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Intraoperative Positive Fluid Balance Improves Tissue Diffusion of Ceftizoxime

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Key Words
Antibiotic · Ceftizoxime · Surgical infection prophylaxis · Intraoperative fluid balance · Pharmacokinetics

Abstract
Aim of Study: To demonstrate that administration of fluids and the consequent improvement of fluid balance during a surgical procedure can modify the tissue diffusion of ceftizoxime. ***Methods:*** Twenty-eight patients (30–79 years) undergoing major abdominal surgery of the colon were administered ceftizoxime 30 mg/kg i.v. at induction of anesthesia. A sample of arterial blood was taken before administration of the drug (t_0) and then again at the time of vascular occlusion of the colon segment to be removed (t_1). A sample of the segment of removed colon was taken. The patients were divided into two groups on the basis of the fluid balance between t_0 and t_1: group A (n = 17) with a fluid balance <1,000 ml and group B (n = 11) with a fluid balance >1,000 ml. The parameters evaluated in each group were: weight, height and age of the patients, serum and tissue antibiotic concentration, percent ratio of serum and tissue concentration, time elapsed between t_0 and t_1, volume of administered fluids between t_0 and t_1, diuresis and hourly diuresis between t_0 and t_1 and body fluid distribution, obtained using a bioelectrical impedance analyzer. The mean results obtained in the two groups were then compared using Student's t test. ***Results:*** The balance of fluids calculated up to t_1 was 675 ± 308 ml for group A and 1,411 ± 405 ml for group B ($p < 0.01$). The means of the recorded values that showed statistically significant differences were: mean percent concentration ratio (43.6 ± 8.4 vs. 84 ± 16%; $p < 0.05$), concentration in the colonic segment (16.3 ± 7.9 vs. 37.2 ± 25.9 mg/ml; $p < 0.05$), urinary volume gathered up to t_1 (538 ± 557 vs. 169 ± 104 ml; $p < 0.05$), hourly urinary volume up to t_1 (311.1 ± 296 vs. 97.6 ± 77.9 ml/h; $p < 0.05$), percent variation of resistance (95.1 ± 5.1 vs. 89.7 ± 8.6; $p < 0.05$). The other means did not show any significant statistical differences. ***Conclusions:*** A higher tissue water level seems to facilitate the penetration of the antibiotic into the tissue according to the pharmacokinetic characteristics of ceftizoxime: high amount of free drug (not bound to plasma proteins) and high hydrosolubility.

Introduction

The effectiveness of perioperative surgical infection prophylaxis depends on the following pharmacological aspects of the antimicrobial agent used: (a) the optimal time for antibiotic administration which is at induction of anesthesia [1]; (b) the highest concentration that must

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be obtained in the tissues where bacteria grow [2]; (c) the antibiotic serum concentration that must be higher than the minimal inhibitory concentration of the possible contaminating bacteria during an intervention [3].

Intraoperative fluid therapy could interfere with these aspects by modifing body fluid compartment distribution. In particular, fluid balance, hemodilution, and interstitial fluid content [4] may influence the tissue diffusion of antimicrobial agents.

The aim of this study was to evaluate whether an intraoperative positive fluid balance can modify the tissue diffusion of a cephalosporin (ceftizoxime) with a high amount of free drug (not bound to plasma proteins) and high hydrosolubility, administered for short-term surgical infection prophylaxis.

Patients and Methods

Thirty-five consecutive ASA I-II patients undergoing major colon surgery under general anesthesia, were admitted to the study. All the patients were informed about the goals of the study and gave their signed, written consent. All the patients were submitted to the same bowel preparation and were weighed immediately before the start of the intervention. The surgical procedures were performed by the same surgeon and via the same cutaneous xiphopubic incision with removal of a segment of colonic tissue. Seven patients requiring blood transfusions, blood derivatives, vasoactive drugs administered for hemodynamic instability or diuretics up to resection of the colon segment were excluded from the study.

