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The Five-Herb Medication XueBiJing is highly Pharmacokinetically Compatible with Antibiotics Used in Sepsis Treatment

Chen Cheng*

Department of Drug Research, Shanghai Institute of Matera Medica, China

Abstract

Managing the deregulated host response to infection remains a major challenge in sepsis care. Chinese treatment guideline recommends adding XueBiJing, a five-herb medicine, to antibiotic-based sepsis care. Although adding XueBiJing further reduced 28-day mortality via modulating the host response, pharmacokinetic herb–drug interaction is a widely recognized issue that needs to be studied. Building on our earlier systematic chemical and human pharmacokinetic investigations of XueBiJing, we evaluated the degree of pharmacokinetic compatibility for XueBiJing/antibiotic combination based on mechanistic evidence of interaction risk. Considering both XueBiJing–antibiotic and antibiotic–XueBiJing interaction potential, we integrated informatics-based approach with experimental approach and developed a compound pair-based method for data processing [1]. To reflect clinical reality, we selected for study XueBiJing compounds bioavailable for drug interactions and 45 antibiotics commonly used in sepsis care in China. Based on the data of interacting with drug metabolizing enzymes and transporters, no XueBiJing compound could pair, as perpetrator, with the antibiotics, organic anion transporters 1/2 and/or organic anion-transporting polypeptide 1B3, pair with senkyunolide I, tanshinol and salvianolic acid B, the potential interactions (resulting in increased exposure) are likely desirable due to these XueBiJing compounds' low baseline exposure levels. Inhibition of aldehyde dehydrogenase by 7 antibiotics probably results in undesirable reduction of exposure to protocatechuic acid from XueBiJing. Collectively, XueBiJing/antibiotic combination exhibited a high degree of pharmacokinetic compatibility at clinically relevant doses. The methodology developed can be applied to investigate other drug combinations [2].

Keywords: XueBiJing; Antibiotic; Combination drug therapy; Sepsis; Pharmacokinetic compatibility

Introduction

Drugs in a combination drug therapy, particularly for multifactorial diseases, can have distinct mechanisms of action and exert enhanced pharmacodynamics effect. To ensure such therapeutic benefit, a high degree of pharmacokinetic compatibility (PKC) is desired among the co-administered drugs; PKC is defined as absence of unintentional or unmanageable pharmacokinetic (PK) drug interaction that can lead to decreased drug efficacy or increased drug toxicity.

Sepsis is life-threatening organ dysfunction caused by a deregulated host response to infection4. Because infection caused by pathogens is the triggering event in sepsis, prompt initiation of appropriate antibiotic therapies to eradicate the pathogens is a cornerstone of sepsis care. However, even after successful treatment of the primary infection, the host response often remains deregulated, and organ dysfunction and unwanted clinical outcome may occur. Hence, attenuating the host response is also important. Although substantial developments have been made in understanding the pathophysiology of the host response, which is characterized by overabundant innate immune, uncontrolled release of inflammatory mediators, inefficient use of the complement system, coagulation abnormalities, endothelial capillary leakage syndrome, immunosuppression and organ dysfunction the search for pharmacotherapies to modulate the host response has been unsuccessful. XueBiJing is the only medicine approved (2004) by the Chinese National Medical Products Administration (NMPA, formerly China Food and Drug Administration) specifically for treatment of sepsis and multiple organ dysfunction syndrome [3]. It is a standardized intravenous injection, which is prepared from a five-herb combination, comprising Carthamus tinctorius flowers (Honghua in Chinese), Paeonia lactiflora roots (Chishao), Ligusticum chuanxiong rhizomes (Chuanxiong), Angelica sinensis roots (Danggui) and Salvia miltiorrhiza roots (Danshen); the manufacturing procedure for XueBiJing is described in Supporting Information. Chinese treatment guideline for sepsis care and expert consensuses on sepsis care recommend adding XueBiJing to antibiotic-based sepsis care. It has been shown that adding XueBiJing to the conventional sepsis care further reduces patients' 28-day mortality and incidence of complications, improves their APCHE II scores and prognosis and shortens their stay in the ICU, with low incidence of side effects [4].

