

Short Report: Intra-Cystic Drug Concentration of Albendazole Sulphoxide in Patients with *Echinococcus granulosus* Cysts

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Abstract. Albendazole therapy—alone or in combination with surgery—remains the standard of care for human echinococcosis depending on the stage of disease. However, only limited data are available on target site concentrations in liver cysts and data for non-liver cysts are lacking. We report on intra-cystic concentrations of the biologically active metabolite albendazole sulphoxide in non-liver cysts indicating a relative intra-cystic drug concentration of 48–156% compared with plasma levels. These data are evidence for a satisfactory penetration of albendazole sulphoxide into *Echinococcus* cysts localized in other organs than the liver and underline the usefulness of albendazole therapy for this indication.

Echinococcosis is caused by the ingestion of eggs of the dog tapeworm or fox tapeworm belonging to the genus *Echinococcus*. *E. granulosus* causes considerable human morbidity and mortality, with the highest prevalence in rural areas because of close co-habitation of humans, animal intermediate hosts, and final hosts. Oncospheres migrate after ingestion to different organs and form cysts most commonly located in the liver (60–70%) and lungs (20%). Other localizations of cysts, including the kidney, spleen, muscles, bone, pancreas, central nervous system, and soft tissue, have been described but are less common.^{1–3}

Treatment recommendations for *E. granulosus* cysts include long-term therapy with albendazole alone or in combination with praziquantel, percutaneous drainage, and surgical removal of the lesions.^{4–6} Albendazole is a benzimidazole derivative and is highly active against echinococcal protoscolices. However, the *in vivo* therapeutic response is limited by its low and erratic bioavailability.^{7–10} Nevertheless albendazole is the most commonly used drug for pre- and post-operative anthelmintic treatment and continued suppressive therapy of inoperable hydatid cysts.¹¹ On the background of its variable absorption, the penetration of albendazole and its active metabolite albendazole sulphoxide into cysts is of major importance for adequate *in vivo* activity. Whereas limited data are available for *Echinococcus* cysts of the liver, little is known about the intra-cystic concentrations of albendazole in patients treated for echinococcal cysts located in other organs than the liver. In this study, we aimed to assess the ability of albendazole and its active metabolite albendazole sulphoxide to penetrate into *E. granulosus* cysts of two patients with non-liver cysts.

A 60-year-old woman of Turkish origin (Patient A) residing in Austria for > 5 years was diagnosed with a painless tumor on the left thigh, which became noticeable after voluntary weight loss of 25 kg. The second patient (Patient B), a 30-year-old Turkish citizen, presented at the hospital with progressive cough, night sweats, and dyspnea. Inflammation markers were

increased in both patients, with C-reactive protein at 8.7 and 2.4 mg/dL for Patients A and B, respectively (normal range, < 1 mg/dL). Marked eosinophilia was recorded (550 and 3,020/ μ L blood for Patients A and B, respectively) in differential blood count, and serologic investigation by enzyme-linked immunosorbent assay and Western blot confirmed the diagnosis of *E. granulosus* infection. Computer tomography and magnetic resonance imaging showed a cystic lesion in the proximal *Musculus satorius* of 7.5 cm diameter in Patient A. Patient B had a distinctive pleural effusion on the right side of the lung with transgression of the diaphragm. Following current treatment recommendations, patients were prescribed 400 mg albendazole to be taken twice daily with a fatty meal for 5 and 4 days before surgical removal, respectively.¹² Histologic examination of cyst tissues confirmed diagnosis by visualization of typical protoscolices. Patients continued anthelmintic treatment for 1 month after surgery and had no signs of recurrence of *Echinococcus* cysts.

Venous blood samples for drug analysis were taken in the morning of surgery before albendazole intake and during the intervention. Undiluted cyst fluid was obtained during operation and was subsequently stored at -80°C until further analysis. Concentrations of albendazole and albendazole sulphoxide in plasma and cyst fluid were measured by a validated high-performance liquid chromatographic (HPLC) method using an “UltiMate 3000” system (Dionex, Sunnyvale, CA). Separation of albendazole sulphoxide was carried out using a Hypersil BDS-C18 column (Thermo Fisher Scientific, Waltham, MA) with an acetic acid/methanol mobile phase. The limit of quantification for albendazole and albendazole sulphoxide was 0.063 and 0.072 $\mu\text{g/mL}$, respectively. Coefficients of accuracy and precision for both compounds were < 8%.

HPLC measurement showed that, in all clinical samples, albendazole was below the limit of detection. However, albendazole sulphoxide—the active metabolite—was quantified in pre-operative and intra-operative samples in the range of 0.10 and 1.3 $\mu\text{g/mL}$ in plasma. Furthermore, the analysis of cystic fluid samples also showed albendazole sulphoxide concentrations of 0.16 and 0.6 $\mu\text{g/mL}$, indicating a relative intra-cystic drug concentration of 48% and 156% compared with plasma, respectively (Table 1).

These data show—besides the known variability of plasma concentrations—good tissue penetration of albendazole sul-

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TABLE 1
Albendazole sulphoxide ($\mu\text{g/mL}$) and relative intra-cystic drug concentration

	Pre-operative plasma	Intra-operative plasma	Cyst fluid	Relative intra-cystic drug concentration
Patient A	1.26	1.24	0.59	48%
Patient B	0.18	0.10	0.16	156%

phoxide into echinococcal cysts, with ~50% variation compared with plasma drug concentrations. In general, plasma concentrations of albendazole A previous report indicated maximum plasma levels for albendazole sulphoxide in the range of 0.45–2.96 $\mu\text{g/mL}$ and intra-cystic drug concentrations between 0.06 and 0.42 $\mu\text{g/mL}$.^{12,13} Morris and others¹⁴ reported an ~20% intra-cystic concentration of albendazole sulphoxide in patients treated with 10 mg/kg albendazole for 1 month before surgery. Although these data are in line with our results for plasma drug concentrations, the relative intra-cystic drug concentration of albendazole sulphoxide was significantly higher in our patients. Interestingly, in a previous study, praziquantel, another anthelmintic drug with activity against tape-worms, led to a considerable increase in albendazole plasma levels.¹⁵ In that report, the activity against protoscolices was significantly higher in patients treated with a combination of albendazole and praziquantel.

Thus far, most data on target site drug concentrations derive from echinococcal cysts of the liver and information on intra-cystic drug penetration for other organs are scarce. Despite the limited number of patients in this study, our data indicate that drug penetration in cysts located in the pleural cavity and the skeletal muscle is comparable or potentially higher compared with previous data on liver cysts.

Albendazole has been used for the treatment of human echinococcosis since the 1980s and—depending on the stage of the disease—continuous long-term albendazole therapy shows cure rates between 30% and 80%. Although the oral bioavailability of albendazole is characterized by significant variation, intra-cystic drug penetration seems less variable and comparable to plasma drug levels. Although many questions about the optimal medical treatment of echinococcosis remain, the use of albendazole has been shown to allow safer manipulation of liver cysts during surgery, thus minimizing the chance of secondary recurrence. Based on our data, this may similarly be true for cysts localized in other organs.^{16,17} Further data on anthelmintic combination therapy and the development of novel anthelmintic drugs with improved oral bioavailability are desirable to further improve the management of echinococcosis.

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