

Fluconazole dose adjustment by PK/PD approach for drug effectiveness in ICU septic burned patients with fungal infection caused by *Candida glabrata* MIC 32 mg/L



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Background

- Burned patients are easy target for fungal colonization/infection due to normal skin barrier disruption and immunocompromised state associated with burn lesions.
- Systemic inflammatory response syndrome in critically ill burned patients leads to altered pharmacokinetics affecting drug exposure.
- Higher than usual doses seems to be necessary even for typical susceptible microorganisms.
- PK/PD approach contributes to optimization and individualization of antimicrobial therapy.

Objectives

To investigate fluconazol empirical usual dose regimen attainment to PK/PD recommended target.

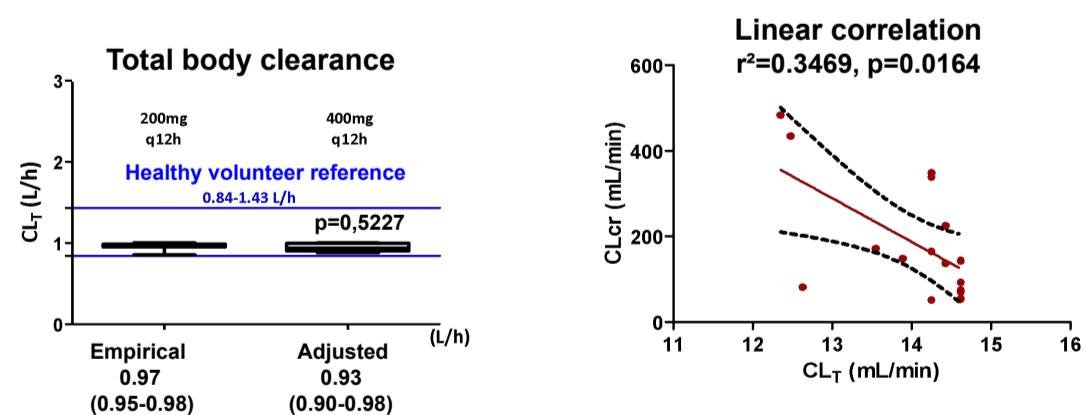
Results

Critically ill burned patients characteristics

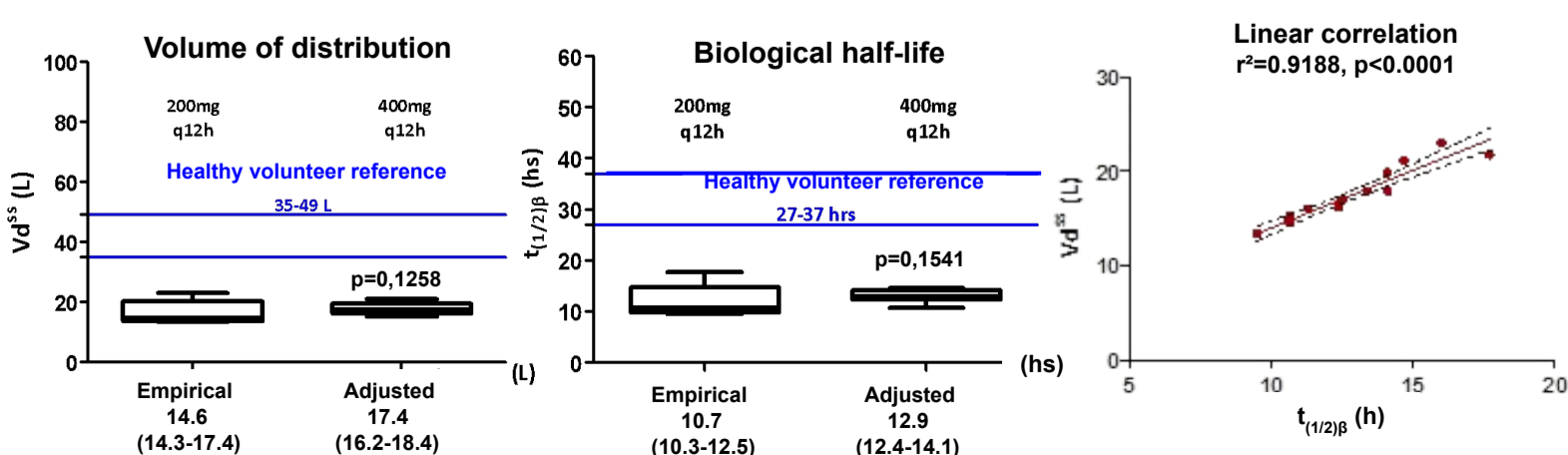
Patient	Gender	Age (years)	ABW (kg)	IBW (kg)	^a BSA (m ²)	^a BMI (kg/m ²)	Burned TBSA (%)	Burn type	MV IL	SAPS-3	Surgery (n)	ICU LOS (days)
#1	M	43	102	70	2.20	35	18	E	N	55	12	47
#2	M	33	70	70	1.82	24	75	T	Y	61	15	53
#3	F	32	60	51	1.64	23	55	T	Y	55	5	41
#4	M	42	70	70	1.82	24	34	E	Y	53	15	180
#5	F	29	65	55	1.73	24	45	T	Y	64	8	62
#6	F	36	70	55	1.80	26	47	T	Y	61	3	30
#7	M	48	75	70	1.89	26	50	E	Y	69	10	59
#8	F	31	60	51	1.64	23	42	T	Y	70	4	36
Median (IQR)	4F/4M	35 (32-42)	70 (64-71)	63 (54-70)	1.81 (1.71-1.84)	24 (23-26)	46 (40-51)	5T/3E	7/8	61 (55-65)	9 (5-13)	50 (40-60)