Materials and Method

Study Methods

This study was designed to provide comprehensive insight into the degree of PKC between the five-herb medicine XueBiJing and various antibiotics used in sepsis care in China, based on mechanistic evidence of drug interaction risk. Evaluating PKC degree, considering both XueBiJing-antibiotic (XueBiJing as perpetrator and the antibiotic as victim) and antibiotic-XueBiJing (the antibiotic as perpetrator and XueBiJing as victim) interaction potential, requires information on the pharmacokinetics/disposition of XueBiJing and antibiotics and their related drug interaction liabilities. A data processing method is also needed to estimate the degree of PKC and to identify interaction risk in the combination. Data on human pharmacokinetics of compounds,

***Corresponding author:** Chen Cheng, Department of Drug Research, Shanghai Institute of Matera Medica, China, E-mail: Chencheng@gmail.com

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bioavailable for drug interactions, from dosed XueBiJing were obtained from our earlier research on the herbal medicine [5]. Literature mining was performed to identify antibiotics used for sepsis care in China and to obtain information regarding their pharmacokinetics/disposition and drug interaction liabilities, as well as information on interaction liabilities of XueBiJing and related herbal compounds. Due to literature-mined information alone being insufficient, in vitro studies were performed to obtain additional required information on interactions of the XueBiJing compounds, and of the identified antibiotics, with relevant drug metabolizing enzymes and transporters [6]. Data processing was then performed in steps, i.e., pairing the compounds, assessing the desirability of the pair-associated interactions and estimating PKC index for the combination. Low interaction potential indicated by static-mechanistic-model-based investigation usually correlates with low clinical interaction potential, but high interaction potential indicated by such investigation does not necessarily translate to high clinical interaction potential. To this end, only the identified undesirable interactions with high potential would be further investigated by performing dynamic-model-based prediction and, if necessary, relevant clinical studies. [7].

Materials

Hydroxysafflor yellow a (X1), paeoniflorin (X2), oxypaeoniflorin (X3), albiflorin (X4), senkyunolides I (X5) and G (X7), tanshinol (X8), salvianolic acid B (X10), protocatechuic acid (X11), frolic acid (X12) and 45 antibiotics (A1–A45) were obtained commercially. Senkyunolide I-7-O-β-glucuronide (X6) and 3-O-methyltanshinol (X9) were prepared in-house using the method described previously. Purity of the compounds was ≥98%. CDNA-expressed human P450 enzymes, uridine 5′-diphosphoglucuronosyltransferases (UGT), pooled human liver microtomes and pooled human liver cytosols were obtained from Corning Gentlest (Woburn, MA, USA) [8]. Cryopreserved primary human hepatocytes from four donors XSM, HVN, DQB and OMA were obtained from BioreclamationIVT (Baltimore, MD, USA) and human embryonic kidney 293 (HEK-293) cells were obtained from American Type Culture Collection (Manassas, VA, USA). Human solute carrier (SLC) transporter expression plasmids were constructed commercially. Inside-out membrane vesicles [prepared from insect cells expressing human ATP-binding cassette (ABC) transporters] were obtained commercially. Probe substrates and positive inhibitors of test enzymes and transporters and positive inducers of P450 enzymes were also obtained commercially. [9].

Conclusion

Nucleotide analogues play an important role within the treatment of cancer and viruses. Since the rate-limiting step within the formation of triphosphate is conversion of glycoside analogues to its monophosphate, monophosphate organic compound prodrugs of glycoside analogues were designed in an effort to bypass the initial phosphorylation activation step. However, each glycoside analogues and monophosphate organic compound prodrugs of glycoside analogues area unit polar molecules and have restricted membrane porosity. Hence, traverse of viscos animal tissue membrane is usually restricted. Over the past decade, many artistic prodrug methods are utilised to beat these limitations. The examples represented during this review illustrate the numerous analysis efforts done to enhance the oral bioavailability of glycoside analogues. Ancient prodrug approaches by enhancing lipophilicity are applied to enhance passive diffusion. Prodrugs targeted to PepT1 are found terribly helpful for enhancing oral absorption of polar medicine. PepT1 has become a promising target since they're extremely expressed within the bowel with high capability and numerous substrate specificity. Advances in prodrug style have improved the worth of glycoside compounds as metastatic tumor and antiviral agents. The example represented during this article any prove that prodrug approach is an efficient strategy for up oral absorption of glycoside analogues [10].

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