The anesthetic technique was the following: premedication with morphine (10 mg i.m.) followed by the induction of anesthesia with Fentanyl (1.5 μg/kg), Propofol (2 mg/kg) and Atracurium (0.6 mg/kg), Isoflurane MAC95 in O_2 and air, and continuous intravenous administration of Atracurium (0.4 mg/kg/h until reawakening).

As the administration of different volumes of fluids can modify the clearance of the antibiotic, the protocols of fluid infusion were the same during the period of the study; crystalloid solutions (Ringer acetate) were given to all the patients at the dosage of 15 ml/kg/h during the first hour and 12 ml/kg/h up to the end.

Ceftizoxime 30 mg/kg was administered over 10 min through a peripheral vein at induction of anesthesia. A 5-ml arterial blood sample was taken immediately before the induction of anesthesia (t_0) to obtain the baseline standard serum antibiotic concentration and the hematocrit values. A second 5-ml arterial blood sample was taken at the time of vascular occlusion of the colonic segment to be removed (t_1) to measure the serum antibiotic concentration and hematocrit.

A fragment of the removed segment of approximately 5 × 1 cm was washed with saline, dried with sterile gauze and conserved in a test tube at –20°C. The tissues were weighed, diluted 1:1 (wt/vol) in sterile normal saline (pH 6.3), homogenized with a Polytron PT 10–35 homogenizer (Kinematica, Lucerne, Switzerland), and centrifuged at low speed; the supernatant was used for the assay [5].

The concentration of the antibiotic in serum and tissues was determined in triplicate by a validated large-plate agar diffusion technique, according to Good Laboratory Practice (GLP) standards [6, 7]. Ceftizoxime concentrations were determined using the Antibiotic Medium II (BBL) as the culture medium and *Escherichia coli* Sc 12,355 as the test organism, with a lower limit of sensitivity of 0.125 mg/l. Standard concentrations were prepared daily in pooled serum for blood samples and in normal saline for tissue specimens. The test organism was added by the surface layer technique. After homogeneous distribution of the culture, the excess liquid was removed with a pipette. The plates were incubated at 37°C in air overnight.

Best-fit standard curves were obtained by linear regression analysis. The linearity was $\log y = 0.102x - 1.8$ for plasma samples and $\log y = 0.103x - 1.95$ for tissues; the correlation coefficient was not less than 0.99. Intra-assay precision ranged from 4.5 to 9.8% for serum samples and from 1.3 to 7.4% for tissue samples. Inter-assay precision at a level of 1 mg/l ranged from 1.83 to 4.82% for serum and from 1.4 to 5.8% for tissues.

The ratio of serum antibiotic concentration at t_1 to tissue antibiotic concentration was calculated as percent ratio. The fluid balance between t_0 and t_1 was obtained by calculating the difference between the volume of the administered fluids and the intraoperative losses due to fasting (2 ml/kg/h), perspiratio insensibilis (8 ml/kg/h of surgery) and diuresis. A cutoff value of intraoperative fluid balance was chosen (1,000 ml) to divide the patients into two groups on the basis of the intraoperative fluid balance reported in other works [8, 9] and the time between the induction of anesthesia and the time of vascular exclusion of the colonic segment to be removed previously measured (about 90 min): group A (n = 17) with in a fluid balance between t_0 and t_1 <1,000 ml and group B (n = 11) with in a fluid balance >1,000 ml. The mean weight, height and age were calculated in the two groups. To evaluate the effect of fluid balance on tissue diffusion of the antibiotic, the following parameters were registered or calculated: tissue concentration of the antibiotic (mg/ml); ratio of tissue to plasma concentration (%); diuresis between t_0 and t_1 (ml); hourly diuresis between t_0 and t_1 (ml/h), hematocrit between t_0 and t_1 (expressed as percentage), and time elapsed between t_0 and t_1 (min).

To evaluate the body compartment distribution of administered fluids, an impedance analyzer (BIA/STA^{TM} Akern S.r.l. Florence, Italy) [10–12] was used to measure the variation of resistance between t_0 and t_1 (%), which expresses conductor opposition to the flow of alternate currents, and is inversely proportional to total body fluids, and the variation in capacitive reactance between t_0 and t_1 (%), which expresses condenser opposition to the flow of alternating current, and is directly proportional to cellular mass.