Abbreviations: M – male; F – female; ABW – actual body weight; IBW – ideal body weight; BSA – body surface area; BMI – body mass index; TBSA – total body surface area of burn; E – electrical burn; T – thermal burn; Y – yes; N – no; MV/IL – mechanical ventilation/inhalation lesion; SAPS-3 – Simplified Acute Physiology Score 3; ICU LOS – intensive care unit length of stay; IQR – interquartile range.
Note: ^aBSA and BMI equations are based in ABW.
Statistic: Prism v.5.0; median (IQR)

No statistical difference was observed in median serum creatinine, creatinine clearance, C-reactive protein, leukocytes/neutrophil cell count and pharmacokinetics parameter between empirical and adjusted set.



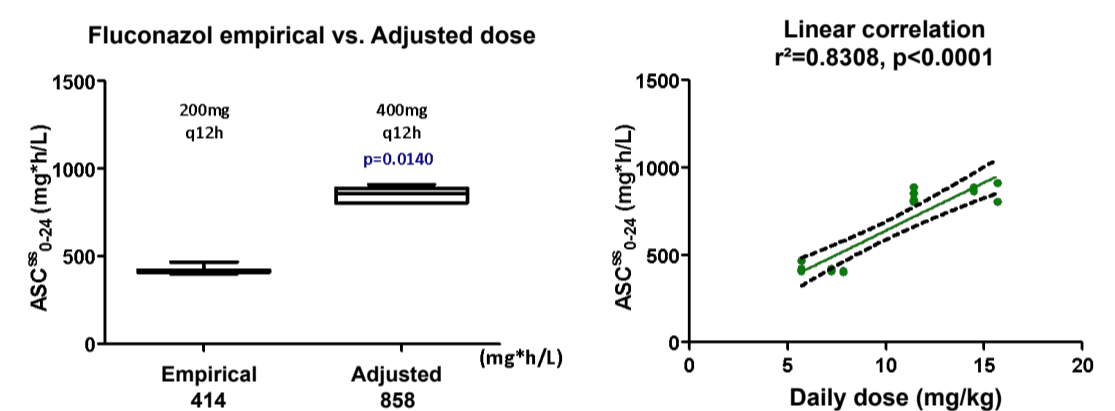
Total body clearance seems to be unchanged compared to healthy volunteers. There was a significant linear correlation between creatinine clearance and total body clearance.



