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PHARMACOLOGY

Ethambutol Is Cleared by a Contemporary High-Flux Hemodialyzer, and Drug Monitoring Ensures Safety and Therapeutic Effect

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ABSTRACT It is uncertain, given the lack of recent data and the inconclusive nature of previous data, whether ethambutol is cleared by hemodialysis using contemporary dialyzers. We measured serum ethambutol concentrations before, during, and 1 h after hemodialysis in a 75-year-old Caucasian man receiving ethambutol for disseminated Bacille Calmette-Guérin infection. There was a mean 41% decrease in serum ethambutol concentration during dialysis, confirming the hemodialyzability of ethambutol and the utility of drug monitoring in ensuring safety.

KEYWORDS drug monitoring, ethambutol, hemodialysis

Ethambutol, a dextro-2,2′-(ethylenediimino)-di-1-butanol dihydrochloride with a molecular weight of 277.23, is highly active against *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and certain nontuberculous mycobacteria but not against *Mycobacterium simiae*, *Mycobacterium ulcerans*, or *Mycobacterium haemophilum* (1). The hydrochloride salt has two apparent dissociation constants of 6.35 and 9.35 pKa, and the monohydrochloride predominates in solution at neutrality (2). The logarithm of its partition coefficient (log P) is −0.14 (2).

The MIC of ethambutol for wild-type *M. tuberculosis* is 0.5 to 2 mg/liter (3), while the MIC for Bacille Calmette-Guérin (BCG) strains of *M. bovis* is 2 to 4 mg/liter (4, 5). Ethambutol is used as part of the primary treatment regimens for tuberculosis and systemic BCG infection but has significant potential side effects. The most serious adverse effect of ethambutol is optic neuritis, which is dose related (3, 6). A study by Griffith et al. (7) found that the incidence of optic neuritis when ethambutol was taken for >2 months at a dose of 25 mg/kg daily was 5% to 6%, whereas with a dose of 15 mg/kg daily, it was 1%.

Eighty percent of absorbed ethambutol is excreted unchanged by the kidney, with the remainder excreted as inactive metabolites, also in the urine (8). Given its high degree of renal clearance, the risk of ocular toxicity is increased with impaired renal function (9), especially as the half-life of 4 h may be more than doubled in end-stage renal disease (10). This poses a serious problem in patients on hemodialysis who require treatment with ethambutol, particularly because there is an increased risk of tuberculosis in this population (11). While the risk of toxicity with ethambutol is dose dependent, the doses at which adverse events occur vary with individual patients and the rates at which they clear the drug. Therefore, the exact dose adjustment to be made should be guided by therapeutic drug monitoring to suit the individual pharmacokinetics of ethambutol for a particular patient with end-stage renal disease.

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The peak concentration is reached between 1 and 4 h postdose (1), but it is unclear if ethambutol is cleared by hemodialysis. Two earlier studies gave conflicting results (12, 13). One reported only 1.5% clearance with a high-flux dialysis membrane (13). The other showed higher clearance values of 34 ± 5.3 to 52 ± 1.5 ml/min for ethambutol with various older dialyzers that were in use in 1975. In comparison, clearance values for creatinine were between 60 ± 6.4 and 106 ± 10 ml/min (12). It is likely that the type of dialyzer influences clearance (12), but no recent studies have been conducted using contemporary high-flux dialyzers. Furthermore, while most authors agree that a dose of 15 to 25 mg/kg thrice weekly in hemodialysis patients is appropriate (14), they disagree on whether to give ethambutol before or after dialysis (13, 15–17). One local guideline from the United Kingdom recommends a prehemodialysis trough concentration of <1 mg/liter and administration of ethambutol postdialysis, aiming for a peak concentration of 2 to 6 mg/liter (18). This peak concentration target was also recommended in a review of antituberculous therapy by Alsultan and Peloquin (19).

In this study, we aimed to shed further light on whether ethambutol is cleared by a contemporary high-flux dialyzer in use at our institution, the ELISIO-19H synthetic hollow-fiber high-flux dialyzer (Nipro, St. Leonards, Australia), and to assess the utility of drug concentration monitoring in preventing toxicity while ensuring therapeutic effect. We measured serum ethambutol concentrations in a hemodialysis-dependent patient using high-performance liquid chromatography at 0, 1, 2, and 3 h during a 270-min dialysis session and at 1 h postdialysis, once a week for 5 weeks.

