EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS, 1984, No 3, pp. 267-274

Pharmacokinetics of oxiracetam following intravenous and oral administration in healthy volunteers

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Received for publication: January 30, 1984

Key-words: Pharmacokinetics, oxiracetam, bioavailability

SUMMARY

The kinetics of oxiracetam after single intravenous and oral doses (2000 mg) were investigated in four healthy volunteers. Following intravenous administration, the decline in serum levels showed a prolonged, rapid phase followed by a delayed terminal phase. Mean residence times ranged from 3.9 to 6.5 h. Volumes of distribution ranged from 0.9 to 1.81 $\cdot kg^{-1}$, whereas clearance values ranged from 100 to 119 $ml \cdot h^{-1} \cdot kg^{-1}$ More than 90% of the intravenous dose was recovered unchanged in the urine within 48 h. Oral administration resulted in peak levels within 1-2 h; thereafter, the decline in serum levels showed a pattern similar to that observed after the intravenous dose – almost 50% of the oral dose was excreted in the urine within 6 h. The absolute availability of oral oxiracetam was $75 \pm 7\%$.

INTRODUCTION

Oxiracetam (ISF 2522) (Figure 1) is a recently developed psychotropic agent. This compound, which is classified as a nootropic agent, has been shown to improve learning and memory in normal animals as well as in animals with acute and chronic cerebral impairment (1,2). The drug has been reported to stimulate the turnover of phospholipids in the brain (3). In addition, oxiracetam has recently been shown to reduce the cognitive impairment secondary to inhibition of acetylcholine synthesis or blockade of muscarinic receptors, an effect which is probably mediated by increased acetylcholine utilization (4).

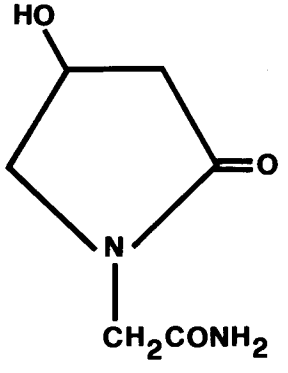

Fig. 1. Structure of oxiracetam (4-hydroxy-2-oxo-1-pyrrolidinacetamide) (ISF 2522).

In normal volunteers, single oral doses of oxiracetam (200-2400 mg) have been described to cause a significant increase in the α activity of the EEG (5). In a controlled study, Itil et al. (6) found oxiracetam (400-2400 mg daily for 12 weeks) to be superior to piracetam in improving memory function in patients with organic brain syndrome. Tolerability has been excellent in all studies.

So far, the kinetics of oxiracetam in man have not been characterized, due to the lack of an adequate assay. We have now developed a highly specific high performance liquid chromatography technique that allows the detection of concentration as low as 0.5 μg/ml in human serum and urine. In the study described here, this method was used to investigate the serum level profile and urinary excretion of oxiracetam after single oral and intravenous administration in healthy volunteers.

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METHODS

Subjects and protocol

Four healthy male volunteers aged between 20 and 26 years (weight 71-84 kg) gave their written informed consent to take part in the study. Each subject received, in random order and at an interval of at least 2 weeks, one oral and one intravenous dose of oxiracetam (2000 mg). The oral formulation consisted of 5 x 400 mg capsules, whereas for the parenteral study a 10-ml aqueous solution (200 mg/ml) was injected slowly into an antecubital vein over 5 min. On both occasions the drug was given after an overnight fast; no food was allowed during the following 4 h. Blood samples were collected at 0, 0.5, 1, 2, 4, 7.5, 10 and 24 h. Fractional urine collections were obtained from each subject over the following intervals: 0 (pre-drug), 0-2, 2-4, 4-6, 6-12, 12-24 and 24-48 h after oral administration and 0, 0-24 and 24-48 h after intravenous administration. Urine and serum were kept frozen at $-20°C$ until analyzed.

Analytical method for oxiracetam in biological fluids

Aliquots of urine (0.1 ml) or serum (0.5 ml) were extracted twice with 1 ml of toluene, lyophilized, mixed with triphenylchlorosilane (300 mg) and piridine (1 ml), and incubated at 60°C for 5 h. The mixture was neutralized with a saturated aqueous solution of citric acid (8 ml), extracted with methylene chloride (10 ml), and evaporated to dryness under a stream of nitrogen. The residue was reconstituted with methylene chloride (2 ml), purified on Sep-Pak cartridges by washing with a solution (10 ml) of methylene chloride: acetonitrile (9:1), and eluted with 7 ml of acetonitrile: methanol (1:1). Then, 0.1 ml of a solution of the 0-benzoyl ester of oxiracetam (internal standard) in acetonitrile (50 µg/ml for urine and 5 µg/ml for serum) was added to the eluate, which was then dried under vacuum at 50°C and reconstituted with 0.5 ml of acetonitrile. Fifty µl of the final solution was injected into a Hewlett-Packard HP 1080 B high performance liquid chromatograph connected to a UV detector (Perkin Elmer LC 55) set at 230 nm. The chromatographic separation was carried out under isocratic conditions using a silica column (5 µm, Brownlee Laboratories) and a mixture of hexane: isopropranol: water in the ratio of 77 : 22.5 : 0.5 as eluent. The retention times were 6 min for oxiracetam and 14 min for the internal standard. The limits of quantitation of the method were 0.5 µg/ml and below 50 µg/ml for serum and urine, respectively. All samples were analyzed in duplicate (serum) or triplicate (urine). The precision and accuracy were better than 4% and 3%, respectively.

Pharmacokinetic analysis

Following intravenous administration, the disappaearance of oxiracetam from serum was characterized by a rapid phase followed after 7.5 to 10 h by a slower phase. The kinetic profile could be described by fitting the data to a two-compartment open model, assuming that the decrease in serum concentration after 7.5 h (subject 2) or 10 h (subjects 1, 3 and 4) reflected the terminal phase (β). Any possible error in the characterization of the terminal phase is unlikely to affect to an important extent the estimate of the degree of excretion, since the urinary recovery of the drug at 24 h was already 90% (see Discussion). Individual kinetic parameters were calculated as previously described (7,8). The steady-state volume of distribution (Vd_{SS}) with respect to the two-compartment model was calculated as $Vd_{ss} = (1 + K_{12}/K_{21})V_1$ (9,10).

In view of the limitation of compartmental analysis (see Discussion), intravenous data were also analyzed by model-independent calculations. The areas under the curve (AUC) and the areas under the first moment of the curve (AUMC) were determined by the trapezoidal rule. Extrapolation to infinity was achieved by conventional methods (9), assuming that the last concentration values reflected the terminal phase (λ_2). The latter was estimated on the same points used to calculate β. For the AUC, the extrapolated part comprised only $4 \pm 1\%$ of the total area. For the AUMC, the extrapolated area represented a greater fraction ($28 \pm 6\%$). The mean residence time (MRT), total body clearance (Cl), renal clearance (Cl_{ren}), volume of distribution (Vd_{area}) and volume of distribution at steady state (Vd_{ss}) were calculated according to the following equations (7,9,11,12): MRT = AUMC/AUC; Cl = dose/AUC; Cl_{ren} = amount excreted in urine from 0 to 24 h/AUC from 0 to 24 h; $Vd_{area} = \text{dose}/(\text{AUC} \cdot \lambda_2)$; $Vd_{ss} = \text{dose} \cdot \text{AUMC}/(\text{AUC})^2$. The oral availability was estimated from the ratio between AUCs after oral and intravenous administration.

RESULTS

Serum level data

The time course of serum oxiracetam concentrations following oral and intravenous administration in each of the four subjects is illustrated in