Should Herbs Take All the Blame? Causality Assessment of a Serious Thrombocytopenia Event

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Abstract

Background: With the increasing use of herbal medicines, the causality assessment of adverse drug-related reactions becomes more complicated because of the concomitant use of herbs and conventional medications. Epidemiological causal inference can be a central feature of such judgment but may be insufficient. Other scientific considerations include study design, bias, confounding, and measurement issues. The approach of this study is to establish an active safety surveillance system for finished herbal products (FHPs) and to review each adverse event regularly.

Method: A single case of serious thrombocytopenia was found in 136 subjects taking FHPs on a clinical trial for 12 weeks, for which the cause was sought.

Results: Because at the end of the first month the patient's platelet counts were normal and the thrombocytopenia developed after the co-medication with conventional drugs, it was suspected that the thrombocytopenia might not be attributed to the use of FHP.

Conclusions: This report summarizes the criteria of causality assessment under mixed use of herbs and conventional medicine and recommends a feasible process for careful evaluation of adverse drug reactions related to all herbal medicine.

Introduction

THE OCCURRENCE OF ADVERSE DRUG-RELATED events (ADRs) among herbal users has been progressively documented and reviewed.^{1–6} When both conventional and herbal medicines are available to lay people, there seems a tendency for them to be used concomitantly.^{7,8} Thus, based upon the current understanding of each single herb, along with their known interactions with conventional types of medication, it would seem inappropriate to infer the net effects of a mixed herbal regimen.⁹ Public health professionals, therefore, do not have the luxury of waiting for progress; rather, public health professionals involved in herbal medicine have a moral obligation to consider the need for herbal safety recommendations, given the available evidence.

Herbal safety recommendations cannot easily be separated from causal conclusions, which are a form of scientific statement that emerges from the application of criteria-based

inferential methods. At a minimum, the set of criteria includes temporality, consistency, strength of association, dose response, and plausibility. The current practice, methods, and theory of causal inference in this case report permit flexibility in the choice of criteria, their relative priority, and the rules of inference assigned to them, which mostly follow the World Health Organization global introspection method.¹⁰

Finished herbal products (FHPs) were concentrated herbal extracts manufactured from one or more herbs into granular forms by pharmaceutical companies. Such a dosage form of FHPs is generally very convenient for patients in Korea, China, Japan, and Taiwan as traditional medicine, and for consumers in the United States as health foods or over the counter drugs. As a supplement to the current pharmacovigilance methods for the use of FHPs or for compounds of these products used in traditional Chinese herbal medicine (TCHM), we established an active safety surveillance system

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that followed the principles of good clinical practice, and then carried out periodic evaluation of the patients for signs of any adverse events. To test the feasibility of the system, we first applied it to the evaluation of the safety and efficacy, in women in the climacteric, of a combination of three TCHM formulae, referred to as “TMN-1” and comprising 21 constituents (Table 1). After gaining the formal approval of the Joint Institutional Review Board, this study was carried out at four sites, where 136 subjects were recruited to take the medication; follow-up of the study subjects was then undertaken for a period of 12 weeks.¹¹

During the study period, there was an isolated occurrence of a serious adverse event (SAE)—acute thrombocytopenia. This article describes how causal criteria are used to help meet the challenge of making herbal safety recommendations in the face of complex scientific evidence.

Case Report

A 52-year-old woman, whose last menstrual period was in March 2004, was recruited into this study on June 6, 2004. She was afflicted with perimenopausal symptoms, including hot flashes, sweating, and irregular menstrual cycle, and had been seeking alternative medication to improve her symptoms. She had been taking TMN-1 3 times a day without any complaints until she discovered gingival bleeding (on the 55th day), which was instantly reported to the study nurse. The patient was required to return immediately to the study site to undergo a careful and thorough examination.

The investigator at the study site found that the woman had numerous petechiae and ecchymoses over her bilateral shoulders, forearms, palms, and thighs. Her complete blood count showed white blood cell count 3700/mm³, red blood cell count 4,150,000/mm³, hemoglobin 12.6 mg/dL, and platelets 2000/mm³. Her vital signs were within the normal range and she had no palpable hepatosplenomegaly or lymphadenopathy. The patient was immediately referred to a nearby medical center where her low platelet count (3000/mm³) was verified. Given that her platelet count on the 28th day after medication had been 254,000/mm³, a diagnosis of acute thrombocytopenia was made and she immediately received 12 units of platelet transfusion.

