CONFERENCE PAPER

Drug Safety 2008; 31 (5): 416-418
0114-5916/08/0005-0416/$48.00/0

The European Herbal Medicines Directive

Could it Have Saved the Lives of Romeo and Juliet?

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Abstract

Herbal medicines have a long tradition of therapeutic use. However, they may occasionally cause dose-related (type A) or idiosyncratic (type B) toxicity and herb-drug interactions are also possible. Toxicity can arise as a result of misidentification or adulteration of the preparation. Legislation (the Directive on traditional herbal medicinal products 2004/24/EC) was enacted on 30 April 2004 to improve public health protection and promote the free movement of traditional medicinal products in the EU. It requires each Member State to set up a simplified registration scheme for manufactured traditional herbal medicines that are suitable for use without medical supervision.

Evidence of 30 years of traditional use, at least 15 years of which should normally be within the EU, is required to permit minor claims, replacing the requirement to demonstrate efficacy. Safety is based on evidence in the published literature, although the regulator can also ask for more data if there are safety concerns. The pharmacovigilance requirements and quality standards are the same as for licensed medicines. Patient information is similar to that for any over-the-counter medicine, with an additional requirement for a statement on labels and in advertisements that the indication is based on traditional use.

A European positive list of herbal substances will set out the indication, strength, dosing recommendations, route of administration and other information on safe use. Where a product complies with the list, the applicant will not need to demonstrate either the traditional use or the safety of the product. The list will be compiled by the recently established Committee on Herbal Medicinal Products at the European Medicines Agency. EU Member States were required to comply with the Directive by 30 October 2005. Traditional herbal medicinal products already on the market when the Directive became law need not comply with its provisions for 7 years after its coming into force.

The public need to be aware that 'natural' does not necessarily mean 'safe' in all circumstances. They should be fully informed about all medicines they take. Consideration also needs to be given to effective regulation of herbal medicines practitioners, so that they are identifiable in law, are governed by professional codes of practice and have agreed standards of training and competency.

There are many references to herbal medicines in Shakespeare's tragedy, *Romeo and Juliet*, which was written around 1595. A herbal medicine (distilled

liquor) was almost certainly used to put Juliet into a deep sleep. A poison, possibly of herbal origin, was used by Romeo to take his own life when he thought his beloved Juliet was dead, rather than sleeping. While European herbal medicines regulation seeks to protect the public health by ensuring the necessary guarantees of quality, safety and efficacy, it was poor communication that appears to have triggered the chain of events leading to the death of Romeo and Juliet. Good communication between regulators, practitioners, patients and the public is necessary so that those who choose to take herbal medicines can do so with acceptable safety.

Herbal medicines have a long tradition of therapeutic use. Shakespeare's son-in-law, Dr John Hall (1575–1635) describes the use of laudanum in dysentery, colchicum for gout and scurvy grass for patients with features we now recognize as consistent with vitamin C deficiency.[1] Although Shakespeare's famous tragedy of two feuding households was written before his own daughter met and married Dr Hall, Shakespeare was already aware of "*the powerful grace that lies in plants, herbs, stones and their true qualities*." (*Romeo and Juliet*, Act 2, Scene 3).

Shakespeare seems to have recognized that therapeutic benefit and toxicity could sometimes come from the same herbal source. In *Romeo and Juliet*, Shakespeare states, through Friar Laurence, that "*Within the infant rind of this weak flower, Poison hath residence, and medicine power*." (Act 2, Scene 3). Dose-related (type A) and idiosyncratic (type B) toxicity have been described in association with some herbal preparations and herb-drug interactions are also possible. Over 400 years later, we also recognize that toxicity can arise due to misidentification or adulteration of the preparation.[2]

