

# Human Pharmacokinetics of Aniracetam

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## Summary

Aniracetam is very rapidly and completely absorbed from the gastrointestinal tract. However, absolute systemic bioavailability is only about 0.2%. Aniracetam has a high volume of distribution (2.5 L/kg, which implies extensive extravascular distribution) and is very rapidly eliminated from the body. Indeed, total body clearance from blood (10 L/min) exceeds cardiac output (implying that the lung is a major clearance organ) and plasma elimination half-life is very short ( $\approx$  0.5 hours). Aniracetam is completely metabolised and the principal metabolites, *N*-anisoyl- $\gamma$ -aminobutyric acid (*N*-anisoyl-GABA), 2-pyrrolidinone, succinimide and anisic acid, are excreted via the urine (84%), the faeces (2%) or as CO<sub>2</sub> in expired air. After multiple dose administration, there is no indication of accumulation of drug or principal metabolites, with the exception of succinimide. Measurable concentrations of 2 main metabolites, *N*-anisoyl-GABA and 2-pyrrolidinone, were found in the cerebrospinal fluid of patients treated with aniracetam for 12 weeks.

## 1. Absorption and Bioavailability

Aniracetam is absorbed very rapidly from the gastrointestinal tract. Indeed, after oral administration in an aqueous solution/suspension, peak plasma concentrations ( $C_{\max}$ ) were observed 5 minutes later (at the first sampling point) [fig. 1]. Within the dose range of 1 to 4g (aniracetam administered as finely milled material suspended in 100ml of orange juice), median values for  $C_{\max}$  and area under the plasma concentration-time curve (AUC) increased nonproportionally with increasing doses. However, individual  $C_{\max}$  values were highly variable and ranged from 42 to 246  $\mu\text{g/L}$  for a 1g dose, 55 to 116  $\mu\text{g/L}$  for a 2g dose and 42 to 1087  $\mu\text{g/L}$  for a 4g dose (Roncari et al. 1984). In contrast, a linear correlation between dose administered and  $C_{\max}$  values was demonstrated when aniracetam was given orally as a tablet formulation in the dose range of 300mg ( $C_{\max}$  2.3  $\mu\text{g/L}$ )

L) to 1200mg ( $C_{\max}$  14.1  $\mu\text{g/L}$ ) [Honma et al. 1986]. These data suggest that the absorption and/or disposition pharmacokinetics of aniracetam are dose proportional over the lower therapeutic dose range, whereas at higher doses nonlinear pharmacokinetics prevail.

The absolute bioavailability of oral aniracetam is extremely low; about 0.2% of an orally administered dose reaches the systemic circulation as intact drug (Wendt et al. 1983). However, this apparent low systemic bioavailability is not a reflection of poor absorption. Indeed, uptake of aniracetam from the gastrointestinal tract into portal vein blood is essentially complete, as demonstrated by equal dose fractions (expressed as total radioactivity) excreted in the urine after intravenous and oral administration of [<sup>14</sup>C]-labelled aniracetam (Wendt et al. 1986). However, following absorption, aniracetam undergoes extensive biodegradation, resulting in the low systemic bioavailability

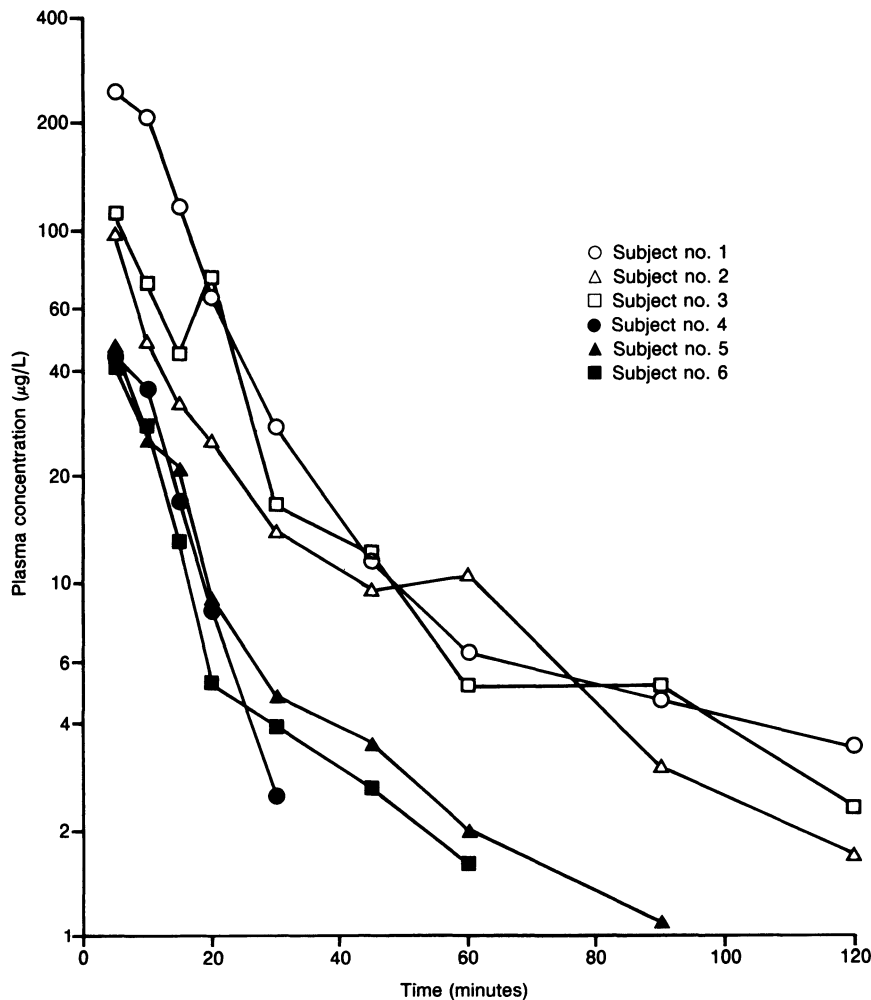


Fig. 1. Plasma concentrations of aniracetam after a single oral 1g dose.

observed. Potential sites for metabolism of orally administered aniracetam, and the extremely large value for the apparent oral clearance are extensively discussed by Mayersohn and colleagues (1993).

Aniracetam is intended for use in geriatric patients. It has been formulated in tablets (750mg) and sugar-free sachets (1.5g). These 2 formulations have been compared with the tablet formulation used in the previously described absolute bioavail-

ability study and found to be bioequivalent (Guenzi et al. 1989a,b).

2. Distribution

Aniracetam has a high volume of distribution at steady state ( $V_{ss}$ ), 2.5 L/kg (range: 1.9 to 4.1 L/kg) [table I]. Such a high value is indicative of distribution outside the vascular space and probable binding to tissue components (Wendt et al. 1983). Binding of aniracetam to plasma proteins is