Exposure to intravenous posaconazole in a critically ill patient during extracorporeal membrane oxygenation (ECMO): first case report

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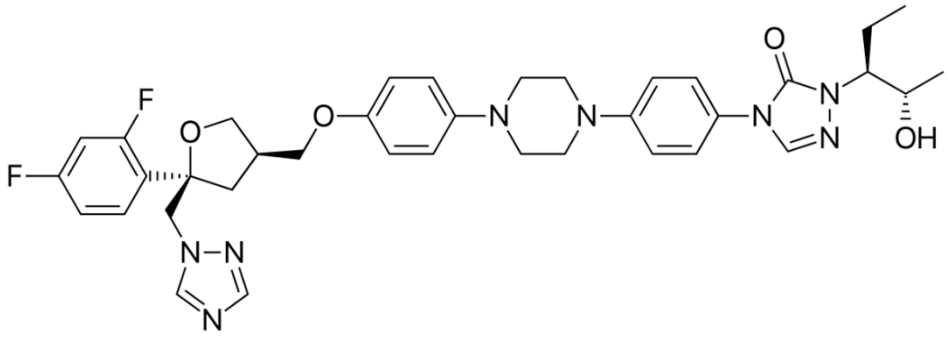
1. Background
2. Methods
3. Results
4. Discussion



1. Background

IV formulation posaconazole

- ⊕ Bioavailability 100%
- ⊕ Administration in mechanically ventilated patients

But…

- ⊖ PK data in critically ill and ECMO are scarce

Question 1

Do you think ECMO can have an influence on the plasma posaconazole concentration?

1. Yes

2. No

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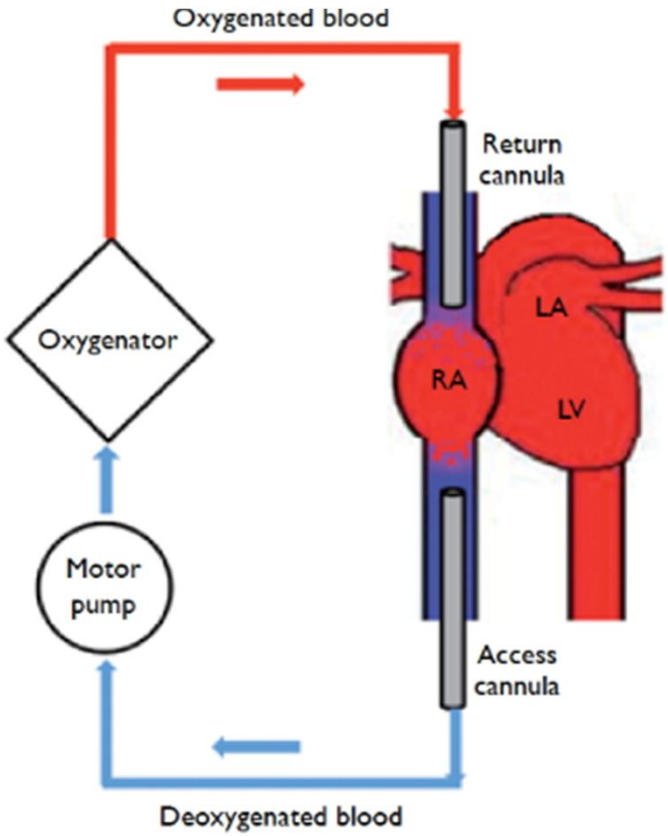
2. No

1. Background

ECMO can possibly influence drug levels

– Vd ↑

– Sequestration circuit



1. Background

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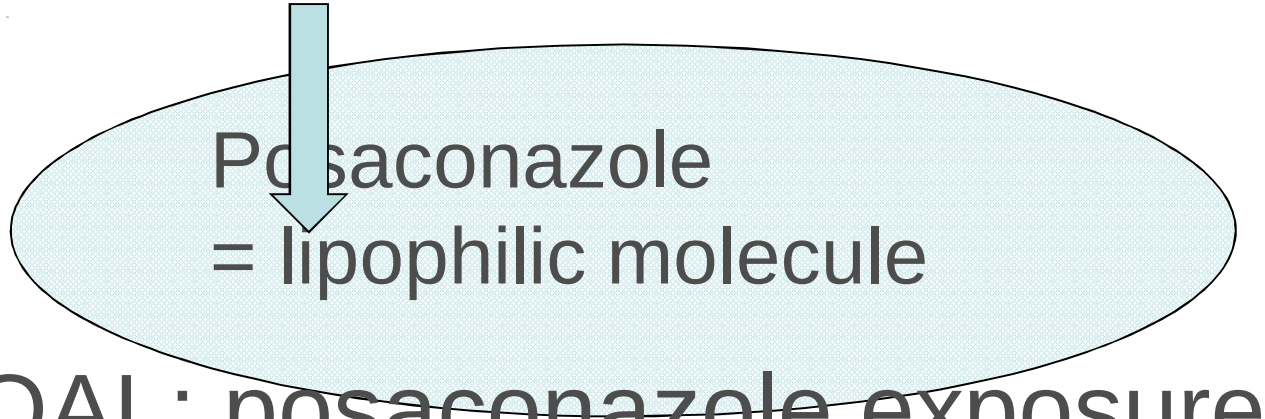
- Vd ↑
- **Sequestration circuit**



