, it was designed to evaluate single-drug adverse reactions not drug-drug interactions[5] and it is not suitable to determine the cause of drug-induced or herb-induced hepatotoxicity, because it is not organ specific and therefore not liver specific.[6]) Horn's Drug Interaction Probability Scale (DIPS) consists of 10 questions. There are three response options for the questions (yes, no, unknown/not applicable) to which a score is assigned. Total DIPS score of greater than 8 is classified as highly probable causation, 5-8 as probable, 2-

4 as possible and a score of less than 2 denotes a doubtful causation. *See Table 1, Appendix*.

RUCAM (Roussel Uclaf Causality Assessment Method) is regarded as a well-established tool for qualitative assessment of causality in cases of suspected drug-induced or herb-induced liver injury. Using RUCAM, the items for assessment are scored between -3 and +3, and the total score for the case can range from +14 to -9 points, with the following causality levels defined: 9 or greater, highly probable; 6–8, probable; 3–5, possible; 1–2, unlikely; 0 or less, excluded.[7]

However, DIPS and RUCAM have not been widely applied to HDIs. Databases of PubMed (Medline), the Cochrane Library and Scopus were searched for publications from January 2001 to August 2017. Full-text articles consisting of 49 case reports and two observational studies were identified. Two independent reviewers conducted causality assessments on the case reports using DIPS.[4]

Of the 49 case reports, 4 (8.2%) were rated as highly probable, 27 (55.1%) as probable, 17 (34.7%) as possible and 1 (2%) as doubtful, based on the total DIPS score. More information for the cases rated with highly probable and probable causality is outlined in Table 2 (Appendix). The information is listed with single herbs presented first, followed by formulae and other substances. Of these 31 cases, only in 9 of them were concomitant drugs not mentioned, the others were taking or using multiple drug medications.[4]

Further details have been obtained from the primary publications.

- At least one of the interactions is not relevant to normal herbal practice. In the interaction between Ginkgo and sodium aescinate, Ginkgo was administered by injection.[8]
- Although the dose of the herb is often not disclosed in the case report, in cases where it is, the dose is usually not considered in the context of normal herbal practice. For example, in the case of tacrolimus and turmeric, the herb was added to food, at approximately "15+ spoonfuls daily" starting roughly 10 days prior to rehospitalisation[9] – the interaction, designated probable, might well occur at such a high dose, will it occur when turmeric is administered at usual doses? In the highly probable interaction with warfarin, the increases INR occurred after "drinking approximately 1.5 quarts (1420 mL) of cranberry juice cocktail daily for 2 days" and subsequently, "after drinking approximately 2 quarts (1893 mL) of cranberry juice cocktail daily for 3-4 days".[10] This is quite a high dose in comparison to normal therapeutic doses.
- Many, if not all of these cases, were self-medicating. The prickly pear interaction could have been anticipated and well managed by health care professionals, as it involved combining a hypoglycaemic herb with hypoglycaemic drugs (affected + concomitant drugs).[11]
- The review also does not consider the plant part used, for example, the potential interaction, rated as possible (score: 3), between myrrh and warfarin, involved the use of "aqueous extract of the boiled roots" of *Commiphora molmol* (which is used in Arab societies traditionally as an antidiabetic)[12] rather than the part used in western herbal medicine, the gum resin.

The authors noted that published case reports often provide inadequate information to draw meaningful conclusions, and that appropriate causality assessment would strengthen this endeavour.[4]

A cross-sectional study of 927 patients hospitalised in a medical centre in Israel evaluated the use of supplements among inpatients, the potential for interactions, and actual adverse events during hospitalisation associated with their use. Of these patients, 458 reported using supplements. Seventeen patients reported adverse effects associated with the use of herbal and other supplements (25 effects in total). Eight effects involved a single herb (including linseed/flaxseed (2)) and another involved sage herb plus peppermint oil. The remainder involved other substances (such as fish oil, vitamin D). The adverse reactions were classified by DIPS score. Interactions occurred more frequently in older patients, those with ophthalmologic or gastrointestinal comorbidities, and those using higher numbers of supplements or drugs. Additional details are provided by the primary publication.[4,13]

