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Impact of one High Dose of Ceftazidime Administrated before Minimally Invasive Multimodal Endoscopic Prostate Surgery

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1. Introduction

Ceftazidime (CFZ) is a generic antibiotic compared to other third-generation cephalosporins of large spectrum useful in the treatment of bacterial Urinary Tract Infections (UTIs). According to pharmacokinetic studies, CFZ is not metabolised in the human body, being eliminated in the same form through biological fluids [1]. CFZ microbial sensitivity is against gram-positive (aerobic: *Staphylococus aureus / faecalis, Streptococcus pyogenes / agalactiae*; anaerobic: *Clostridium perfringens, Peptostreptococcus spp*) and gram-negative (aerobic: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus spp*; anaerobic: *Fusobaterium, Bacteroides*) microorganisms. Its kinetics is linear in the single dose range from 0.5 to 2 g after intravenous or intramuscular administration [2, 3].

The work aim is to evaluate, by HPLC-DAD, the CFZ partition during multimodal endoscopic surgery in the biological material (blood, prostate tissue) of the patients with prostate tumour diagnosis in order to prevent the postoperative UTIs, the contamination from the hospital, and the bacterial resistance, and also to perform an impeccable minimally invasive technique, realised in a minimal amount of time, with reduced blood loss, reduced lavage time, short hospitalisation, and quick catheter suppression.

2. Materials and methods

The biological materials were collected during the endoscopic multimodal surgery (Thulium laser vaporisation + Bipolar TURP (Transurethral Resection of the Prostate) + Plasma vaporisation) from 22 patients with benign prostatic hyperplasia, without urinary infection, with the following average values: age – 65 years, prostate volume – 110 cm^3, PSA – 4.3 ng/mL.

To isolate CFZ from the biological materials, different sample treatments have been applied. The blood samples were collected on heparin treated tubes, after CFZ administration: just before incision (15–45 min), at the end of surgery (1.5–2.5 h) and then at 8 h. The samples were submitted to centrifugation and PTFE filtration. CFZ from tissue was isolated using a modified QuEChERS method [4]. The extracts were analysed by HPLC-DAD at 255 nm, on Luna C18 column with acetonitrile + 1% formic acid, in gradient elution mode [5].

3. Results

Validation of HPLC-DAD method

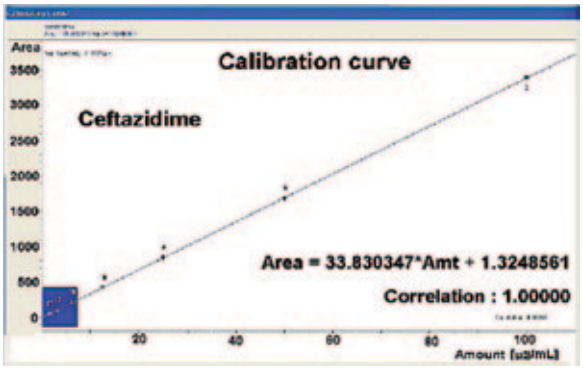

Figure 1 *Validation of HPLC-DAD method. Calibration curve (LOD 0.28 µg/mL) and CFZ chromatograms*

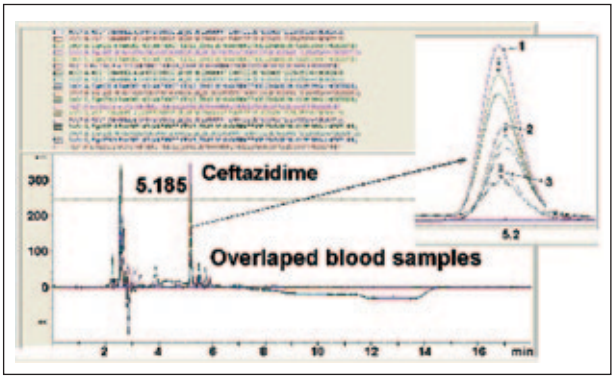

Figure 1 Continued *Validation of HPLC-DAD method. Calibration curve (LOD 0.28 µg/mL) and CFZ chromatograms*

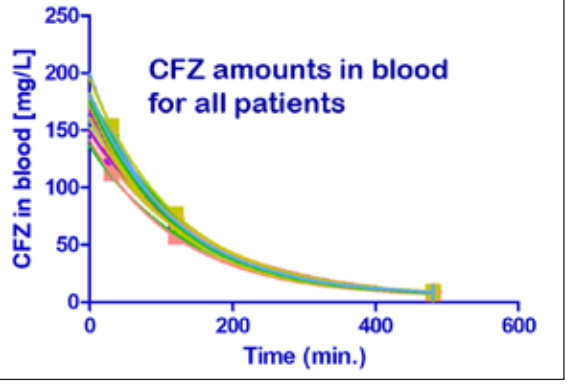

Figure 2 *CFZ amounts found by HPLC-DAD method in the collected blood samples from 22 patients*

