

The pharmacokinetics of EGCG: Preclinical and clinical studies.

James A. Crowell¹, Robert R. Swezey², H.-H. Sherry Chow³, and Yukihiro Hara⁴

1: Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland 20892, 2: SRI Int., Menlo Park, CA 94025 3: University of Arizona, Tucson, AZ 85724, 4: Tokyo Food Techno Co. Ltd., Mitsui Norin Co. Ltd., Shizuoka 426-01, Japan

Summary

The absorption, distribution, and pharmacokinetics of tritiated epigallocatechin gallate (EGCG) were examined in Beagle dogs using oral and intravenous (IV) routes of administration. Following IV administration EGCG distributed rapidly to total body water (0.55 ± 0.04 L/kg) and had a calculated $t_{1/2\alpha}$ of approx. 0.10 hr and a $t_{1/2\beta}$ of 6 hr. When given orally EGCG had a T_{max} of approximately 1 hour with an apparent bioavailability of 20%, representing parent EGCG and metabolites. The major route of elimination was fecal (30-32% of total dose) and urinary (5-9%). Relative to plasma, the EGCG concentrated primarily in the small intestine, colon, esophagus, stomach, prostate gland, and lungs.

The pharmacokinetics of EGCG and a defined complex mixture of polyphenols (Polyphenon E) was evaluated in human volunteers after single and repeated-dose administration using a cross-over design. Five subjects per dose were administered single doses of 200, 400, 600, and 800 mg EGCG or the mixture (based on EGCG content). Based on the plasma concentration-time curve (area under the curve, AUC), the 2 formulations had similar pharmacokinetic characteristics. The 800 mg dose had greater systemic availability than the lower doses and appeared to demonstrate a saturable presystemic elimination. A 28-day repeat dose pharmacokinetic study is ongoing.

Keywords

Pharmacokinetics, Dogs, Humans, Epigallocatechin gallate, Polyphenon E

Introduction

Cancer is the result of a multistep process in which the cumulative effect of successive genetic and molecular alterations leads to a gradual transition, typically over decades, from normal to increasing grades of dysplasia that culminate in an invasive and metastatic phenotype. The sequential accumulation of genetic and molecular alterations over time provides opportunities for the development of clinical interventions aimed both at preventing cancer initiation and at treating premalignant lesions. Chemoprevention is an innovative area of cancer research that focuses on the prevention of cancer through pharmacologic, biologic, and nutritional interventions.

Epidemiological observations and experimental carcinogenesis studies suggest that tea may reduce the risk of epithelial cancers. In the studies reported here the absorption, distribution, metabolism, and elimination of EGCG and related catechins has been characterized both in Beagle dogs and in human subjects.

Materials and Methods

Tritiated EGCG (10 μ Ci/mg EGCG), pure unlabelled EGCG, and the formulation Polyphenon E was provided by Tokyo Food Techno Co., Ltd. (Mitsui Norin Group). Tritiated EGCG was determined to be stable at gastric pH and in urine and not to undergo water exchange. For the clinical studies, pharmaceutical grade EGCG and Polyphenon E, manufactured under Good Manufacturing Practices, was formulated into capsules containing 200 mg EGCG. Clinical studies were conducted under an Investigational New Drug Application to the U.S. Food and Drug Administration.

On study day 1 four male Beagle dogs were intravenously (iv) administered tritiated EGCG at a dose of 25 mg/kg body weight. Blood was collected at hour 0, 0.25, 0.5, 1, 2, 4, 8, & 24; urine and feces were collected over 48 h. Over days 2-14 all residual radioactivity was eliminated. On day 15 an oral dose of 250 mg/kg bwt tritiated EGCG was administered and blood, feces, and urine were collected as on day 1. From day 16-27 the same daily oral dose of unlabelled EGCG was administered. On day 28 a single iv dose of 25 mg/kg bwt tritiated EGCG was administered and the dogs were euthanized after 1 h and tissue samples were collected.

