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Concentrations of *N*-(Phosphonacetyl)-L-Aspartate (PALA) in Plasma and Tears in Man*†

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Abstract—*Plasma concentrations of* N - (*phosphonacetyl*) - L - *aspartate* (PALA) *have been determined in* 23 *patients with advanced malignant disease during phase I/II clinical trial. Drug levels were determined by high pressure liquid chromatography. In* 11 *patients, who received PALA in a* 1-*hr infusion* (*doses ranging from* 1 *to* 4 g/sq m), *curves of plasma concentration vs time were constructed. The average absolute and relative total body clearances were* 95 ± 24 ml/min *and* 1.43 ± 13 ($\pm$ *S.E.*)ml/min, kg, *respectively. Values of* 27 ml/min *and* 0.52 ml/min, kg *were measured in a patient with renal dysfunction. The apparent distribution volume was* 0.29 l/kg, *with an exception of* 0.541 l/kg *for a patient with a considerable amount of ascites fluid. The mean residence time was* 3.2 ± 0.4 *hr. Plasma peak levels and* 24-*hr concentrations of PALA were measured for* 3-*hr PALA infusion. Peak concentrations were lower and* 24-*hr concentrations were the same when compared with* 1-*hr infusion* (4.9×10^{-4} M *compared to* 9×10^{-4} M *and* 2.3×10^{-6} M *compared to* 2.45×10^{-6} M, *corrected for a dose of* 2.5 g/sq m). *In* 7 *patients PALA was measured in tears, due to the occasional occurrence of conjunctivitis during PALA treatment. A rapid increase in drug concentration to* 10^{-4} M–6×10^{-4} M *was measured within* 2 *hr from the start of* 1-*hr infusion in* 7 *patients with an average concentration ratio between plasma and tears of* 3.7.

INTRODUCTION

PALA WAS synthesized as a transition state inhibitor of aspartate transcarbamylase, the second enzyme in *de novo* pyrimidine synthesis [1]. This drug was evaluated in phase I and II clinical trials [2, 3]. So far PALA has shown a low clinical effectivity as a single agent. However, the negligible effect on bone marrow facilitates its combination with more myelosuppressive drugs (e.g. 5-fluorouracil). Using an enzymatic assay, Loo *et al.* [4] reported the pharmacological disposition of PALA for infusions. This paper reports pharmacokinetic measurements for 1-hr and 3-hr infusions of PALA and the appearance of PALA in tears using high pressure liquid chromatography with low-wavelength detection [5]. The measurement of PALA in tears was undertaken because of the occurrence of conjunctivitis [2].

MATERIALS AND METHODS

PALA was obtained from the National Cancer Institute, Division of Cancer Treatment in 10 ml vials containing 1 g PALA. The injection fluid was prepared in 500 ml N saline. Heparinized blood (4 ml) was collected for each sample and plasma was assayed for PALA according to Lankelma *et al.* [5]. Tear samples were collected using Schirmer's paper as for routine tear diagnosis (dimensions 36 mm × 5 mm). This took about 15 min per sample. The volume of the tear sample was determined from the increase in weight. The papers were extracted with 250 μl of water with 95% recovery of PALA. The sample clean-up procedure, as described for plasma [5], was sufficient for removing interferences. Because of the limited amount of tears (20–50 μl per sample), the

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