GOAL: posaconazole exposure in critically ill with ECMO

2. Methods

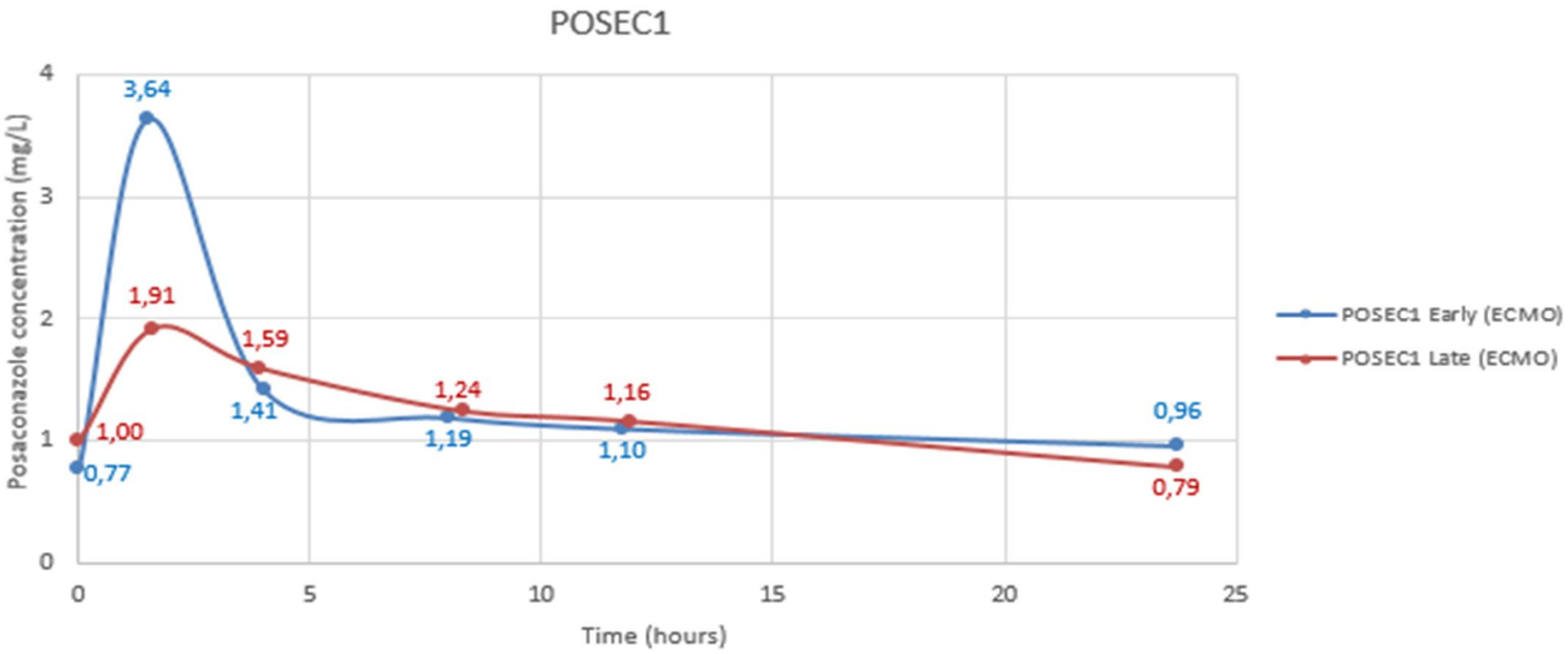
- Study drug

Indication	posaconazole prophylaxis for prevention of influenza associated aspergillosis
Dose	Day 1 300mg BD Day 2-7 300mg OD

- Plasma sampling
  - Early & late day
  - Before and 1.5, 4, 8, 12 and 24h after start infusion