Statistical analysis was performed using Student's t test. A p value < 0.05 was considered significant.

Results

Group A (n = 17) and group B (n = 11) were not statistically different in terms of age (respectively: 57.7 ± 12 vs. 54.7 ± 14 years), weight (68.9 ± 8.4 vs. 72.9 ± 9.1 kg) and height (165 ± 9.9 vs. 168.2 ± 6.6 cm).

Group A patients had a mean fluid balance of 675 ± 308 ml, while group B had a higher mean fluid balance:

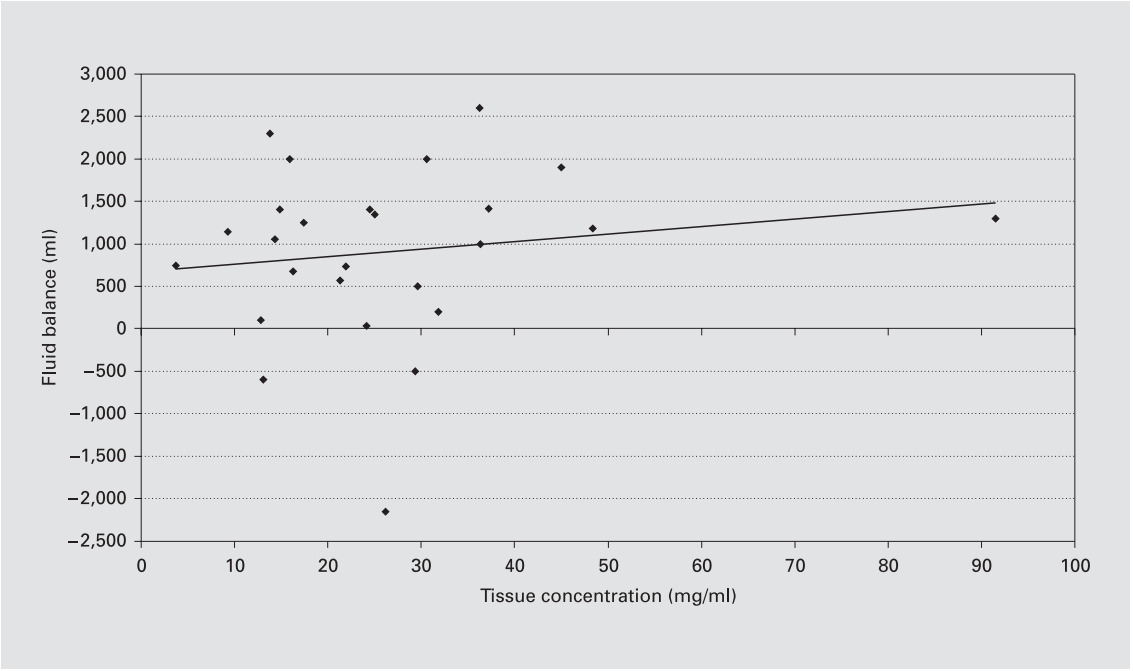

Fig. 1. Linear correlation between tissue concentration of ceftizoxime and intraoperative fluid balance in a series of patients submitted to major colon surgery.

Table 1. Mean (± standard deviation) of the values measured between t_0 (start of intervention) and t_1 (vascular exclusion of the colonic segment to be removed) in two groups of patients: group A: fluid balance <1,000 ml; group B: fluid balance >1,000 ml

	Group A (n = 17)	Group B (n = 11)	p
Fluid balance, ml	675 ± 308	1,411 ± 405	<0.05
Tissue /serum concentration, %	33.6 ± 8.4	93.9 ± 5.9	<0.05
Tissue concentration in the colonic portion, mg/ml	16.3 ± 7.9	37.2 ± 25.9	<0.05
Serum concentration, mg/ml	49.6 ± 24	40.1 ± 26.6	NS
Diuresis, ml	538 ± 557	169.3 ± 104	<0.05
Hourly diuresis, ml/h	311.1 ± 296	97.6 ± 77.9	<0.05
Hematocrit variation, %	83 ± 7.3	81.3 ± 10.4	NS
Resistance variation, %	95.1 ± 5.1	89.7 ± 8.6	<0.05
Capacitive reactance variation, %	108.8 ± 21	106.9 ± 27	NS
Time elapsed between t_0 and t_1, min	79 ± 34	92 ± 22	NS

Statistics: Student's t test; $p < 0.05$ was considered significant.