Measurement of serum ethambutol concentrations was carried out by liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) on a Waters ultraperformance liquid chromatography (UPLC) Acquity system. Briefly, samples (in 1.5 ml Eppendorf tubes) were precipitated with 3 volume equivalents of 100% methanol containing an internal standard (ethambutol d4). After protein precipitation, the samples were centrifuged, and the supernatant was transferred to an autosampler vial. An aliquot of 2 μl was injected, and the analytes were separated on an Acquity BEH amide 2.1 × 100-mm column. The column eluent was directed (without stream splitting) into the ion source of a Waters Premier XE tandem quadrupole MS, operated in positive electrospray ionization mode. The following transitions were utilized: ethambutol (205.4 → 116.4) and ethambutol d4 (209.4 → 120.19). The gradient was returned to initial conditions in preparation for the next sample, with a run time of 2 min/sample. The limit of the detection was 0.6 μg/liter, with an interrun imprecision of 3.7% for ethambutol at 100 μg/liter.

The patient was a 79-year-old hemodialysis-dependent Caucasian male patient being treated for disseminated BCG infection. He was reliant on hemodialysis as renal replacement therapy, with a baseline creatinine level of 500 mmol/liter and an estimated glomerular filtration rate of 9 ml/min/1.73 m^2. The treatment regimen was composed of ethambutol 1,200 mg, isoniazid 900 mg, and rifampin 600 mg for 2 months, followed by the latter two agents for a further 7 months. These drugs were administered three times weekly after hemodialysis. The study was carried out during the three-drug phase of treatment. We aimed for trough and peak serum ethambutol concentrations as recommended by Ahitan et al. (18). We also measured a random dialysate ethambutol concentration in the second week as an additional step to confirm dialyzability. The study was carried out as part of standard clinical care, so no ethical approval was required. We did, however, obtain signed informed consent from the patient.

The patient had received immunotherapy in 2001 with ImmuCyst, a preparation of BCG from the Connaught strain of *M. bovis* (Sanofi-Aventis, Macquarie Park, Australia), which was repeated in 2013, for inoperable transitional cell carcinoma of the bladder. For each immunotherapy treatment, ImmuCyst at a dose of 10.5 ± 8.7 × 10^8 CFU was administered as six intravesicular inoculations over 6 weeks.

The patient was diagnosed with disseminated BCG infection manifesting as epididymo-orchitis in 2014, when he underwent a left orchidectomy after a testicular mass was discovered. BCG was isolated from the testicular material and three separate urine

