

Interferences of herbal medicines in therapeutic drug monitoring

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Scope of the lecture:

This lecture describes the occurrence, implications and possible solutions to the interferences of herbal medicines (mainly cardiac glycosides) in the therapeutic drug monitoring (TDM) of digoxin. A multidisciplinary team, supported by the therapeutics and toxicology laboratory, plays an important role in identifying and preventing adverse herb-drug interactions, while meeting the challenges for new knowledge on potentially beneficial and harmful interactions in diseases of increasing importance.

Learning objectives:

1. Know the widely accessible herbal medicines that can interfere in the immunoassays used for TDM of digoxin
2. Understand the possible determinants and clinical implications of such interactions
3. Appreciate the importance of a multidisciplinary team approach, with the support of the therapeutics and toxicology laboratory
4. Realise the extended roles of TDM and the challenges in assessing any potential benefits versus risks of herb-drug interactions

Extended abstract:

During the concurrent use of herbal medicines and drugs, adverse herb-drug interactions are more likely to be clinically important when potent herbs, narrow therapeutic index drugs (e.g. cyclosporine, digoxin, warfarin, lithium, theophylline and phenytoin) and prolonged use are involved. These adverse events can largely be explained on the basis of pharmacokinetic and pharmacodynamic interactions between herbs and drugs. Very rarely, herbal toxicity develops due to the presence of digitalis or digoxin-like compounds as contaminants or foreign matters. This should be strongly suspected if clinical features of cardiac glycoside poisoning and toxic serum digoxin concentrations occur even though related preparations have not been taken. In addition, herbal medicines containing cardiac glycosides or structurally similar compounds can interfere in the TDM of digoxin.

Digoxin remains widely used globally for its negative chronotropic effect in the rate control of atrial fibrillation and as a positive (albeit weak) inotrope in heart failure. The optimal use of digoxin to maintain therapeutic serum drug concentrations is challenging since the patients are typically elderly with multiple comorbidities, impaired renal function and polypharmacy. Toxicity occurs because of elevated serum digoxin concentrations, electrolyte disturbances (hypokalaemia and hypomagnesaemia) and drug-digoxin, herb-digoxin and digoxin-diseases (e.g. hypothyroidism and heart block) interactions.

TDM is essential in the effective use of digoxin, particularly when toxicity, therapeutic failure, patient compliance and reduced drug clearance in renal failure are a concern. Immunoassays, commonly used for this purpose in hospital laboratories, are susceptible to interferences from endogenous digoxin-like immunoreactive substances (elevated in renal failure, liver disease and other volume-expanded conditions), spironolactone and potassium canrenoate and their metabolite (canrenone), digoxin metabolites, anti-digoxin Fab, and other cardiac glycosides, particularly bufalin in Chan Su and related herbal medicines (Lu Shen Wan and Kyushin).

Herbal medicines rich in cardiac glycosides are widely used in traditional materia medica and folk medicine. Cardiac glycosides are classified as cardenolides (with a 5-membered lactone ring) or bufadienolides (with a 6-membered lactone ring). Most cardenolides are derived from plants – for example, digoxin and digitoxin from the *Digitalis* genus (foxgloves), thevetin A, thevetin B, neriifolin and peruvoside from *Thevetia peruviana* (yellow oleander), oleandrin from *Nerium oleander* (common oleander), convallotoxin from *Convallaria majalis* (lily of the valley) and asclepin from *Asclepias curassavica* (milkweed). Bufadienolides are found in certain animals and plants and are particularly widespread in the *Bufo* family (toads). In traditional Chinese medicine, Chan Su (derived from the venom of *Bufo bufo gargarizans* or *B. melanostictus*) is well known for its medicinal uses and the rich sources of bufadienolides and the more polar conjugates, the bufotoxins. Various products derived from post-collection processing will also be present in Chan Su.

Due to the structural similarity to digoxin, cardiac glycosides in herbal medicines cross-react with antibodies in digoxin immunoassays. The magnitude of this interference depends on the types of herbal medicines and immunoassays involved. Cardiac glycosides content (measured by an immunoassay as apparent digoxin) is much higher in *B. marino* (cane toad) venom than in *T. peruviana*, *N. oleander*, and *A. curassavica* (320 versus 36, 33, and 89 µg/g). Polyclonal antibody-based digoxin immunoassays are more affected by this interference, compared with specific monoclonal antibody-based immunoassays. After exposures to herbal medicines rich in other cardiac glycosides, falsely higher or lower serum digoxin concentrations may be seen, depending on the assay design, etc. Then, the "measured" serum digoxin concentrations might not correlate well with the clinical effects since they largely reflect uncertain proportions of digoxin and other cardiac glycosides with differing potency and cross-reactivity.

Other herbal medicines (non-cardiac glycosides) may also interfere in digoxin immunoassays, depending on the assay methods, etc. Their principle ingredients show structural similarity to digoxin – for example, tanshinones from Danshen (*Salvia miltiorrhiza*), ginsenosides from Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*), and, possibly, epicatechin, chlorogenic acid, isoquercetin and hyperoside in hawthorn (*Crataegus* species).

On the other hand, in patients not taking digoxin but with a history of acute ingestion of other cardiac glycosides, digoxin immunoassays can be used to indirectly confirm such exposures. Cross-reactivity is variable between individual assays, but it provides a convenient means for approximating their serum cardiac glycosides concentrations. However, monoclonal digoxin immunoassays may not have cross-reactivity with non-digoxin cardiac glycosides.

Severe, acute overdoses of digoxin, and other cardiac glycosides, may require treatment with anti-digoxin Fab. Digoxin shows only 25% protein binding. Measurement of the serum free digoxin concentrations is very useful when monitoring the effectiveness of anti-digoxin Fab treatment in these patients. Otherwise, the presence of anti-digoxin Fab, by interfering in the immunoassays, will produce very confusing serum total digoxin concentrations results.

Herb-drug interactions and other potential problems related to the use of herbal medicines are complex, necessitating a multidisciplinary team approach and the support of the therapeutics and toxicology laboratory. Expertise is also needed on risk-benefit assessments of herb-drug interactions in the treatment of important diseases, such as influenza A and atherosclerosis, involving, for example, TCM formulae and Danshen-Gegen (*Pueraria lobata*).

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