Pharmacokinetic studies

In this guide

22. The EMA assessment reports on *E. purpurea* (EMA, 2014) and *E. angustifolia* (EMA, 2012) note that available pharmacokinetic data are limited and primarily focus on alkylamides and, to a lesser extent, caffeic acid conjugates. According to the human pharmacokinetic studies reviewed in the EMA reports, the alkylamides from *E. purpurea* and *E. angustifolia* show good oral bioavailability with rapid absorption and measurable plasma concentration within 20-60 minutes post-ingestion. The reported peak plasma concentration Cmax values for alkylamides varied between studies from 0.04 ng/mL for *E. purpurea* alkylamides (Goey *et al.*, 2012) to over 300 ng/mL for *E. purpurea/E. angustifolia* alkylamides (Matthias *et al*., 2005a). The EMA highlighted that these discrepancies are likely due to differences in the alkylamide profiles between *Echinacea* species, extract concentrations, analytical methods, and study design. Caffeic acid derivatives were not detected in plasma after oral administration and their oral bioavailability was questioned by the EMA assessors (EMA, 2014). The key pharmacokinetic studies from the EMA assessment reports are briefly

outlined below.

E. purpurea

23. In a small clinical study by Goey *et al*. (2012), three cancer patients received 20 drops of a commercial *E. purpurea* extract (65% V/V ethanol extract of freshly harvested *E. purpurea* herb (drug extract ratio (DER) 1:12)) and roots (DER 1:11) three times daily for 14 days. On day 15, plasma levels of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI) were measured. The peak plasma concentration was reached 30 minutes post-dose with Cmax values of 0.04–0.18 ng/mL. The authors stated that the findings indicated low systemic exposure to alkylamides after repeated oral dosing.

E. angustifolia

24. In a randomised, open-label, crossover study, 11 healthy subjects received a single oral 2.5 mL dose of a 60% ethanolic extract from *E. angustifolia* roots (Woelkart *et al*., 2005). The maximum plasma concentration of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI), the main alkylamides in *E. angustifolia* roots, of 10.88 ng/mL was reached at 30 minutes after the dose. The authors noted that highly lipophilic alkylamides with no double and triple bond at the end of the fatty acid chain could not be detected in the blood.

E. angustifolia/E. purpurea

25. Nine healthy volunteers received *Echinacea* orally (4 tablets, each containing extract equivalent to 675 mg of *E. purpurea* root plus 600 mg of *E. angustifolia* root prepared from the dried ethanolic extracts of the two *Echinacea* species) immediately after a high fat breakfast (Matthias *et al*. 2005). Caffeic acid conjugates could not be identified in any plasma sample at any time after tablet ingestion. Alkylamides were rapidly absorbed and were measurable in plasma 20 min after tablet ingestion and remained detectable for up to 12 h. The maximal concentrations for the sum of alkylamides in human plasma were reached within 2.3 hours post ingestion and averaged 336 +/- 131 ng/mL plasma. The authors concluded that alkylamides from *Echinacea* preparations were orally bioavailable and their pharmacokinetics supported the three times daily regimen already recommended for *Echinacea.*