PHARMACOKINETICS of 3-[Bis(2-HYDROXYETHYL)AMINO] ACETOPHENONE-(4,5-DIPHENYLOXAZOL-2-YL)HYDRAZONE (ZIMET 98/69) IN MICE

R. Amlacher, H. Ulbricht

Central Institute of Microbiology and Experimental Therapy,
Research Centre for Molecular Biology and Medicine, Academy of Sciences of the G.D.R.,
6900 Jena, G.D.R.

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In comparison with 10 related hetarylhydrazones, 3-[Bis(2-hydroxyethyl)amino]acetophenone--(4,5-diphenyloxazol-2-yl)hydrazone (ZIMET 98/69) was found to exert the highest antiviral activity against Mengo virus in vitro (*2*) and in vivo (*3*, *4*). Orally, this compound was only effective after daily administration of relatively high doses (4 mmol = 1820 mg/kg) given on 2 or more consecutive days. Previous studies concerning the pharmacokinetics of the drug in rats revealed a moderate bioavailability and marked accumulation after its oral administration (*1*). The results present additional information concerning the distribution of ^{3}H-ZIMET 98/69 after oral administration to male ABD2F$_1$ mice. For this purpose, doses of 10 and 1820 mg/kg were used, the latter corresponding to the effective dose in vivo. It has to be noticed that the total radioactivity (TRA) determined in serum and tissues is representative for ^{3}H-ZIMET 98/69 including its possible metabolites.

The results showed that a single administration of 10 mg/kg leads to maximum serum concentration 7.5% of the dose administered per liter serum, whereas this value amounts to only 0.3% for the 1820 mg/kg dose. Thus, the relative bioavailability of the 1820 mg/kg dose runs only to about 4%. The elimination half-lives were estimated at 28 hr (10 mg/kg) and 42 hr (1820 mg/kg), and 42 hr (1820 mg/kg), respectively. Repeated administration indicated an accumulation ratio of about 2.1, which was also reflected by the course of tissue TRA levels. The highest TRA concentrations were found in the liver, whereas the activity in brain and serum showed little difference.

Dose (mg/kg)	Relative bioavailability (% dose/l)	Tissue serum ratio (6 hr/24 hr)			Half-life (hr)	Accumulation ratio
		liver	kidneys	brain		
10	7.5	2.8/1.6	1.7/1.2	0.8/0.9	28	2.1
1820	0.3		n.d.		42	n.d.

n.d. = not done

The pharmacokinetic data showed weak absorption, rapid distribution but slow elimination of TRA in mice (*3*, *4*). The very low bioavailability following oral administration of ZIMET 98/69 should be considered as one reason why high doses were necessary for the antiviral action of the drug in vivo, demonstrating the importance of investigating the pharmacokinetic properties of any drug to prove its antiviral activity.

References

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