Table 1 *CFZ content in blood and tissue. Values of Body Mass Index (BMI) and Creatinine versus the normal values of 18.5–25 kg/m² and 0.7–1.2 mg/dL respectively*

No.	BMI [kg/m²]	Creatinine [mg/dL]	Blood [mg/L]			Tissue [µg/g]
			15'–45'	1.5–2.5 h	8 h	
1.	31.83	1.15	**120.04**	**64.53**	**7.89**	**8.23**
2.	30.10	0.87	**122.27**	**64.58**	**7.92**	**9.04**
3.	29.28	1.00	**110.41**	**59.32**	**7.53**	**7.30**
4.	29.66	1.19	**128.03**	**68.69**	**8.45**	**8.62**
5.	26.02	1.20	**123.17**	**69.76**	**8.61**	**8.77**
6.	33.80	1.10	**139.32**	**67.59**	**8.19**	**8.46**
7.	31.79	1.20	**131.79**	**63.94**	**7.89**	**7.95**
8.	30.18	1.09	**127.68**	**64.87**	**8.02**	**8.08**
9.	36.15	1.19	**134.51**	**72.69**	**8.86**	**8.18**
10.	24.44	1.02	**135.28**	**73.08**	**8.91**	**8.23**
11.	22.49	0.81	**136.37**	**64.12**	**7.87**	**7.98**
12.	30.71	0.72	**145.28**	**74.51**	**9.03**	**8.43**
13.	29.86	1.02	**151.91**	**69.09**	**8.43**	**8.67**
14.	21.91	0.80	**132.77**	**67.66**	**8.19**	**8.47**
15.	28.37	0.82	**112.12**	**56.75**	**7.19**	**6.05**
16.	29.90	1.20	**139.43**	**72.28**	**8.51**	**10.12**
17.	23.26	1.17	**153.70**	**76.50**	**9.15**	**8.71**
18.	30.11	0.92	**135.83**	**68.98**	**8.37**	**8.66**
19.	29.03	0.85	**142.36**	**69.82**	**8.29**	**8.77**
20.	27.39	1.20	**133.68**	**63.64**	**7.97**	**7.91**
21.	26.66	1.07	**137.68**	**67.85**	**8.18**	**8.50**
22.	28.32	1.11	**142.22**	**70.57**	**8.71**	**9.88**

Statistics

Spearman correlation coefficient values (rS)

	A	B	C	D	E	F	G
1		t1/2	bmi	creat	tissue	15'-45'	1.5-2.5h
2	t1/2						
3	bmi	0.137211					
4	creat	0.137678	0.197735				
5	tissue	0.105085	-0.10169	0.116214			
6	15'-45'	-0.47261	-0.10785	-0.06912	**0.480226**		
7	1.5-2.5h	0.276115	-0.05251	0.089519	**0.618079**	**0.689441**	
8	8h	0.296045	-0.05876	0.206067	**0.561617**	**0.627684**	**0.963842**
9							
10							

The bold values are statistically significant (p<0.05).

Strong correlation:

CFZ conc. in tissue *versus* CFZ conc. in blood at 1.5–2.5 and 8 hours after CFZ administration.

CFZ conc. in blood at 15–45 min *versus* CFZ conc. in blood at 1.5–2.5 and 8 hours after CFZ administration.

Very strong correlation

CFZ conc. in blood at the end of surgery (1.5–2.5 h) *versus* CFZ conc. in blood at 8 hours after CFZ administration.

4. Conclusions

CFZ extraction methods from blood and prostate tissue and an HPLC-DAD method for the CFZ determination were performed.

The UTI antibiotic prophylaxis using a high 2 g dose of CFZ is very useful for the patients with benign prostate hyperplasia of large volume, operated by the minimally invasive multimodal endoscopic surgery (Thulium laser + Bipolar TURP + Plasma vaporisation).

Our work demonstrated the quick CFZ presence into the patient's body after its administration, at a concentration level that ensures the patient's protection against pathogenic agents during the whole intervention of prostate surgery.

Using the multimodal urological endoscopic technique, the quality of life of the patient is improved in comparison with each technique applied separately by: increased urinary flow, minor irritation symptoms, better haemostasis, shorter lavage period, shorter operation time, minor risk of reintervention, shorter duration of catheter

maintenance, shorter hospitalisation, diminished infection risk, absence of complications of antibiotic prophylaxis (diarrhea, candidiasis, antibiotic resistance).

We consider that the use of one CFZ high dose (2 g) before surgery is beneficial in preventing UTI complications. This fact is explained by the CFZ higher concentration in blood and tissue, more than the minimum inhibitory concentration (MIC 8 mg/L) recommended by EUCAST (European Committee on Antimicrobial Susceptibility Testing). Thus, the CFZ concentration in blood and tissue overcomes the critical bacterial resistance.

5. Acknowledgements

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