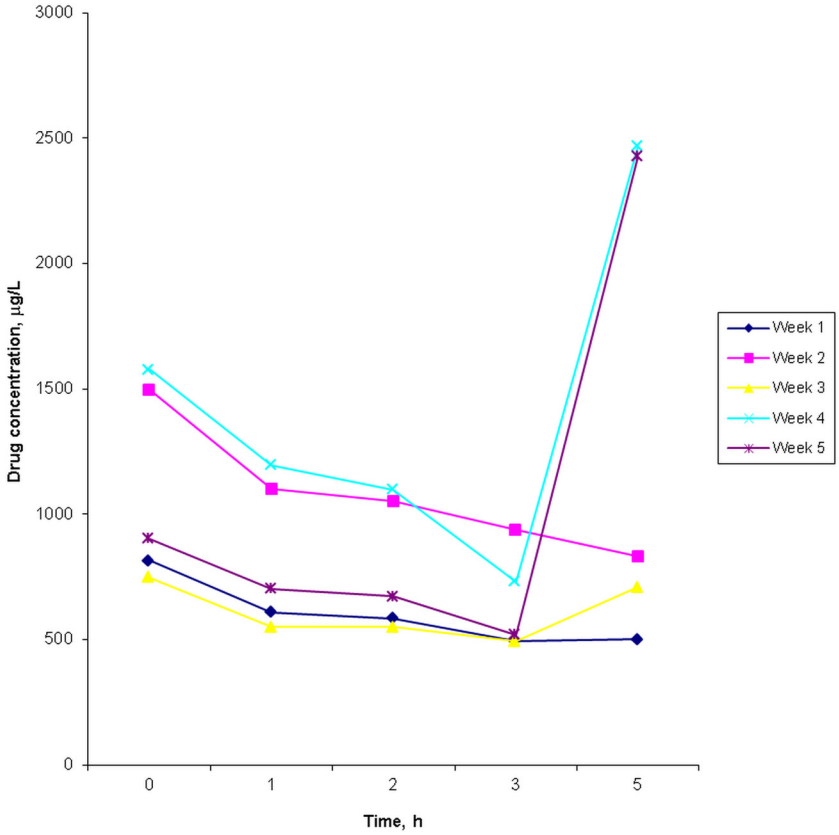

FIG 1 Serum ethambutol concentrations before ($t = 0$), during ($t = 1$ to 3 h), and 1 h after ($t = 5$ h) hemodialysis. The exact times of ethambutol dosing in weeks 1 and 2 were not ascertainable. In weeks 3 to 5, directly observed therapy was instituted, with a 1,200-mg dose of ethambutol administered immediately after dialysis ($t = 3$ h).

samples. His medical history included hypertension, gout, mild cognitive impairment, and seizure disorder; and his regular medications included erythropoietin, sodium valproate, pantoprazole, atorvastatin, and calcium carbonate.

Hemodialysis was performed using an ELISIO-19H synthetic hollow-fiber high-flux dialyzer (Nipro, St. Leonards, Australia) with a surface area of 1.9 m^2. The dialyzer membrane is composed of proprietary Polynephron fibers. The blood flow rate through the dialyzer was set at 300 to 350 ml/min. A clear decline in ethambutol concentration during each dialysis session was observed (Fig. 1). The mean reduction in serum ethambutol concentration was 41% (95% confidence interval, 35% to 48%). The concentration of ethambutol in the dialysate fluid sampled in week 2 was 274 μg/liter, whereas the predialysis level was 1,496 μg/liter. These findings, although not directly comparable to results obtained by authors who calculated clearance rates previously (12, 13), make it highly likely that the ELISIO-19H dialyzer gives a significantly higher clearance rate than the 1.5% quoted by Malone et al. (13).

Drug concentrations 1 h posthemodialysis in weeks 1 and 2 were less than the concentrations at 3 h into dialysis (Fig. 1). On questioning, the patient reported a lack of compliance, which accounted for this finding. This was attributed to his mild cognitive impairment. As such, directly observed therapy immediately after dialysis was commenced from week 3. After directly observed therapy, drug concentrations taken 1 h posthemodialysis were higher than those taken 3 h into dialysis (Fig. 1). Note, however, that as postdialysis concentrations were only taken 1 h after dialysis, it is possible that peak concentrations in weeks 3 to 5 were higher than those measured. No abnormalities of color vision were detected, and the patient did not complain of any visual symptoms. The target peak and trough concentrations were generally achieved (Fig. 1).

As mentioned earlier, the MIC for BCG strains of *M. bovis* ranges from 2 to 4 mg/liter (4, 5). The killing activity of ethambutol is concentration dependent (20), implying that the key pharmacokinetic parameter is the peak concentration. In our patient, the ethambutol concentration 1 h postdose in weeks 4 and 5, when directly observed therapy was carried out, exceeded 2 mg/liter, and the true peak concentration may well have been higher. This aligns with the peak concentration targets recommended by Ahitan et al. (18) and Alsultan and Peloquin (19) and further supports the use of therapeutic drug monitoring to ensure therapeutic effect in cases such as that of our patient.

Two conclusions can be drawn from this study. The first is that with the ELISIO-19H synthetic hollow-fiber high-flux dialyzer, ethambutol is a dialyzable drug. Ethambutol should therefore be given posthemodialysis, which also helps facilitate directly observed therapy and thus compliance, as in our patient. Further studies with other contemporary high-flux dialyzers are needed to provide much-needed evidence so that the guidelines currently in use, which are based on little and dated evidence, can be updated. The second is that therapeutic drug monitoring should be the standard of care for patients on hemodialysis who are receiving ethambutol, as this ensures safety and therapeutic effect.

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