EU member states have had a variety of national arrangements allowing herbal medicines onto their markets and many of these had no sound basis in law. Legislation (the Directive on traditional herbal medicinal products 2004/24/EC) was therefore enacted on 30 April 2004 to address this situation, and also to improve public health protection and promote free movement of traditional medicinal products in the EU.[3] The Directive first defines a traditional herbal preparation. It then requires each Member State to set up a simplified registration scheme for manufactured traditional herbal medicines that are suitable for use without medical supervision. Evidence of 30 years of traditional use, at least 15 years of which should normally be within the EU, is required to permit minor claims, replacing the requirement to demonstrate efficacy. Safety is based on evidence in the published literature, although the regulator can also ask for more data if there are safety concerns. The pharmacovigilance requirements and quality standards are the same as for licensed medicines. Patient information is similar to that for any over-the-counter medicine, with an additional requirement for a statement on labels and in advertisements that the indication is based on traditional use.

A European positive list of herbal substances will set out the indication, strength, dosing recommendations, route of administration and other information on safe use. Where a product complies with the list, the applicant will not need to demonstrate either the traditional use or the safety of the product. The list will be compiled by the recently established Committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency. The HMPC was established to assist the harmonization of procedures and provisions concerning herbal medicinal products laid down in EU Member States and to further integrate herbal medicinal products in the European regulatory framework.

One of HMPC's other tasks is to produce relevant monographs on traditional herbal products. Although traditional herbal registrations are granted on a national basis, the product can benefit from the mutual recognition procedure when it complies with the positive list or a published monograph. EU

Member States were required to comply with the Directive by 30 October 2005. Traditional herbal medicinal products already on the market when the Directive became law need not comply with its provisions for 7 years after its entry into force.

One can only speculate on the identity of the "*distilled liquor*" given to Juliet by Friar Laurence to induce in her a long and deep sleep on that fateful day in fair Verona (Act 4, Scene 1). Some authorities suggest it was mandrake (*Mandragora officinarum*), to which Juliet herself later refers (Act 4, Scene 3), and which is described in two other Shakespeare plays as having hypnotic properties. It was considered to be relatively safe for this indication, and was used in the Elizabethan period as an anaesthetic during surgical operations.

However, there were no controls on the purity of herbal preparations at that time. Codes of good agricultural and manufacturing practice did not exist. Even if there had been 30 years of traditional use in Europe of the product in question, it is most unlikely that there would have been a body of published information on its traditional use or its safety. Nevertheless, the particular herbal product to which Shakespeare referred was efficacious in helping Juliet sleep for "*two and forty hours*".

Romeo himself knew something of the properties of herbal medicines, advising Benvolio that plantain leaf (*Plantago* sp.) would help his "*broken shin*" (Act 1, Scene 2). However, he was not a health professional and it was his erroneous diagnosis of Juliet's death in the darkness of that Capulet crypt that caused him to take his life, from a dram of poison obtained illegally from a poor apothecary for forty ducats. Juliet, on waking, could not bear to live without her beloved Romeo, and killed herself with his dagger.

European herbal medicines regulation seeks to protect the public health by ensuring the necessary guarantees of quality, safety and efficacy, so that those who choose to take herbal medicines are able to do so with acceptable safety. However, the public need to be aware that 'natural' does not necessarily mean 'safe' in all circumstances. They should be fully informed about all medicines they take. Consideration also needs to be given to effective regulation of herbal medicines practitioners, so that they are identifiable in law, are governed by professional codes of practice and have agreed standards of training and competency. Regulation is not a panacea. However, the European Directive accords with the WHO Traditional Medicine Strategy, with its four primary objectives of (i) framing policy; (ii) enhancing safety, efficacy and quality; (iii) ensuring access; and (iv) promoting rational use of traditional medicines.[4]

As to the fate of our two "*star-cross'd lovers*"? It was perhaps beyond the influence of any form of medicines regulation and was firmly sealed when Juliet decided that "*I'll to the friar to know his remedy, if all else fails I can but die*." (Act 3, Scene 5).

Acknowledgements

No sources of funding were used to assist in the preparation of this conference paper. The author has no conflicts of interest that are directly relevant to the content of this conference paper.

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