Fluid and potassium replacement during amphotericin treatment: When just a little bit won't do

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Background

Treatment of cryptococcal meningitis with prolonged intravenous (IV) amphotericin poses a challenge in managing acute kidney injury (AKI) and electrolyte disturbance, both common and serious complications of therapy[1]. Nephrotoxicity occurs via two mechanisms: pre-glomerular vasoconstriction; as well as altered membrane permeability leading to distal tubular cell damage, renal tubular acidosis (RTA), urinary concentrating impairment and electrolyte abnormalities[1,2] (Figure 1).

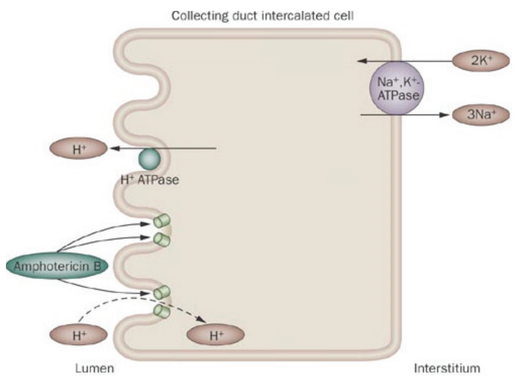


Figure 1. Tubular cell membrane pore formation and passive diffusion of hydrogen ions into the cell causing RTA[2].

Objective

To describe two cases where pharmacist input was integral to managing considerable fluid and electrolyte replacement during amphotericin therapy.

Clinical Features

Patient 1 is a 25 year-old male (weight 119kg, height 185cm) with cryptococcal meningitis treated with amphotericin for 29 days (conventional 100mg IV daily - 5 days, lipid complex 500mg IV daily - 24 days).

Patient 2 is a 70 year-old male (weight 74kg, height 171cm) with cryptococcal meningoencephalitis who received amphotericin for 26 days (conventional 75mg IV daily - 2 days, with-held for 2 days due to creatinine rise, lipid complex 400mg IV daily - 24 days).

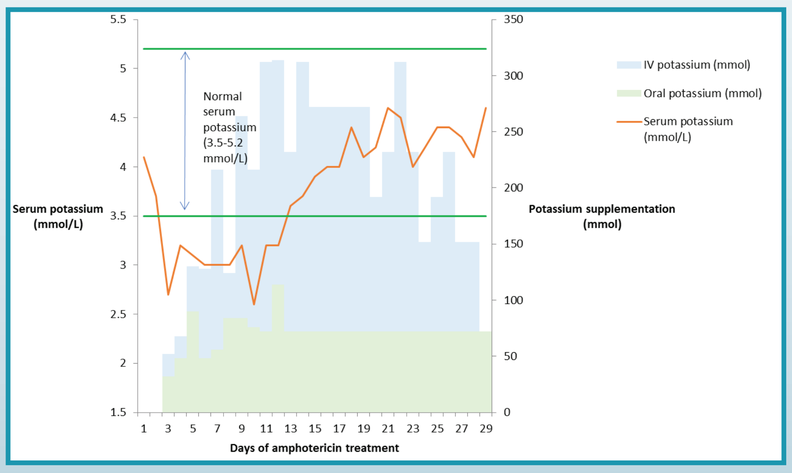
Both patients were also treated with oral flucytosine, dose-adjusted according to renal function and informed by therapeutic drug monitoring.