1,411 ± 405 ml ($p < 0.05$). Mean tissue concentration (16.3 ± 7.9 of group A vs. 37.2 ± 25.9 of group B, $p < 0.05$), mean ratio of tissue to serum concentration (43.6 ± 28.4% of group A vs. 84 ± 16% of group B; $p < 0.05$), mean diuresis (538 ± 557 ml of group A vs. 169 ± 104 ml of group B, $p < 0.05$), mean hourly diuresis (311.1 ± 296 ml/h of group A vs. 97.6 ± 77.9 of group B, $p < 0.05$) and mean percent variation of the resistance (95.1 ± 5.1 of group A vs 89.7 ± 8.6 of group B, $p < 0.05$) were statistically significantly different in the two groups ($p < 0.05$). The results are reported in table 1. The linear correlation between tissue concentration versus intraoperative fluid balance is shown in figure 1.

Discussion and Conclusion

The ideal characteristics of short-term antimicrobial prophylaxis include: use of antibiotic with a narrow spectrum of activity that includes the main pathogens responsible for postoperative infections, bactericidal effect, high therapeutic index, high tolerability, favorable kinetic parameters such as intravenous administration, long half-life of elimination and good tissue penetration [1].

The tissue diffusion of the antibiotic mainly depends on the gradient existing between plasma and tissue concentrations [13]. The gradient can be reduced if the antibiotic has a high percentage of protein binding: only the drug not bound to protein diffuses into tissue.

Anesthesia and surgical trauma can interact with tissue diffusion of drugs: hemodilution and replacement of intraoperative blood loss can determine homeostatic modifications in body fluid: general anesthesia and vasoactive drugs can modify the vascular system [14–16]. In addition, the depression of sympathetic tone observed at induction of anesthesia can cause previously adequate refilling pressure to become insufficient [17, 18]. Therefore, it may be necessary to expand the circulating volume before or immediately after the induction of anesthesia and during the intervention [19, 20].

Finally, the vascular splanchnic capacity can suddenly increase when intra-abdominal pressure is rapidly reduced by a laparotomy [21]. These physiological modifications, induced by anesthesia and surgery, require administration of fluid and a fluid balance between the administered fluids and the intraoperative losses must be achieved. The imperceptible losses include the amount of fluid that must be reinfused as a basal requirement (2 ml/kg/h) to maintain equilibrium and that lost due to surgery, which depends on the type of surgery (minor: 4 ml/kg/h, intermediate: 6 ml/kg/h, major: 8 ml/kg/h) [22]. The fluid balance must be calculated during surgery because fluid overload may be responsible for the onset of interstitial edema that can lead to hypoxemia at the pulmonary level and cause prolonged postoperative intensive care in patients with reduced cardiopulmonary capacity [23]. Instead, hypovolemia may lead to oliguria which, in addition to the reduction in glomerular filtration caused by the anesthetics, reduces cardiac output (and thus oxygen transport), decreasing the ability to tolerate and adapt to significant hematocrit and hemoglobin reduction [24].

The aim, therefore, is to re-establish the volume, which must be empirically evaluated by measuring the systemic arterial pressure, maintaining a value that can assure blood distribution to all the organs in a way that allows an adequate supply (DO_2) and consumption (VO_2) of oxygen.

The effects of hemodilution on the administered drug concentration during anesthesia and on the diffusion of these drugs in the interstitium are not well understood. Antibiotic tissue distribution during the intraoperative period and its relationship with intraoperative fluid balance has not been studied enough.