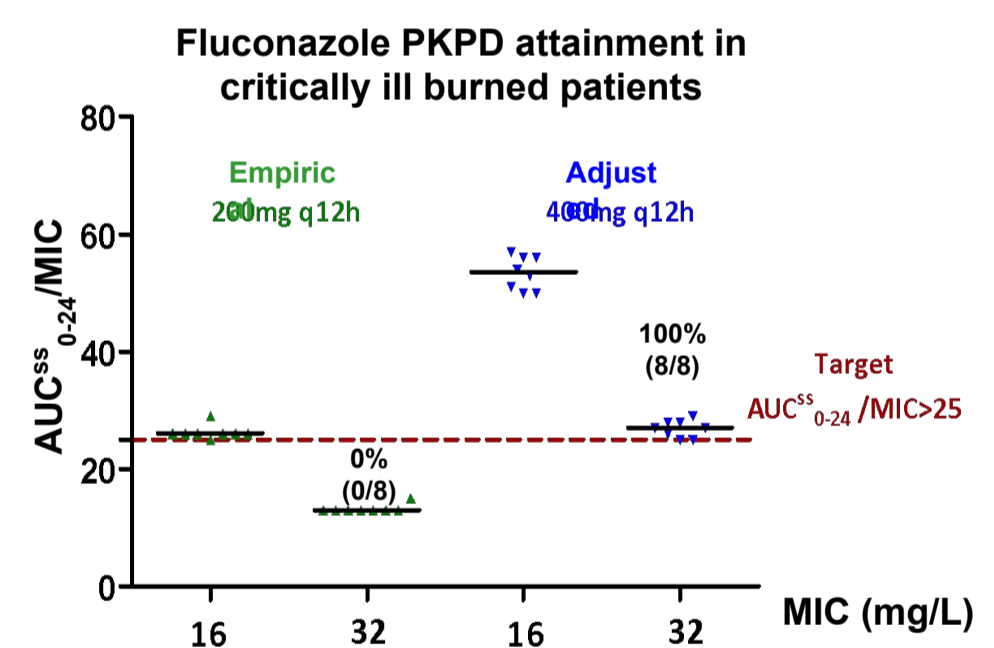
Important changes were observed in volume of distribution and biological half-life, both reduced about three times in these burn patients compared with data reported in healthy volunteers.

Casuistry and Methods

- Inclusion criteria
 - Burned patients in septic shock with use of vasopressor drug
 - Confirmed infection by *Candida glabrata*
 - Fluconazole therapy ≥72 hours
- Exclusion criteria:
 - Neutropenia and renal impairment/renal replacement therapy
- PK/PD was investigated in two settings: after empirical usual dose (200 mg q12h) and after adjusted dose (400 mg q12h).
- Drug serum concentration was measured in blood sampling at the end of one-hour pump infusion, two hours after infusion (3rd hour) and before the next dose (12th hour) by HPLC-UV.
- PK/PD approach was performed based on the area under the concentration-time curve over 24-hours (AUC^{SS}₀₋₂₄). Predictive index for drug effectiveness AUC^{SS}₀₋₂₄/MIC > 25 was considered.



There was a significant linear correlation between fluconazole daily dose and AUC^{SS}₀₋₂₄.



An increase of fluconazole daily dose from 5.7 to 11.4 mg/kg was necessary to achieve PK/PD target according to antifungal therapy individualization for *Candida glabrata* MIC 32 mg/L.

Conclusion

- Fluconazole pharmacokinetics is altered in critically ill burn patients with impact on desired outcome.
- Dose adjustment was required for target attainment against *Candida glabrata* (MIC 32 mg/L) and clinical cure for all patients.
- Drug serum measurements and PK/PD approach improve effectiveness in burn patients by real time therapy individualization.

Disclosure

All authors declare no conflict of interest. Copyrighted - Reproduction prohibited.

Acknowledgment:



FCF-USP