Interventions, case progress and outcomes

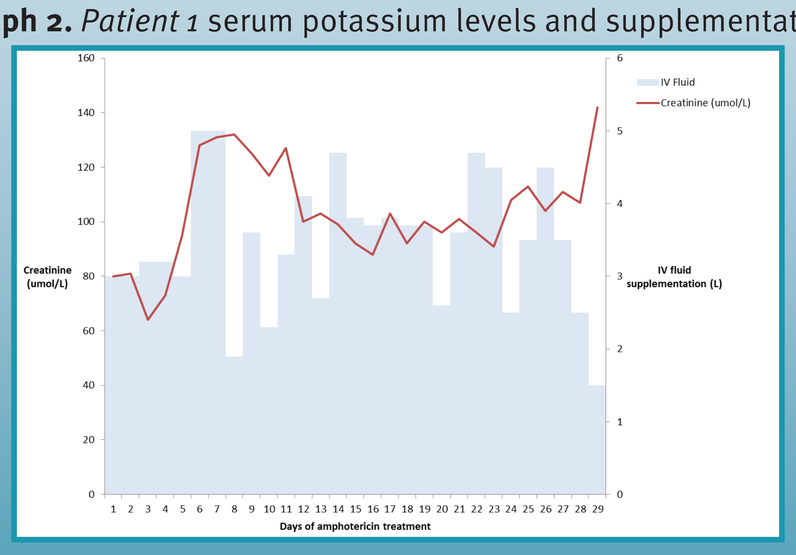
Patient 1

Throughout the 28-day amphotericin course, Patient 1 had profound potassium losses requiring ongoing oral and intravenous replacement (Graph 1). The pharmacist was proactively involved in logistical planning to enable administration of up to 200mmol of IV potassium per day. Significant challenges included maintaining adequate IV potassium supplementation within administration rate and concentration constraints, and management of PICC lumen time. The insertion of a PICC allowed usual peripheral concentrations to be exceeded, enabling the use of 40mmol/100mL bags over 2 hours, alternating with 1L bags. Potassium administration rate did not exceed 20mmol/hr, hence cardiac monitoring was not required. One lumen was allocated for continuous fluid and electrolyte supplementation, and the other for amphotericin administration. It was necessary to reserve at least 4 hours of "rest" time for the fluid lumen, to allow for delays between bag changes, and to use the infusion pump for amphotericin administration. Magnesium levels were maintained on 4-6 Magmin tablets per day from Day 4 onwards. Patient 1 had a decline in renal function which fluctuated throughout the course and was managed with IV fluid administration (Graph 2). Due to the long terminal half-life of amphotericin (approximately 16 days)[2], it was expected that the patient would need to maintain a high oral fluid intake even after therapy was complete. Creatinine peaked from a baseline of 80µmol/L to 151 µmol/L the day after completing amphotericin therapy, corresponding to the scaling back of IV fluids and encouragement of oral fluids for the previous two days as part of discharge planning. Creatinine returned to baseline approximately one month after the completion of amphotericin therapy.

Graph 1. *Patient 1* serum potassium levels and supplementation



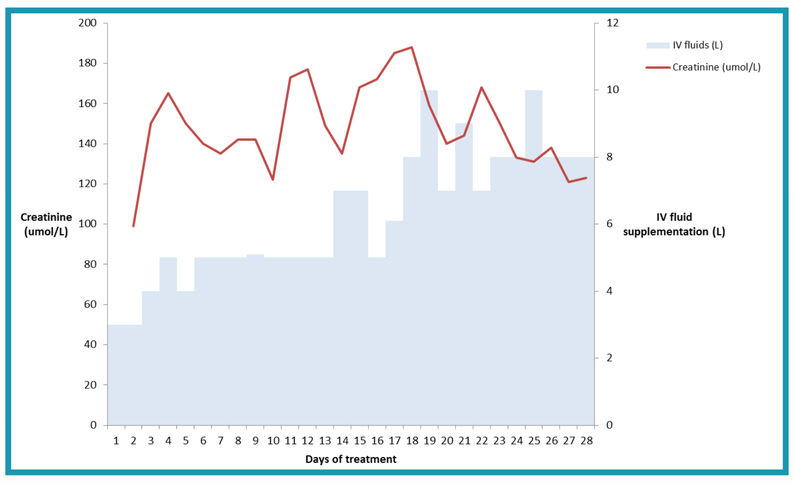
Graph 2. *Patient 1* serum potassium levels and supplementation