3. Results

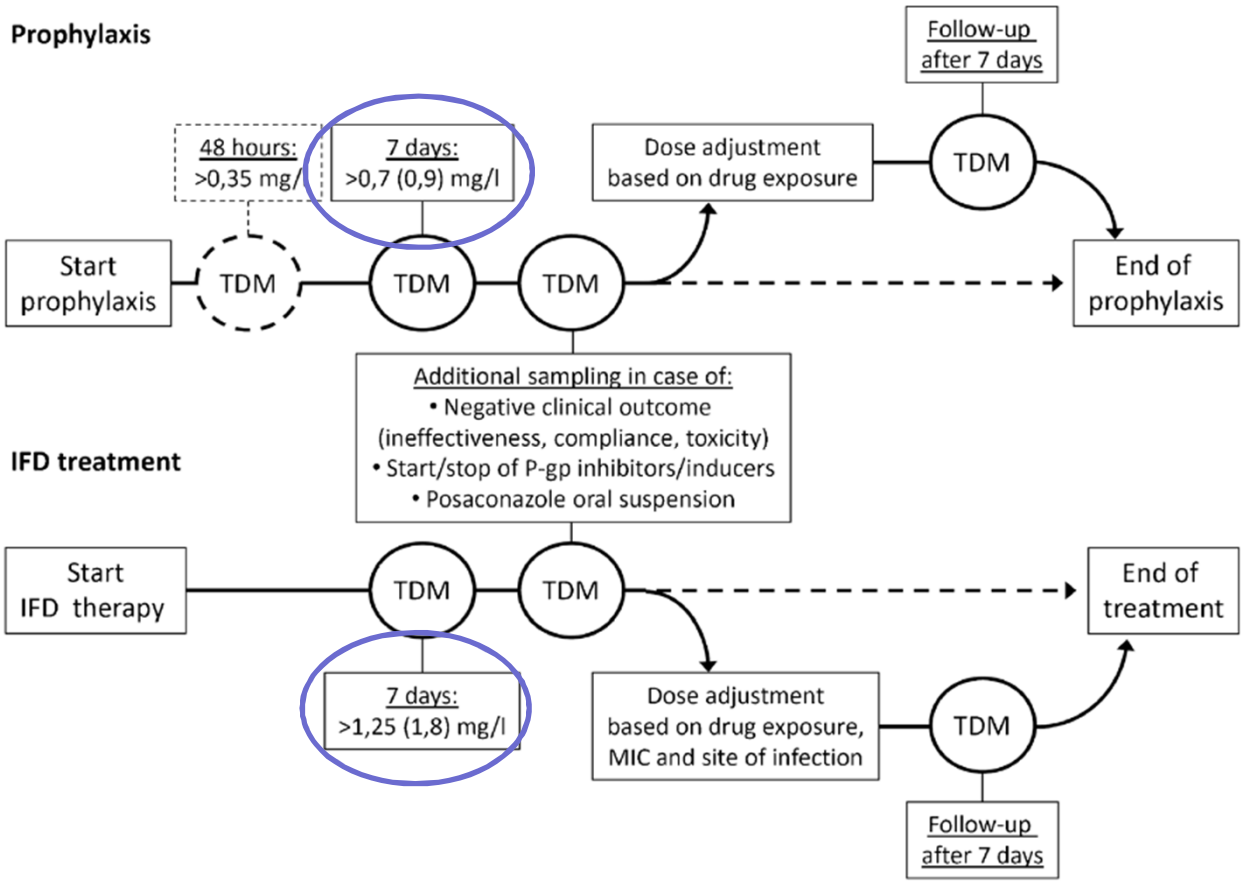
Population	Time	C_{min} (mg/L)	C_{avg} (mg/L)	C_{max} (mg/L)	AUC_{0-24} (mg.h/L)
ICU+ECMO	Day 2	Day 2: 0.77 Day 3: 0.96	1.32	3.64	31.74
	Day 7	Day 7: 1.00 Day 8: 0.79	1.19	1.91	28.52



4. Discussion

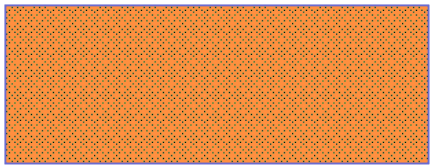
All C_{min} > 0.7 mg/L but < 1.25 mg/L

C_{min} (mg/L)
Day 2: 0.77
Day 3: 0.96
Day 7: 1.00
Day 8: 0.79



Dekkers et al. Curr Fungal Infect Rep. 2016;10:51–61.

4. Discussion



Time	C_{avg} (mg/L)
Day 2	1.32
Day 7	1.19

within EMA target range of 0.5 – 2.5 mg/L

The exposure target range for the use of POS IV solution in subjects was set as below:

Mean steady-state Cavg of around 1,200 ng/mL (or AUC[0-24] of 28,800 ng.hr/mL) with at least 90% of the subjects between 500 ng/mL (or AUC[0-24] of 12,000 ng.hr/mL) and 2,500 ng/mL (or AUC[0-24] of 60,000 ng.hr/mL); and

• No subject with mean Cavg at steady-state above 3,650 ng/mL (or AUC[0-24] above 87,600 ng.hr/mL); and

• No subject with mean Cavg at steady-state below 200 ng/mL (or AUC[0-24] below 4,800 ng.hr/mL).

