

Continuous infusion of amphotericin B deoxycholate reduced overall mortality, side effects, and nephrotoxicity more than did rapid infusion

Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ*. 2001 Mar 10;322:579-82.

QUESTION

Is amphotericin B deoxycholate less toxic when given by continuous infusion than by conventional rapid infusion?

DESIGN

Randomized {allocation concealed*}†, unblinded,* controlled trial with 3-month follow-up.

SETTING

University hospital in Zurich, Switzerland.

PATIENTS

80 patients (median age 47 y, 61% men, 91% with neutropenia) who were starting treatment with amphotericin B deoxycholate. Exclusion criteria were a baseline serum creatinine concentration > 300 μmol/L or systemic treatment with amphotericin B deoxycholate in the previous 7 days. All patients were included in the intention-to-treat analysis.

INTERVENTION

Patients were allocated to receive amphotericin B deoxycholate given by continuous infusion at 0.97 mg/kg of body weight over 24 hours ($n = 40$) or by rapid infusion at 0.95 mg/kg over 4 hours ($n = 40$). All

patients received infusions of saline as standard care; pretreatment of chills and fever was prohibited on the first study day.

MAIN OUTCOME MEASURES

Side effects related to infusion, nephrotoxicity, and mortality.

MAIN RESULTS

Analysis was by intention to treat. Continuous infusion of amphotericin B deoxycholate was associated with fewer chills or rigors ($P < 0.001$), less vomiting ($P = 0.004$), fewer headaches ($P = 0.05$)‡ (Table), and a greater creatinine clearance end-of-study-to-baseline ratio (median difference 0.19, 95% CI 0.09 to 0.29, $P = 0.001$) than was rapid infusion.

Continuous infusion was also associated with lower overall mortality at 3 months ($P = 0.03$)‡.

CONCLUSIONS

Patients who had continuous infusion of amphotericin B deoxycholate had reduced nephrotoxicity and fewer side effects related to infusion than did those who received rapid infusion. Overall mortality was lower in patients who received continuous infusion.

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*See Glossary.

†Information provided by author.

‡ P value calculated from data in article.

Continuous vs rapid infusion of amphotericin B deoxycholate at 3 months§

Outcomes	Continuous	Rapid	RRR (95% CI)	NNT (CI)
Chills or rigors	20%	63%	68% (41 to 84)	2 (2 to 5)
Vomiting	28%	60%	54% (22 to 74)	3 (2 to 9)
Headache	10%	28%	64% (2 to 87)	6 (3 to 327)
Mortality	10%	30%	67% (12 to 88)	5 (3 to 40)

§Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Amphotericin B deoxycholate has been the mainstay for treatment of invasive fungal infections for many years. However, the use of this agent is problematic because of the high frequency of adverse effects.

Amphotericin B deoxycholate delivered in lipid formulation decreases these side effects but is costly (1). Eriksson and colleagues reasoned that amphotericin B deoxycholate delivery by continuous rather than standard 4-hour infusion might mimic delivery by lipid formulation, with slower delivery to tissues, and thus decrease drug-related toxicities.

Patients randomly allocated to continuous infusion had a significant and clinically important decrease in the frequency of amphotericin B toxicities. Infusion-associated fever, chills or rigors, vomiting, and headache occurred in one third to one half as many patients as in those receiving rapid infusion, with an accompanying decrease in drug use to manage these side effects. Furthermore, decline in creatinine clearance rate was significantly slowed with continuous infusion. Patients who received rapid infusion also had more dose reductions or infusion interruptions, which was probably attributable to side effects. This result possibly accounts for the difference in mortality at 3 months favoring

continuous infusion. The frequency of side effects observed in patients who received continuous infusion is comparable to those who have received amphotericin B lipid formulations in previous studies (1, 2).

The observations from this study are convincing, and the clinical problem of amphotericin B deoxycholate toxicity is important enough that continuous infusion should now be considered the appropriate regimen. A comparative trial of continuous-infusion amphotericin B deoxycholate with amphotericin B lipid formulation would be an important next step in understanding the optimal use of this agent.

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References

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