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Distribution of Azithromycin into Brain Tissue, Cerebrospinal Fluid, and Aqueous Humor of the Eye

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To measure the concentrations of azithromycin in the central nervous system, 20 patients with brain tumors (group I) received a single 500-mg oral dose of azithromycin either 24, 48, 72, or 96 h prior to the tumor removal operation and 10 patients with cataracts undergoing surgery (group II) and 7 patients scheduled to undergo lumbar puncture (group III) received the same dose of azithromycin 24 h prior to the operation or procedure. Serum from all patients, brain tissue from group I, aqueous humor from group II, and cerebrospinal fluid from group III were assayed for azithromycin concentration. The mean concentrations of azithromycin in brain tissue 24, 48, 72, and 96 h after administration were 2.63 ± 2.58, 3.64 ± 3.81, 0.74 ± 0.37, and 0.41 μg/g, respectively. In contrast, the concentrations of azithromycin in cerebrospinal fluid and aqueous humor of the eye were very low or undetectable. Therefore, these data show that azithromycin appears to be widely distributed into brain tissue but not into cerebrospinal fluid or aqueous humor of the eye.

Azithromycin, a new 15-membered ring azalide antibiotic, is structurally related to the macrolide erythromycin, but its antimicrobial activity and pharmacokinetic properties are different from those of the prototype macrolide. Previous in vitro studies have shown that azithromycin is superior to erythromycin against some common respiratory tract pathogens, including *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Legionella pneumophila* (7, 8). In addition, a previous study with mice showed that azithromycin at a dosage of 200 mg/kg of body weight per day for 10 days protected 80% of mice infected intracerebrally with *Toxoplasma gondii*. Thus, this drug appears to be parasitostatic and has potential for the treatment of *T. gondii*, the most common cause of cerebral mass lesions in patients with AIDS (1). Azithromycin has excellent pharmacokinetic properties, especially body fluid or tissue and intracellular distribution (6), and these properties are one of the essential factors for evaluation of the drug's performance. However, there have been no published data on humans to show the distribution of this drug into the central nervous system. Therefore, the purpose of the present investigation was to measure concentrations of azithromycin in the human central nervous system, including brain tissue, cerebrospinal fluid (CSF), and aqueous humor.

Our studies were performed with three groups of patients.

Group I. Twenty patients, 10 males and 10 females, with brain tumors who were undergoing elective brain tumor removal were eligible to participate in the study. Brain tissue samples were taken from the periphery of the tumor mass (18 samples from cerebral cortex and 2 samples from cerebellum). The mean age of the patients was 36.30 ± 21.32 (range, 12 to 89) years, and their mean weight was 51.42 ± 13.25 (range, 27 to 65) kg.

Group II. Ten patients, five males and five females, with cataracts who were undergoing elective surgery were eligible to participate in the study. Their mean age was 64.30 ± 14.77 (range, 35 to 78) years, and their mean weight was 59.96 ± 13.17 (range, 40 to 86) kg.

Group III. Seven patients, five males and two females, who were scheduled to undergo lumbar puncture were eligible to participate in the study. Their mean age was 38.17 ± 17.72 (range, 16 to 61) years, and their mean weight was 55.50 ± 11.50 (range, 43 to 73) kg.

Exclusion criteria were pregnancy or lactation, known hypersensitivity to macrolide antibiotics, any condition which might affect absorption of orally administered drugs, antibiotic administration within the previous 2 weeks, a history of drug or alcohol abuse, or positive antigen for hepatitis. All patients gave informed consent to participate, and the protocol was approved by the Ethics Committee of Songklanagarind Hospital.

Patients in group I received a single 500-mg oral dose of azithromycin either 24 (range, 23.5 to 25), 48 (range, 47 to 49), 72 (range, 71.5 to 72.5), or 96 h prior to the operation, and patients in groups II and III received the same dose of azithromycin 24 (range, 23.5 to 24.5) h prior to the operation or procedure. Doses were administered at least 2 h after food intake, and no meal was taken until 1 h after the dose. To control for contamination with blood, the brain tissue samples were rinsed with saline isotonic solution and dried with gauze. Aqueous humor and CSF with traumatic tapping were excluded. Blood samples to obtain 3 ml of serum were taken for assay of azithromycin prior to the dose and again at the time of the operation or procedure. Serum from all patients, brain tissue from patients in group I, aqueous humor from patients in group II, and CSF from patients in group III were stored at −80°C until assayed. Azithromycin concentrations in samples from all patients in the three groups were determined by agar well diffusion bioassay using *Micrococcus luteus* (ATCC 9341) as the test organism by the method of Foulds et al. (4). For this assay, accurately weighed brain tissue was homogenized with 9 volumes of 0.5% dibasic potassium phosphate buffer containing 1% Tween 80, adjusted to pH 8.0. The mixture was centrifuged, and the supernatant was used for the bioassay. The dynamic range of the assay was 0.008 to 0.12 μg/ml in serum, aqueous humor, and CSF and 0.12 to 1 μg/g in brain tissue.