In the clinical study 20 healthy male & female subjects ≥ 30 years of age were administered EGCG dosages on day 1 of 200, 400, 600, or 800 mg (5 subjects / dose level). Blood was collected at hour 0, 0.5, 1, 2, 4, 6, 8, & 24; urine was collected at 0-4, 4-8, & 8-24 h. After a 2-week washout, subjects were randomized and crossed-over to the same protocol but the defined mixture Polyphenon E at the same EGCG-based dosages was administered.

Tritiated EGCG was measured by liquid scintillation counting after sample homogenization and combustion. EGCG and catechins were measured by reversed phase HPLC. Plasma samples were hydrolyzed in the presence of glucuronidase and sulfatase to determine unconjugated catechins. Pharmacokinetic parameters were calculated using WinNonlin software.

Results and Discussion

Following a single iv administration to Beagle dogs, [^3H]-EGCG was eliminated from the plasma with a half-life of approximately 6 hours. The clearance rate was low (1.19 ml/min-kg) and was consistent with relatively slow metabolism and a mean residence time of 8.30 hours. The volume of distribution (0.59 L/kg) indicated that the radioactivity was distributed to total body water. The blood/plasma ratios of the radioactivity over 24 hours were 0.61 to 0.77 and indicate preferential distribution to plasma water.

Following a single oral administration to Beagle dogs, absorption was rapid with a maximal concentration in plasma at approximately 1 hour. The elimination half-life of 6.8 hours was similar to that seen after iv administration. The apparent bioavailability, calculated as the ratio of the iv to the oral route of administration, was 20.3%.

One hour after the dogs received their final dose of [^3H]-EGCG on day 28, they were euthanized and the radioactive content of the tissues was determined. The total amount of radioactivity recovered was approximately 46%. Significant radioactivity was in the excreta. Based on the distribution study as well as the iv and oral pharmacokinetic studies, approximately 30-32% of the radioactivity was eliminated in the feces and, 5-9% in the urine. The liver also concentrated a significant amount of radioactivity. By the 1 hour time point the plasma appeared to reach equilibrium with the small intestine, colon, esophagus, prostate gland, and lungs.

Following a single oral administration to human subjects, plasma levels of EGCG increased over 3-4 hours and returned to baseline by 24 hours. The plasma concentration-time curves of EGCG were similar for both pure EGCG and the Polyphenon E formulation. Glucuronidase and sulfatase treatment of plasma samples after a single dose of 600 mg EGCG did not show a significantly increased amount of EGCG in the plasma. After a single dose of 600 mg Polyphenon E the plasma concentration-time curve was similar to that after 600 mg EGCG. Glucuronidase and sulfatase treatment of plasma samples after a single dose of 600 mg Polyphenon E show that epigallocatechin (EGC) and epicatechin (EC) are present in plasma in the conjugated forms.

The pharmacokinetic parameters for EGCG and Polyphenon E were similar at similar doses. The AUC and C_{max} values for both formulations at doses of 200, 400, and 600 mg were not statistically different but showed a dose-response increase. The AUC and C_{max} values for both formulations at the 800 mg dose were significantly higher than the values at the lower doses,

although the T_{\max} and $t_{1/2}$ were not different across doses. The increased AUC for EGCG at the 800 mg dose suggests saturation of a presystemic elimination system.

The AUCs of total EGC and EC (free and conjugated forms) were \geq than the AUCs of EGCG, although the EGC and EC content of the Polyphenon E formulation was $<20\%$ that of EGCG. However, the free forms of EGC and EC in plasma after Polyphenon E administration were lower than that of EGCG and indicate that EGCG is more bioavailable than EGC and EC.

Neither free or conjugated EGCG were detected in urine. Microgram amounts of total EGC and EC were detected in urine after milligram doses of Polyphenon E. No subjects experienced any significant adverse events in this study. A twenty-eight day repeat daily dose study is currently being completed.

While bioavailability in human subjects appears to be low, and lower than that in Beagle dogs, the plasma EGCG concentration achieved after administration of pure EGCG or the commercial product Polyphenon E appear equivalent and the presence of EGC and EC may provide additional benefits. The apparent saturation of presystemic elimination systems, at \geq approximately 8 cup equivalents, suggests that pharmacological concentrations could be achieved in humans if necessary to achieve additional benefits from tea.