To be included in the study, the supplements had to have been used in the week preceding hospitalisation. There do not appear to be concomitant drugs involved in these cases (i.e. the interaction potentially occurred between supplement and affected drug). The interactions involving herbs/essential oil are listed below. These adverse effects occurred in 7 patients, with two patients taking multiple herbal and other supplements, but each potential interaction was assessed separately, with 4 interactions rated as probable and 6 as possible:

- green tea and digoxin (score 3, i.e. possible interaction);
- turmeric and clopidogrel (score 5, i.e. probable);
- sage and methadone (score 3, i.e. possible);
- sage and simvastatin; peppermint oil and simvastatin (both score 3, i.e. possibles);
- flaxseed and aspirin (score 5, i.e. probable);
- psyllium and antihypertensive drugs (score 3, i.e. possible); there were other potential interactions noted in this patient (involving fish oil);
- flaxseed and warfarin (score 6, i.e. probable); chamomile and warfarin (score 3, i.e. possible); sage and warfarin (score 3, i.e. probable); there were other

potential interactions noted in this patient (involving fish oil).

Interestingly, the authors of the cross-sectional study presented the cases to three experts in clinical pharmacology. They evaluated causality using a simple scale of 1–5 (definitely not, probably not, possibly, probably, definitely). Of these 10 potential interactions the experts agreed with the DIPS causality assessment in 7 and disagreed with three:[13]

- two cases were rated higher (probable rather than possible);
- one case was rated lower (possible rather than probable).

In the prospective study of 313 inpatients who were hospitalised in two Korean hospitals from August 2008 to October 2010, 57 patients were treated with herbs alone and 256 patients were treated with herbs and drugs. All patients were given liver and renal function tests at the start of hospitalisation and at approximately 2-week intervals thereafter, until discharge. All patients received traditional herbal formulae as a decoction containing 6 to 13 herbs. The median hospital stay was 26 days for the whole group. Herbal treatment was changed according to the patients' symptoms and traditional practice. The incidence of induced liver injury was 0% in the herbal group and 2.3% in those who had received a combination of herbs and drugs. These 6 patients showed abnormal liver function without related clinical symptoms.[4,14]

Liver injury was judged according to CIOMS laboratory criteria, and determined when one of the following criteria was satisfied: (1) direct bilirubin level of more than twice the upper limit of normal (ULN); (2) ALT (alanine aminotransferase) level of more than twice the ULN; or (3) total bilirubin, AST (aspartate aminotransferase), or ALP (alkaline phosphatase) level of more than twice the ULN plus another of these parameters at levels above the ULN. The liver function parameters were only slightly elevated. Four of the 6 patients were admitted to hospital with cerebral infarction, one had subdural haematoma and the other, Bell's palsy.[14]

After slight modification or cessation of medications in the 6 patients, their liver function profiles returned to normal within one week. RUCAM scores were derived for the 'drugs' taken by the patients:[14]

- patient 1: cefuroxime (6), paracetamol/acetaminophen (6), diclofenac (6)
- patient 2: sarpogrelate (0), Actobacillus (Lactobacillus?: 0)
- patient 3: prednisolone (3)
- patient 4: paracetamol/acetaminophen (7), diclofenac (7), aspirin (7), clopidogrel (7), rebamipide (5)
- patient 5: roxoprofen (6), baclofen (6), cimetidine (6)
- patient 6: amoxicillin (4), serratiopeptidase (4)

Given that no adverse hepatic effects occurred in those treated only with herbs, this suggests that the herb-drug combinations were the probable cause of the liver injury in 3 patients. In two patients the adverse effect was the possible result of the combination. The adverse effect in the remaining patient may have been caused by the herbal formula alone, as no relationship was found for the drugs (scores of 0), or there was another cause.

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Appendix

Directions:
- ☐ Circle the appropriate answer for each question, and add up the total score.
- ☐ Object drug: drug affected by the interaction; Precipitant drug: Drug that causes the interaction.†
- ☐ Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (e.g. no dechallenge; dose not changed etc).