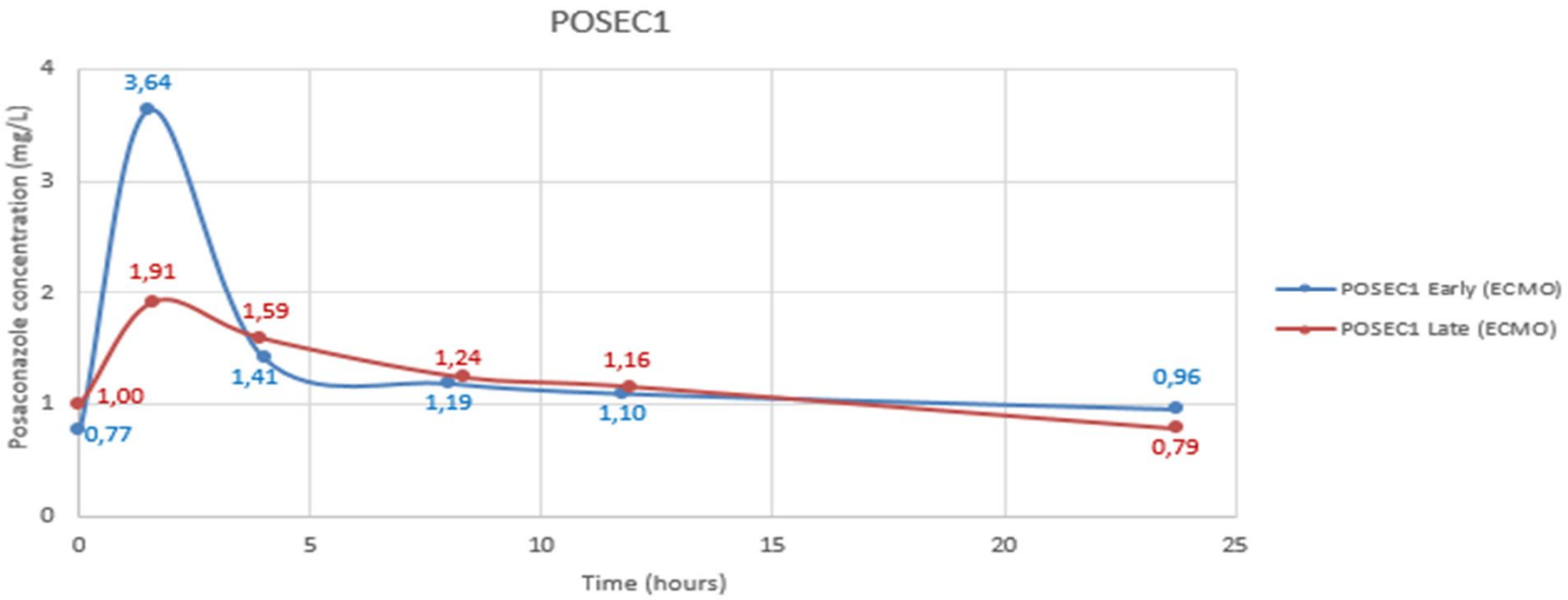
Cavg was the exposure parameter used in studies with POS oral suspension and therefore this was the major bridging PK parameter. In addition to the Cavg as the major bridging parameter, the Cmin is taken into account and evaluated against the Cavg requirements.

European Medicines Agency. Assessment report 2014. Noxafil.

4. Discussion

Remarkable difference in C_{max}

Time	C_{max} (mg/L)
Day 2	3.64
Day 7	1.91



Question 2

Do you have an explanation for the difference in C_{max} between day 2 and day 7?

Time	C_{max} (mg/L)
Day 2	3.64
Day 7	1.91

1. The further in ECMO therapy, the more pronounced the influence on drug concentrations will be
2. The difference is due to the loading dose on day 1
3. On the late day, the patient was dialysed
4. More research is needed to answer this question

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4. Discussion

	Population	Time	AUC_{0-24} (mg.h/L)	C_{max} (mg/L)	C_{min} (mg/L)	C_{avg} (mg/L)
Case	ICU+ECMO	Day 2	31.74	3.64	Day 2: 0.77 Day 3: 0.96	1.32
		Day 7	28.52	1.91	Day 7: 1.00 Day 8: 0.79	1.19
Cornely *et al.* (J Antimicrob Chemother 2017; 72:3406-3413)	Hematology	Day 10 or 14	36.10	3.28	1.09	1.50

- Posaconazole exposure ≈ Cornely *et al.*
- Variable exposure might be explained by patient- and disease-specific characteristics

4. Discussion

- C_{min} and C_{averg} within the provided target ranges
- Exposure ≈ Cornely *et al.*

⇒ Based on this patient no dramatic influence on posaconazole concentrations is observed

⇒ More research needed

THANK YOU FOR YOUR ATTENTION