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Bioanalysis and Pharmacokinetics of Carbamazepine

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SUMMARY

Carbamazepine (5-*H*-dibenz (b,f)azepine-5-carboxamide), a derivative of iminostilbene, is frequently used in the treatment of trigeminal neuralgia and certain types of epilepsy.
This thesis presents the results of an investigation concerning the bioanalysis and pharmacokinetics of carbamazepine. It is divided into three parts.
Part one, entitled "Introduction", consists of two chapters.

Chapter 1 gives a profile of the drug at issue. In it some analytical chemical, pharmacokinetic, pharmacological and toxicological properties of this drug are reviewed.

Chapter 2, introduces some fundamental aspects of modern liquid chromatography. Special attention is paid to factors affecting optimization of the analysis.

Part two deals with the bioanalysis of carbamazepine and some of its metabolites. It is entitled "Bioanalysis".

In *Chapter 1* the development of a sensitive and selective method for the determination of carbamazepine and carbamazepine-epoxide in biological material is described. After a single extraction, the components are separated and determined quantitatively by means of modern liquid chromatography. A chromatographic system with a high separation efficiency for the analysis of several anticonvulsants has been obtained with a mixture consisting of dichloromethane and tetrahydrofuran as eluent and silica gel as stationary phase. The method proved to be sufficiently sensitive to measure the concentrations of both substances in various body fluids and tissues. The quantitative method for the determination of carbamazepine by liquid chromatography is compared with a gas chromatographic assay procedure.

In *Chapter 2* the procedures for the isolation and quantitative determination of some metabolites of carbamazepine are described. After being isolated from bile, urine or tissue homogenates by means of extraction or adsorption, the components are determined quantitatively by means of modern liquid chromatography.

Part three is entitled "Pharmacokinetics". In this part various aspects of the pharmacokinetics of carbamazepine, viz. absorption, distribution,

elimination and metabolism, are discussed.

Chapter 1 deals with the pharmacokinetics of carbamazepine in man during and after repeated administration. The results obtained in this study demonstrate that the plasma half-life of carbamazepine after multiple dosing is considerably shorter than after single dose experiments. Concomitant administration of other anti-epileptic drugs seems to cause a further shortening of the carbamazepine half-life. Special attention is paid to the concentration-time curve of carbamazepine in saliva.
It is concluded that salivary concentration measurements offers a convenient alternative to plasma analysis, with particular advantage when serial samples are needed.

Chapter 2 reports on the pharmacokinetics of carbamazepine in the rat. The chapter is divided into two sections.

Section 2.1. deals with the pharmacokinetics of carbamazepine in unanesthetized rats following single and multiple doses. The animals were provided with a permanent double heart catheter, allowing both continuous infusion and frequent sampling without disturbing the animal. In some animals a bile canule was also implanted. The drug was administered by means of a zero-order infusion. Several pharmacokinetic models were investigated to describe the plasma concentration-time curves of carbamazepine and its epoxide metabolite. Calculations were performed with the non-linear least squares computer program NONLIN. The plasma half-life of carbamazepine in rats appear to be much shorter than that observed in man. The epoxide metabolite, however, appears to be eliminated much slower than the parent drug, resulting in an accumulation of the former during chronic treatment. Repeated administration of the drug to rats results in a significant increase in the elimination rate constants of both parent compound and epoxide metabolite. This led to the conclusion that carbamazepine possesses enzyme-inducing properties. Analysis of the data according to the organ perfusion model shows that in rats the delivery of the drug to the liver by the blood stream is a limiting factor in the elimination of the drug during repeated administration. In rats the gastrointestinal absorption appears to be rather slow; and only about 50% of the orally administered dose reaches the systemic circulation unchanged. The ratio between the epoxide metabolite and the parent compound concentration in plasma after oral administration differs substantially from that found after intravenous administration. This is an indication for the existence of the

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so-called "first-pass" effect. Carbamazepine is excreted almost exclusively in the form of metabolites. From the bile a new N-glucuronide of carbamazepine was isolated and identified. The possible contribution of the latter metabolite to an entero-hepatic circulation of carbamazepine is briefly discussed.

In section 2.2. it is shown that the biotransformation of carbamazepine *in vitro* is affected by pretreatment of the rats with carbamazepine, phenytoin or phenobarbital. Moreover, only pretreatment with carbamazepine has a significant effect on the metabolism of carbamazepine-epoxide.

Chapter 3 describes the influence of the route of administration on the availability and metabolism of carbamazepine in dogs. For this purpose, the drug was administered orally and intravenously both via the hepatic--portal vein and directly into the systemic circulation. It appears that 14%-43% of the absorbed oral dose is eliminated (metabolized) at its first passage through the liver.

Chapter 4 deals with the distribution of carbamazepine and its metabolites in the monkey and the (pregnant) mouse. After administration of labeled drug, the distribution patterns are studied by means of macroautoradiography. Additional information was obtained from chromatographic analysis in conjunction with liquid scintillation counting of the tissues and body fluids left after sectioning for autoradiography. In the monkey, high concentrations of radioactivity were found in the excretory organs. In the brain the radioactivity was localized predominantly in the white matter structures. High concentrations of radioactivity were also found in the pituitary gland and some peripheral nerves. Moreover, the drug appears to possess a high affinity for melanin and elastin containing tissues. The placental passage of the drug has been studied in pregnant mice. It appears that the drug reaches the fetus, albeit at a slower rate than the maternal tissues.

The last chapter of this thesis (*chapter 5*) reports on the binding of carbamazepine and its epoxide metabolite onto synthetic melanin. The possible pharmacological and toxicological implication of this binding are discussed briefly.