Questions	Yes	No	Unk or NA
1. Are there previous *credible* reports of this interaction in humans?	+1	−1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	−1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	−1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0
5. Did the interaction remit upon dechallenge of the *precipitant* drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)	+1	−2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	−1	0
7. Are there reasonable alternative causes for the event?*	−1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	−1	0
Total Score: > 8: highly probable, 5-8: probable, 2-4: possible, < 2: doubtful			

Table 1. Drug Interaction Probability Scale (DIPS).[5]

Notes: † In the case of herb-drug interactions, the precipitant drug is the herb. * Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (e.g. age, inappropriate doses of object drug). A no answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Substance	Affected Drug	Signs or Symptoms of Suspected Interaction	DIPS Score
Highly Probable			
cranberry juice	warfarin	increased INR	10
goji berry (*Lycium barbarum*)	warfarin	increased INR	9
noni juice	phenytoin	low phenytoin level in blood	9
St John's wort*	cyclosporine	decreased cyclosporine concentration	9
Probable			
betel quid	doxorubicin, cyclophosphamide, paclitaxel	grade IV mucositis, dysuria, mouth pain, and furunculosis.	5
boldo (*Peumus boldus*)	tacrolimus	asymptomatic	6
chamomile tea	cyclosporine	decreased cyclosporine level	7
Ginkgo biloba	efavirenz	increased viral load at 1350 copies/mL	6
Ginkgo§	valproic acid and phenytoin	seizure disorder leading to death while swimming	7
Ginkgo biloba (by injection)	sodium aescinate (by injection)	elevated serum creatinine and BUN levels	5
ginseng (undefined) and deer antler velvet	lamotrigine	DRESS syndrome: pruritic rash, eosinophilia, myalgias, elevated liver enzymes	5
Korean ginseng (*Panax ginseng*)	imatinib	right upper quadrant pain, elevated liver enzymes	5
Korean ginseng (*Panax ginseng*) and vitamins	raltegravir plus lopinavir/ritonavir	generalised pruritus, scratching lesions, increased transaminase, visible jaundiced skin and mucous membranes	6
green tea	simvastatin	elevated liver enzymes, increase simvastatin lactone levels	7
goji juice (Himalayan)	warfarin	ecchymosis, epistaxis, and one episode of haematochezia, elevated INR	7
Lycium barbarum (fruit; concentrated tea)	warfarin	elevated INR	6
prickly pear cactus	glipizide	hypoglycaemic	8
St John's wort	warfarin	upper gastrointestinal bleeding, increased INR	6
St John's wort	clozapine	increased disorganisation and tension	6
turmeric (*Curcuma longa*)	tacrolimus	abdominal distention, scrotal and peripheral oedema, increased creatinine	7
boldo-fenugreek	warfarin	increased bleeding time	5
Bu Zhong Yi Qi Wan	temozolomide	grade II thrombopaenia and elevated liver enzymes	5
ginseng, *Fomes fomentarius*, *Inonotus obliquus*, *Phellinus linteus*	gefitinib	increased shortness of breath	5
Quilinggao	warfarin	gum bleeding and epistaxis, elevated INR	5
multiple products†	sertraline	moderate and severe depression	6
arejin and daiokanzo-to	enalapril	mild anaemia, liver dysfunction, mildly elevated CK level, and severe hypokalaemia and hypochloraemia	7
Sheng Mai-yin	warfarin	consciousness disturbance – right hemiplegia and active pupils, increased INR	8
Efamol,‡ *Rheum frangula* tablets and colayur syrup (laxative)	lopinavir, ritonavir	diarrhoea, toxic lopinavir plasma level	8
diosmin	trabectedin	rhabdomyolysis, increase serum myoglobin, creatinine phosphokinase and liver function	5
sweet clover supplement^ and lutein supplement	interferon β-1b	jaundiced palms, elevated ALT, periventricular and juxtacortical hyperintense signal lesions	5
bee pollen granules	warfarin	elevated INR	5

Table 2. Case reports of herb-drug interactions assessed as having highly probable or probable causality using DIPS.

Abbreviations: ALT: alanine transaminase; BUN: blood, urea and nitrogen; CK: creatine kinase; DIPS: Drug Interaction Probability Scale; DRESS: drug reaction with eosinophilia and systemic symptoms; INR: international normalised ratio

Notes: * herbal tea mixture containing St John's wort[15] § patient was "self-medicating with a cornucopia of herbal supplements and nutraceuticals, prominent among which was ginkgo biloba"[16] † Arthritis QR, Cholesterol QR, Triphala churna, Yogaraja Guggulu, Mentat, Rumalaya, Decoction-1, Decoction-2 ‡ based on the brand name: contains evening primrose oil, rich in gamma-linolenic acid ^ supplement containing coumarin at 10 mg/day, noted as twice the recommended daily dose[17]