Phytochemical and pharmacological aspects of valerian compounds. With special reference to valepotriates.
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SUMMARY

The investigation described in the present thesis has been divided into a phytochemical section (chapters I and II) and an applied pharmacological part (chapters III and IV). In the phytochemical part the preparation of extracts, the isolation of valepotriates and essential oil together with a qualitative as well as a quantitative analysis of these compounds are discussed. In the chapters concerning the pharmacological studies the central and peripheral actions of extracts, isolated valepotriates and essential oil components are presented.

Chapter I deals successively with the preparation of Valerian extracts containing a high concentration of valepotriates, the isolation of various valepotriates and a qualitative thin layer chromatographic analysis of these compounds and their degradation products. Moreover, a quantitative determination of isovaltrate/valtrate with a densitometric TLC and a HPLC procedure is discussed.

Extracts were prepared of Valeriana 'mexicana' because in this species the amount of valepotriates is about 10 times higher than that found in Valeriana officinalis L. s.l. The extraction method used was a modification of a known procedure, by which a reduction of the decomposition of valepotriates was obtained. By the application of a new thin layer chromatographic solvent system a better separation of the main valepotriates and their degradation compounds, such as baldrinal and homobaldrinal could be achieved.

Valepotriates were separated and isolated with column chromatography using a modification of a procedure reported in the literature. By using silica gel of a high purity grade and by reducing the time of passage through the column we were able to reduce the degradation of the unstable valepotriates. In this way the following valepotriates were isolated and subsequently purified: isovaltrate/valtrate as a mixture, didrovaltrate and isovalerohydroxydidrovaltrate.

It appeared that isovaltrate and valtrate formed the major valepotriates in subterranean parts of Valeriana officinalis L. s.l. With a two-dimensional TLC method it was shown that isovaltrate predominated over valtrate as
determined via their decomposition products homobaldrinal and baldrinal, respectively. The mixture of isovaltrate and valtrate was also shown to be the main valepotriates in roots of Valeriana 'mexicana'.

For the quantitative determination of the total amount of isovaltrate/valtrate in various Valerian preparations both a TLC and a HPLC method were developed and compared with each other. It was found that the reproducibility of both methods was not different, but the HPLC determination proved to be faster and was therefore used for the quantitative determination of isovaltrate/valtrate.

Before the quantitative determination of isovaltrate/valtrate two extraction techniques i.e. a percolation method and a soxhlet procedure, were compared with respect to their effectiveness in extracting isovaltrate/valtrate from Valeriana 'mexicana' roots. It appeared that with both extraction techniques an equal amount of isovaltrate/valtrate was obtained, but the soxhlet method, being less laborious was used in further experiments.

The positional isomers isovaltrate and valtrate were separated with the aid of a preparative liquid chromatograph and isolated as pure compounds. This allowed us to investigate the pharmacological properties of both positional isomers, separately.

Chapter II discusses the isolation of the essential oil of Valeriana officinalis L. s.l. A qualitative and quantitative analysis of the composition of the oil was studied using capillary gas chromatography. In this way a large series of compounds was separated and then identified with the aid of spectroscopic techniques. A total of 45 compounds were identified which were not reported in the literature before, as constituents of the essential oil of Valeriana officinalis L. s.l. Out of the Valeriana officinalis L. s.l. field a series of twelve samples was randomly selected and the composition of their essential root oils analysed. On the basis of differences in amounts of some characteristic marker components present in the essential oils, it was possible to divide the samples into three different subtypes. In this respect valeranone was of special interest, because this compound was absent in one type, present in a relatively high concentration in a second type and present in a moderate concentration in a third type.
The isolated valepotriates, the essential oil and valeranone were investigated in various pharmacological tests to study their possible central and peripheral activities.

Chapter III deals with the investigation of extracts, essential oil but mainly of valepotriates in a series of animal behavior tests, which are known to detect compounds with central depressant and/or anxiolytic activities. It was found that out of the valerian preparations and compounds the extract of Valeriana officinalis L. s.l. caused a significant reduction of locomotor activity of mice, whereas of the valepotriates only didrovalcrate was found to be active in this test model. In all other animal tests, in which the compounds were screened for muscle relaxant, anticonvulsant and/or anxiolytic activities, it appeared that they were inactive.

Because valepotriates were found to be inactive in the test models used, in contrast to well known reference drugs such as barbiturates, meprobamate and benzodiazepines, we conclude that valepotriates do not have a pharmacological spectrum of activities like that of the reference drugs mentioned. It is therefore unlikely that valepotriates have a central depressant or an anxiolytic activity. The sedative action of valepotriates, as suggested in the literature, has on the basis of our findings at least to be considered as doubtful.

During the experiments used for the investigation of central effects of the valeriana compounds it was found that when valepotriates and a Valeriana 'mexicana' extract were administered intraperitoneally to mice and rats, toxic effects were observed. In the General Discussion these findings are discussed in the light of toxic properties of valepotriates which have been recently reported in the literature.

The inhibition of the spontaneous locomotor activity of mice induced by the Valeriana officinalis L. s.l. extract in the ambulation test, prompted us to investigate possible peripheral effects of the extract constituents, such as the valepotriates and the essential oil compounds. In chapter IV an in-vivo and in-vitro investigation of valepotriates and valeranone on guinea-pig ileum smooth muscle preparations is described. It was found that
didrovaltrate and valeranone were able to relax stimulated smooth muscle preparations with a potency comparable to that of papaverine. Moreover, it was shown that these valeriana compounds induced smooth muscle relaxation via a musculotropic action, which is also known to be the case for papaverine. This reduction of smooth muscle spasms as found for didrovaltrate and valeranone, might explain the literature reports of slow and poor absorption of valepotriates in laboratory animals after an oral administration. Such an observation can be a consequence of a reduction in the motility of the gastrointestinal tract.

Moreover, a smooth muscle relaxant effect might in principle reduce feelings of tensions characterized by spasms within the gastrointestinal region, which may be a part of a kind of vicious circle: nervousness → gastrointestinal spasms → difficulties to get asleep → more nervous tensions, and so on. By interrupting such a chain of symptoms through reducing gastrointestinal spasms, valepotriates and valeranone might have a 'calming effect' and could possibly facilitate sleep.

We conclude therefore, that didrovaltrate and valeranone might be of therapeutical usefulness in the treatment of nervousness characterised by spasms in the gastrointestinal tract, a symptom often reported in relation to nervousness and feelings of anxiety or apprehension. However, the claim that Valerian preparations based on didrovaltrate and valeranone are indeed of therapeutic usefulness, can only be justified by well documented double-blind clinical studies with an adequate number of patients, with a clearly defined pattern of complaints. Such a study is of importance because Valerian preparations are being increasingly used, although until now data on their effectiveness in man are still lacking.