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The coefficient of variation was 4% in all assays. No azithromycin concentrations were detected in five serum, four brain tissue, five aqueous humor, and five CSF samples from patients who did not receive this drug. All patients received treatment with a variety of drugs, predominantly tranquilizers and anesthetic drugs, none of which were known to interact with the pharmacokinetics of azithromycin.

The mean concentrations of azithromycin in brain tissue 24, 48, 72, and 96 h after the dose were 2.63 ± 2.58, 3.64 ± 3.81, 0.74 ± 0.37, and 0.41 μg/g, respectively, while the mean concentrations in serum at the same time were 0.031 ± 0.044, 0.016 ± 0.011, 0.012 ± 0.005, and 0.008 μg/ml, respectively. The mean ratios of the concentration of drug in brain tissue to that in serum 24, 48, 72, and 96 h after the dose were 255.76 ± 429.39, 199.06 ± 188.90, 62.71 ± 5.60, and 51.25, respectively. The concentrations of azithromycin in aqueous humor ranged from undetectable to 0.008 μg/ml, and those in CSF ranged from undetectable to 0.015 μg/ml. No toxicity was observed in any patient.

Azithromycin is distinguished from other antibiotics by its unusual pharmacokinetics—notably high and sustained concentrations in tissue and a long half-life in tissue. The high affinity of this drug for tissue is due to the presence of two basic tertiary amine groups which give it amphiphilic properties (5). A previous study with an animal model has shown that azithromycin attains high concentrations in the brain tissue of *T. gondii*-infected mice (2). The concentrations in brain tissue were 10 times higher than those in serum after treatment for 10 days, and the concentrations in the brains of infected mice were approximately twice as high as those in the brains of noninfected mice (2). In addition, a in vitro study showed that the concentration of azithromycin which inhibited 50% of the growth of *T. gondii* was 1.2 μg/ml (3). Our present studies have demonstrated that the concentrations of this drug in noninfected human brain tissue were much higher (approximately 200 times) than concentrations in serum. Although our studies investigated noninfected brain tissue with a single 500-mg oral dose of azithromycin, the concentrations of drug were still high and were sustained longer than 48 h. Therefore, the concentrations from multiple-dose regimens of azithromycin at a steady state in infected brain tissue should be even higher and more sustained than the tissue drug concentration data obtained from our studies. However, we cannot conclude that the drug concentrations from these multiple-dose regimens are high enough for the treatment of brain infections, and further studies are required. In contrast to the results obtained from brain tissue, the concentrations of azithromycin in CSF and aqueous humor of the eye were very low or undetectable, and this may be due to the lipophilic property of the drug. Thus, these data suggest that azithromycin cannot be used for the treatment of infections in CSF and eyes.

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REFERENCES

1. **Araujo, F. G., D. R. Guptill, and J. A. Remington.** 1988. Azithromycin, a macrolide antibiotic with potent activity against *Toxoplasma gondii*. Antimicrob. Agents Chemother. **32:**755–757.
2. **Araujo, F. G., R. M. Shepard, and J. S. Remington.** 1991. In vivo activity of the macrolide antibiotics azithromycin, roxithromycin and spiramycin against Toxoplasma gondii. Eur. J. Clin. Microbiol. Infect. Dis. **10:**519–523.
3. **Derouin, F., and C. Chastang.** 1990. Activity in vitro against Toxoplasma gondii of azithromycin and clarithromycin alone and with pyrimethamine. J. Antimicrob. Chemother. **25:**708–711.
4. **Foulds, G., K. H. Chan, J. T. Johnson, R. M. Shepard, and R. B. Johnson.** 1991. Concentrations of azithromycin in human tonsillar tissue. Eur. J. Clin. Microbiol. Infect. Dis. **10:**853–855.
5. **Gladue, R. P., G. M. Bright, R. E. Isaacson, and M. F. Newborg.** 1989. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infections. Antimicrob. Agents Chemother. **33:**277–282.
6. **Lode, H.** 1991. The pharmacokinetics of azithromycin and their clinical significance. Eur. J. Clin. Microbiol. Infect. Dis. **10:**807–812.
7. **Peters, D. H., H. A. Friedel, and D. McTavish.** 1992. Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs **44:**750–799.
8. **Williams, J. D.** 1991. Spectrum of activity of azithromycin. Eur. J. Clin. Microbiol. Infect. Dis. **10:**813–820.