



Centrum für Therapiesicherheit in der Chinesischen Arzneitherapie

Center for Safety of Chinese Herbal Medicine

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C T C A l e t t e r M a y 2 0 1 8

Dangerous cardiac arrhythmias associated with Evodia rutaecarpa?

A report published by the Neue Zürcher Zeitung and the Aargauer Zeitung on May 2, 2018, appears alarming. Researchers from the Universities of Basel and Vienna reportedly identified that the constituents dehydroevodiamine and hortiamine, which occur in relatively high concentrations in the Chinese medicinal plant *Evodia rutaecarpa*, block cardiac potassium channels. Such blockage could potentially induce severe cardiac arrhythmias, including torsades de pointes (TdP) or ventricular fibrillation, thereby leading to sudden cardiac death. Researchers at Utrecht University reportedly confirmed the induction of severe arrhythmias in canine models. *"Sudden cardiac death is insidious and may occur within as little as ten minutes after the onset of TdP arrhythmia,"* stated Steffen Hering of the University of Vienna. *"The precipitating arrhythmia can only be detected by electrocardiography (ECG), and naturally only if the patient reaches the hospital alive. Consequently, it is extremely difficult to retrospectively determine whether sudden cardiac death resulted from such an arrhythmia and whether it was associated with the administration of an Evodia preparation. Therefore, the empirical experience of Traditional Chinese Medicine (TCM), frequently cited by practitioners, cannot be relied upon in the case of Evodia,"* according to Steffen Hering.

The report is based on a recent publication by Baburin et al. (1) in the journal *Pharmacological Research*. The study described findings obtained using a methanolic extract and the isolated compounds dehydroevodiamine and hortiamine in cell-based experiments as well as in rabbit and canine models. The CTCA had already analyzed this publication beforehand and was therefore able to respond to the newspaper articles with a letter to the editor within a matter of hours.

Letter to the editor regarding "Caution is warranted with a substance used in Chinese Medicine," Neue Zürcher Zeitung (NZZ), May 2, 2018

Unwarranted Alarmism

The article raises concerns regarding the Chinese medicinal plant *Evodia rutaecarpa*, suggesting risks that may extend to sudden cardiac death. However, the experimental animal studies cannot be extrapolated to the therapeutic situation in humans for several reasons.

(1) The studies employed either a methanolic extract or isolated purified compounds, which differ substantially from the decoction traditionally used in Traditional Chinese Medicine (TCM).

(2) In Chinese medicine, a mild toxicity of this medicinal plant is recognized; therefore, it undergoes a specific processing procedure intended to reduce toxicity. In its raw form, it is used exclusively for external application.

(3) Extensive clinical experience with *Evodia rutaecarpa* in humans exists within Chinese medicine and spans at least 1,800 years. The herb was already described in the earliest known pharmacopoeia, the *Shennong Bencao Jing*. To the best of our knowledge, serious cardiac arrhythmias have not been observed during its use. The aforementioned researcher, Steffen Hering, argues that sudden cardiac death may occur so rapidly that the underlying cause of death could remain undetected. However, this argument overlooks the expectation that, in a substantially larger number of cases, less severe arrhythmias would be anticipated initially. Since detailed pulse diagnosis constitutes one of the principal diagnostic pillars of Chinese medicine, pulse irregularities or other potentially dangerous arrhythmias would almost certainly have been recognized.

Adverse effects were occasionally not recognized in premodern times when they occurred only after a considerable delay or following chronic use. In the present case, however, the effect under discussion would be expected to occur immediately, and any association with the intake of a medicinal herb would likely have been readily apparent.

A Chinese study (Wang, 2016) systematically reviewed all publications from the previous 30 years concerning adverse effects associated with the category of Chinese medicinal substances to which *Evodia rutaecarpa* belongs, using Chinese databases as well as the U.S. PubMed database. Only two reports of adverse effects related to *Evodia rutaecarpa* were identified. In the first case, the normal dosage range of 1.5–4.5 g had been substantially exceeded, with a dose of 12 g administered. In the second case, an overdose was likewise present, with 6 g administered; additionally, 10 g of an *Aconitum* preparation had been given, a substance known to exert effects on the heart through similar mechanisms. In the first case, moderate adverse effects were observed, including palpitations as the principal cardiac manifestation, while the second case involved bradycardia. To the best of our knowledge, the serious cardiac arrhythmias reported by the researchers were not observed in any case, let alone fatal outcomes.

When used according to established guidelines, there is no reason for concern. Extensive clinical experience in humans provides substantially more relevant evidence than animal experiments involving substances or preparations that do not correspond to therapeutic use conditions. Nevertheless, I would advise against concomitant administration with digitalis preparations or with medications known to affect cardiac rhythm.

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References:

(1) Baburin I, Varkevisser R, Schramm A, et al. Dehydroevodiamine and hortiamine, alkaloids from the traditional Chinese herbal drug *Evodia rutaecarpa*, are IKr blockers with proarrhythmic effects in vitro and in vivo. *Pharmacol Res* 2018;131:150-163

(2) Wang Y. Chinese materia medica for warming the interior: Safety analysis and pharmacovigilance considerations. *Zhonghua Zhong Yiyao Zazhi*. 2016;31(7):2688–2693.

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