Abstract

OBJECT The blood-brain barrier (BBB) limits the intracerebral penetration of drugs and brain tumor treatment efficacy. The effect of ultrasound-induced BBB opening on the intracerebral concentration of temozolomide (TMZ) and irinotecan (CPT-11) was assessed. METHODS This study was performed using 34 healthy New Zealand rabbits. Half had unilateral BBB opening, and half served as controls. Sonications were performed by pulsing a 1.05-MHz planar ultrasound transducer with a duty cycle of 2.5% and an in situ acoustic pressure level of 0.6 MPa after injection of a microbubble ultrasound contrast agent. Drugs were injected either 5 minutes before (ChemoPreUS) or 15 minutes after (ChemoPostUS) the ultrasound sonication. The plasma and intracerebral concentrations of both drugs were quantified using ultra-performance liquid chromatography. RESULTS The mean intracerebral tissue-to-plasma drug concentration ratio in the control hemispheres was 34% for TMZ and 2% for CPT-11. After BBB opening, these values increased by up to 21% for TMZ and up to 178% for CPT-11. Intracerebral concentrations of drugs were enhanced in regions where the BBB was opened compared with the contralateral hemisphere (p < 0.01 and p < 0.0001 for CPT-11, p = 0.02 and p = 0.03 for TMZ, in ChemoPreUS and ChemoPostUS, respectively) and compared with the control group (p < 0.001 and p < 0.0001 for CPT-11, p < 0.01 and p = 0.02 for TMZ, in ChemoPreUS and ChemoPostUS, respectively). The intracerebral distribution of drugs was heterogeneous, depending on the distance from the ultrasound source. CONCLUSIONS Ultrasound-induced opening of the BBB significantly enhances the intracerebral concentration of both TMZ and CPT-11 in rabbits.

KEYWORDS: BBB = blood-brain barrier; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea; CPT-11 = irinotecan; IV = intravenous; MGMT = O-6-methylguanine-DNA methyltransferase; TMZ = temozolomide; UCA = ultrasound contrast agent; blood-brain barrier; brain tumors; drug delivery; irinotecan; oncology; temozolomide; ultrasound

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