Ceftizoxime is a third-generation cephalosporin that, in recent years, has been widely used in the prophylaxis of postoperative infection for its particular efficacy against Enterobacteriaceae involved in the infections occurring in 'clean-contaminated' surgery. It has, therefore, become an alternative prophylaxis in abdominal surgery. After a bolus administration, the pharmacokinetics of ceftizoxime are well suited for prophylaxis. The concentrations reached after intravenous bolus administration of 1 g are 107–136 mg/l [25]. The volume of distribution studied in healthy volunteers is 15–28 liters [26]; the elimination half-life is 1.1–2.2 h [27]; serum clearance is 110–200 ml/min and renal clearance is 100–160 ml/min, just high enough to enable 70% of the drug to reach the urine within 2 h of administration [27]. Ceftizoxime does not pass the blood-brain barrier, and concentrates more in peripheral tissue [26]. The peak tissue concentrations are obtained 1–3 h after administration [27]. Ceftizoxime has a mean protein binding of 30% [28].

Ceftizoxime is mostly eliminated via glomerular filtration with a small component of unmodified elimination in urine through a tubular secretion mechanism [27]; its elimination is directly related to renal function and the dosage must be reduced in proportion to the decrease in creatinine clearance [29].

In clinical trials, prophylactic ceftizoxime has been shown to be able to reduce the incidence of postoperative infections just as cefazolin and cefamandole [30].

The pharmacokinetic characteristics of ceftizoxime (high water solubility, low protein binding, high renal clearance) could make its serum and tissue concentration curve particularly susceptible to fluid modifications. In fact, in a clinical trial on 53 patients undergoing emergency explorative laparotomy, Rosemurgy et al. [31] found that significant blood losses and subsequent abundant fluid replacement caused serious reductions in antibiotic serum concentrations that are significantly related to the appearance of postoperative infection.

In our study, we attempted to demonstrate that the tissue concentrations of ceftizoxime are increased by a high fluid balance.

To evaluate the body compartment distribution of administered fluids, an impedance analyzer was used to measure resistance, which expresses conductor opposition to the flow of alternating current, and is inversely proportional to total body fluids, and the capacitive reactance, which expresses condenser opposition to the flow of alternating current, and is directly proportional to cellular mass. These measurements were useful for assessing nutritional status [10] and dialysis-related modifications of body fluid distribution [11, 12].

The results of this paper demonstrate that in patients with higher fluid balance, in whom we observed reduced resistance to fluid accumulation, antibiotic diffusion and tissue concentration were higher.

On the basis of these results we hypothesize that if diuresis is reduced and the fluid balance increases during an operation, the total body fluid increases and a high fluid content at the tissue level allows the passage of a higher amount of drug in the tissues.

The differences observed in diuresis could be related, among others, to a relative preoperative dehydratation (but the bowel preparation was similar in all the patients) as well as to the effect of mechanical ventilation, or intraoperative minimal variation of kidney perfusion.

The passage of a higher amount of drug in the tissues is in agreement with the pharmacokinetic characteristics of ceftizoxime described above: i.e. highly free (not bound to plasma protein) and hydrosoluble drug [30].

Bioelectrical impedance is essential for the evaluation of the effects of fluid balance and provided significant supporting data. In a recent study, bioimpedance analysis variations demonstrated a strict correlation with fluid losses during hemodialysis, In that case, the bioimpedance analysis variation of 20% was equivalent to a body weight decreased by 2.8 ± 0.8 kg [32]. This value is comparable with the variation (7% for 1 liter of fluid balance) found in our study.

In our series of patients, the time elapsed from the administration of drug is not significantly related to the tissue concentration of ceftizoxime. This lacking correlation could mean that during a surgical intervention the tissue distribution of ceftizoxime is modified by fluid distribution more than by peak drug concentration.

Further study seems to be necessary to achieve a better understanding of the relationship between fluid administration and tissue penetration of antibiotic agents. Knowledge of the mechanisms of tissue diffusion of antimicrobial agents could help explain the infrequent but not rare failures of surgical infection prophylaxis, particularly in colon surgery [33]. For these reasons as well, the controversy over the choice of antibiotic for surgical prophylaxis is still open [34, 35].

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