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PHARMACOKINETIC STUDY OF STOBADINE

Š. Bezek[1], L. Šoltés[1], V. Ščasnár[1], K. Bauerová[1], Z. Kállay[1], M. Ďurišová[1], D. Mihalová[1], P. Bohov[1],V. Faberová[2], M. Kukan[3], T. Trnovec[3], V. Koprda[1]

Institute of Experimental Pharmacology[1], Slovak Academy of Sciences, Bratislava; Drug Research Institute[2], Modra; Institute of Preventive and Clinical Medicine[3], Bratislava, Slovak Republic

Summary

The aim of this paper is to provide a brief overview of most important results of stobadine kinetic studies in rats, dogs, and human volunteers. In these studies, stobadine dihydrochloride and stobadine dipalmitate was used for intravenous and oral administration, respectively. To evaluate kinetic properties of stobadine and its metabolites, TLC, HPLC, GLC, GC-MS, radiometric, and fluorometric methods were developed and used.

Key Words: pharmacokinetics, antioxidative agent, stobadine

Stobadine, cis-(-)-2,3,4,4a,5,9b-hexahydro-2,8-dimethyl-1H-pyrido-[4,3b]indole, is an effective cardio- and neuroprotective agent with a high antioxidative capacity (1,2). As part of a complex pharmacological study of this substance, its kinetic was investigated in animals and human volunteers.

Methods

The radiochemical purity and stability of ^{3}H-stobadine was determined according to studies (3) and (4), respectively. Stobadine absorption, distribution, metabolism, and elimination was identified as described in studies (5,6,10). The spectrofluorometric method was used to determine stobadine in serum and urine extracts in dogs (7,8). The gas liquid chromatographic method was employed to estimate stobadine and two of its metabolites formed during incubation with liver microsomes in rats (9). The gas chromatographic method combined with mass spectrometry was utilized to evaluate the relative bioavailability of stobadine dihydrochloride and stobadine dipalmitate oral dosage forms in dogs (11).

Results

In rats, stobadine was rapidly eliminated from plasma after intravenous administration and its basic pharmacokinetic parameters were as follows: $T_{1/2\ el}$ = 85.6 min, AUC = 4.65 % of dose/min/ml, and Cl_{tot} = 105.3 ml/min/kg. The uptake of stobadine by extravascular tissues was rapid and avid as indicated by its steady-state volume of distribution V_{ss} = 4780 ml/kg. Stobadine brain uptake index was 78.2 %, showing that the subbstance readily passed the blood

brain barrier. A marked first-pass effect of stobadine was observed upon oral administration, since only 19.7 % of the administered dose reached the systemic circulation. The heterogenous distribution of stobadine was found in the organs and tissues, following both intravenous and oral administration, with the highest levels in lungs and kidneys (12). Liver was the main organ of stobadine biotransformation. The two major stobadine metabolites, *i.e.* N-monodesmethyl and N-oxide derivative were isolated in the liver microsomal system (13,14). Biotransformation was the main elimination mechanism of stobadine, since only 5 % of the parent substance was recovered in excreta, mainly in urine. Following intravenous and oral administration, 62 % and 65 % of the administered radioactivity, respectively, was excreted in urine (12). Following multiple doses of stobadine within 26 days, 41 % of ^{3}H-stobadine derived radioactivity was excreted into urine and 49.7 % into feces (15). The data indicated no accumulation of ^{3}H-stobadine and ^{3}H-stobadine-derived radioactivity in the body.

In dogs, the absorption of stobadine as determined by the chronic ileal loop method was rapid and almost completed within the time period of 1 h (16). The mean relative bioavailability of stobadine dipalmitate compared with dihydrochloride was 46.4 %. Individual values of the ratio C_{max}/AUC ranged between 0.0022-0.0047 min^{-1} for both stobadine dosage forms (11).

Table 1. Mean pharmacokinetic parameters of stobadine in dog

Parameter	Stobadine dihydrochloride	Stobadine dipalmitate
$T_{1/2\ ab}$ (min)	24 ± 2.5*	32 ± 4.6
$T_{1/2\ el}$ (min)	312 ± 28.8	196 ± 20.6
Lag-time (min)	2 ± 5.2	15 ± 1.2
T_{max} (min)	97 ± 5.3	100 ± 7.1
C_{max} (ng/ml)	1282 ± 44	823 ± 27
AUC (ng.min/ml)	715526 ± 38254	331827 ± 18015
Cl_{tot} (ml/min)	7 ± 0.37	15 ± 0.82

* - standard error mean

In human volunteers, stobadine dipalmitate administered in single oral doses ranging from 0.79 to 2.5 mg/kg was well tolerated in all the subjects. The corresponding peak serum stobadine concentrations were found to lie in the interval from 12 to 289 ng/ml (10).

Discussion

Various aspects of the pharmacokinetics of stobadine were reported in studies (3-16). These investigations provided much in the way of information on the fate of this substance and its metabolites in the animal and human body. Although no specific requirements have been brought forward for the distribution of an antioxidant in the body, the pharmacokinetic characteristic of such a substance may be useful for understanding mechanisms of its action. This is also true for the elucidation of the cardioprotective and neuroprotective action of stobadin (1,2) and for the prediction of possible pharmacological activities of new stobadine-like derivatives.

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