Since her platelet count had returned to 99,000/mm³ by the following day, following consultation with a hematologist, she was subsequently discharged. As a result of the occurrence of this SAE, the patient was instructed to stop taking all medications (prescribed or otherwise) and dietary

supplements. In her two subsequent follow-up visits, 1 week and 1 month after the SAE, she showed consistently normal platelet counts. The question that therefore arises from this SAE was whether the FHP should take all the blame, or whether some of the blame should be apportioned to TMN-1. During the process of looking for all possible causative agents, we found that there were concomitant uses of conventional medicines and other folk herbs before the occurrence of this SAE. We therefore pursued further details.

Assessment of the Causality of the SAE

Based upon ethical considerations, we did not rechallenge the patient with TMN-1, nor did we conduct any laboratory studies with any of the suspected drugs (including drug–drug or drug–herb combinations).

Despite Hill’s criteria having first been proposed in the 1960s, different authors have proposed and emphasized different criteria of causality inference.^{12–15} From a refutational point of view, proposing necessary criteria can reduce the difficulty of determining causality, as such criteria will allow one to rule out other possible causal relationships. We proposed to prioritize causal criteria for herbal users, as follows:

The Only Necessary Causal Criteria: Temporality

Recently published epidemiology textbooks^{16,17} seem to regard “temporality” as the only necessary criterion, with all others being generally regarded as incrementally adding credibility to the inference of causality.

The SAE (platelet levels 3000/mm³) occurred in this patient after she had been taking TMN-1 for a period of 54 days (having consumed 147 sachets). Prior to the event, her platelet counts had been checked both before taking the drugs and at the 28th day of the trial: Her platelet levels were 241,000/mm³ at the outset, and 254,000/mm³ at the 4-week point (when she had consumed 58 sachets). By definition of temporality, TMN-1 taking should precede this SAE, and a universal law of nature should remain in other participants, other clinical settings, and other time during the study period. To apply the criteria in this case, we must also take the minimal induction time and maximal latency period for TMN-1 to produce acute thrombocytopenia into consideration. For most participants who completed the trial, they had consumed TMN-1 with higher dose level and had exposed to the study drug with longer time period than the

TABLE 1. CONSTITUENTS OF TMN-1

<i>Angelica sinensis</i> (Oliv.) Diels (<i>dong quai</i>)	<i>Rehmannia glutinosa</i> Libosch. (Chinese foxglove)
<i>Atractylodes macrocephala</i> Koidez. (<i>bai zhu</i>)	<i>Cornus officinalis</i> Sieb. et Zucc. (Japanese cornel)
<i>Paeonia lactiflora</i> Pall. (garden peony)	<i>Dioscorea opposita</i> Thunb. (Chinese yam)
<i>Bupleurum chinense</i> DC. (<i>chai hu</i>)	<i>Alisma orientalis</i> Juzep. (water plantain)
<i>Poria cocos</i> (Schw.) Wolf (<i>poria</i>)	<i>Anemarrhena asphodeloides</i> Bge. (<i>zhi mu</i>)
<i>Glycyrrhiza uralensis</i> Fisch. (licorice root)	<i>Phellodendron chinense</i> Schneid (Chinese corktree)
<i>Paeonia suffruticosa</i> Andr. (tree peony)	<i>Panax ginseng</i> C. A. Meyer (ginseng)
<i>Gardenia jasminoides</i> Ellis (gardenia)	<i>Citrus reticulata</i> Blanco (tangerine)
<i>Zingiber officinale</i> Rosc. (ginger)	<i>Pinellia ternata</i> (Thunb.) Breit. (<i>ban xia</i>)
<i>Mentha haplocalyx</i> Briq. (corn mint)	<i>Amomum villosum</i> Lour. (cardamom seed)
<i>Aucklandia lappa</i> Decne. (<i>yunmuxiang</i>)	

TMN-1, combination of three traditional Chinese herbal medicine formulae.

SAE women. In addition, because the patient's platelet count remained almost the same level both before entering the trial and after taking 4 weeks of TMN-1. We could exclude the possibility for its long latency the thrombocytopenia is already present and processing at the time the SAE occurred after taking 4-week TMN-1. It therefore seemed extremely unlikely that the TMN-1 alone could have induced such acute thrombocytopenia in the patient.