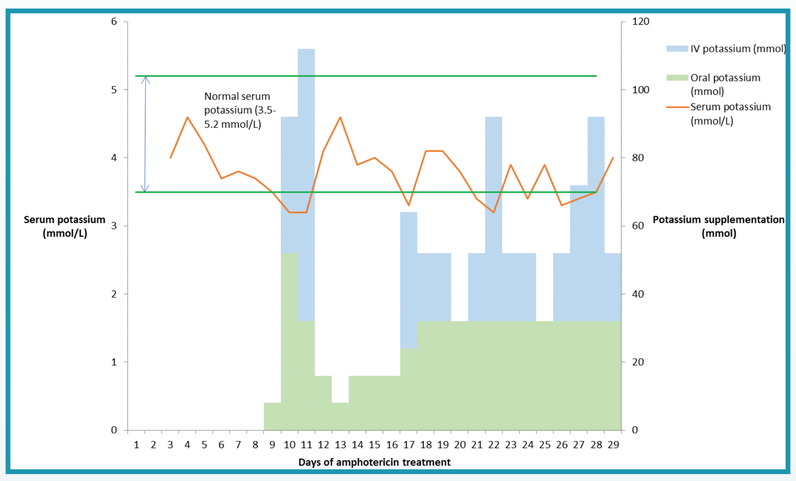
Patient 2

Patient 2 had significant AKI during amphotericin therapy, responsive to large volume IV fluid replacement up to 10L per day (Graph 3). After the first two days of conventional amphotericin, therapy was with-held for two days due to a rapid rise in creatinine (from a baseline of 81µmol/L to 150µmol/L on Day 3), and then switched to amphotericin lipid complex thereafter. Despite intensive IV fluid hydration, creatinine peaked at 188 µmol/L on Day 18. In response, IV fluid was increased to 10L on Day 19, after which time the creatinine steadily declined for the remainder of the course. Due to the large volumes of IV fluids administered and concurrent confusion in the setting of meningoencephalitis, Patient 2 experienced frequent episodes of urinary incontinence which necessitated the insertion of an indwelling catheter. Due to the long half-life of amphotericin, IV fluids continued for 2 weeks after completion of therapy with gradual transition to an oral fluid target. Ongoing cognitive deficits made it difficult to achieve the required oral fluid target, and there was a second peak in creatinine (202µmol/L) 7 days after ceasing amphotericin therapy, hence the ongoing requirement for IV supplementation. Creatinine returned to baseline 3 months after completing therapy. Potassium supplementation was required from Day 9 onwards (Graph 4). Magnesium levels were maintained on 6 Magmin tablets per day from Day 8 onwards, also frequently requiring IV top-ups of between 10-40mmol per day.

Graph 3. *Patient 2* serum creatinine and IV fluid supplementation



Graph 4. *Patient 2* serum potassium levels and supplementation



Summary Table. Maximum and mean 24-hourly fluid and electrolytes administered during amphotericin treatment course

Administration over 24 hours		*Patient 1*	*Patient 2*
IV fluid	Maximum	5L (Day 6 & 7)	10L (Day 19 & 25)
	Mean	3.5L	6.3L
Potassium	Maximum	314 mmol (Day 12) 200 mmol IV 2 Chlorvescent® 9 Span-K®	112 mmol (Day 10) 80 mmol IV - 4 Span-K®
	Mean	195 mmol	37 mmol
Magnesium	Maximum	26 mmol (Day 11 & 12) 20 mmol IV 4 Magmin®	49 mmol (Day 14) 40 mmol IV 6 Magmin®
	Mean	8 mmol	15 mmol

Conclusion

AKI and profound electrolyte disturbances are significant challenges of amphotericin therapy requiring proactive and intensive fluid and electrolyte replacement. Pharmacists can play a key role by recognizing and raising prescriber awareness of the ongoing and potentially severe nature of AKI and electrolyte deficits, as well as assisting to prevent complications through careful planning of daily fluid and electrolyte requirements and administration practicalities.

References

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2. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol 2009;5(4):193-202.
3. Adedoyin A, et al. A pharmacokinetic study of amphotericin B lipid complex injection (Abelcet) in patients with definite or probable systemic fungal infections. Antimicrob Agents Chemother 2000; 44: 2900-2.

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