Traditionally, one might apply the induction method to propose that TMN-1 was the cause of acute thrombocytopenia after observing this event. It is also known that one cannot easily prove a causality such as A causes B. However, a hypothesis can be refuted or proven to be false. For this case, the search for truth and causal mechanism is not end; the process of conjecture and refutation should continue indefinitely. However, the temporal conclusion can still be drawn that the study drug would be unlikely to induce acute thrombocytopenia alone.

Causal Criteria:

Consistency of Association

The principle of consistency stipulated that a natural law guarantees that everyone will share a similar response profile from exposure to a specific toxic substance. A causal relationship can be found consistently under different times, participants, and settings. After careful review, among the 21 constituents of TMN-1 (Table 1), *Angelica sinensis* (*dong quai*) was once reported to have interacted with warfarin to cause prolonged thrombin time¹⁸; however, since none of the remaining constituents in TMN-1 has ever been reported to have any association with thrombocytopenia, the likelihood of the delayed effect described above would be very low. In addition, all participants were monitored carefully throughout the period of this trial. There was 1 participant who had an initial abnormal platelet count; however, this was attributed to her pre-existing diagnosis of von Willebrand disease, type I. This patient's platelet levels did not show any significant reduction during the study period, which might have been attributable to TMN-1. Her platelet levels were 114,000/mm³ at baseline, 64,000/mm³ 4 weeks after first taking TMN-1, and 82,000/mm³ at the 12-week point of the trial. Thus, there was not a consistent response of thrombocytopenia to TMN-1 among any other subjects.

Causal Criteria:

Search for Alternative Explanations

As a result of a detailed inquiry into the history of the patient with SAE, it was found that she had intermittently taken diclofenac, chlorzoxazone, and oxetacaine tablets for her shoulder pain, beginning on the 11th day of the TMN-1 medication, with the total dosage being five tablets of each prior to the SAE. In addition, the patient disclosed that, at about the 5- to 11-day period prior to the SAE, she had occasionally consumed *Moringa oleifera* tea. The tea was usually prepared by brewing about 5 g of *M. oleifera* tea leaves in 500 cm³ of hot water, of which she drank about 100–200 cm³. However, there were no similar symptoms among any of her family members who drank more of this beverage than she did.

Most importantly, we discovered that 4 days prior to the occurrence of the SAE, the patient had been taking continuous prescribed doses of acetaminophen, mefenamic, and

chlorpheniramine for a sore throat condition. Given that all of these drugs had once been reported to have caused, or to have been associated with, thrombocytopenia,^{19–29} they were immediately suspected as the major alternative hypotheses.

Drug-induced thrombocytopenia is, however, a rare untoward medical occurrence,¹⁹ which is difficult to verify because of the diverse clinical pictures produced by various specific immunological platelet interactions.³⁰ Clearly, therefore, the most important measure in determining the causal agent—the prompt withdrawal of the suspected drug²⁴—does not seem feasible when multiple drugs (drug–drug and drug–herb interactions) are being used concomitantly.

Discussion

It is our view that when criteria are used in causal inference for the purpose of making herbal safety recommendations, no single criteria (of these five: consistency, strength of association, dose response, biologic plausibility, and temporality) is absolutely critical or absolutely irrelevant. We therefore conclude that, in the vast majority of situations, the criteria of causality assessment summarized in this report may be a feasible process for careful evaluation of adverse drug reactions related to all herbal medicine, namely, with appropriate temporality as the necessary criterion, followed by consistency of association and ruling out all alternative explanations.

Our establishment of an active safety system, within which we adopted a prospective observational method of monitoring subjects' untoward reactions, was aimed at providing a supplement for many of the drawbacks noted above. We believe that it is quite feasible for the detection of symptoms or signs for most, if not every, adverse event to be achieved as a result of the close cooperation between investigators trained in both conventional and Chinese medicine, along with the periodic monitoring of patients.

Taking this event as an example, the subject herself did not consider the gingival bleeding as abnormal, and regarded the petechiae and ecchymoses as ordinary signs of contusion injury. She even showed some signs of hesitation toward her proposed admission into intensive care, despite having already been informed of her low platelet counts. Nevertheless, following our emergency management, the patient is now fully aware that she may be susceptible to acetaminophen, mefenamic, or chlorpheniramine, and she is also aware that she must be careful to avoid these medications for the rest of her life.

Within our safety system, the active surveillance of the patient's platelet counts provided us with an opportunity to exclude the possibility that herbs alone were the cause of this SAE; we found that this was in fact related to the subject's co-medication with conventional drugs. Such a combined approach to the consensual assessment of causality of this event would appear to have made the conclusion of this case much more objective and reliable.

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