Pancreatology 16 (2016) 719–725

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Theoretical approach to local infusion of antibiotics for infected pancreatic necrosis

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ARTICLE INFO

Article history:
Received 18 January 2016
Received in revised form
3 May 2016
Accepted 29 May 2016
Available online 30 May 2016

Keywords:
Acute necrotizing pancreatitis
Wall-off necrosis
Pancreatic drainage
Local antibiotic
Antimicrobials diffusion

ABSTRACT

Background/objectives: Infected pancreatic necrosis is a major complications of acute pancreatitis. If drainage is required, local administration of antibiotics through transmural nasocystic or percutaneous catheter may allow increasing local antibiotic concentrations. Drug diffusion becomes the main factor influencing local drug tissue penetration. The present study aims at providing the rationale for the design of new research protocols evaluating the efficacy of local antibiotics for infected pancreatic necrosis.
Methods: A review of microbiological data was performed for the most common organisms causing the infection, antibiotics spectrum and minimum inhibitory concentrations (MIC). A search of the physicochemical properties of antibiotics was performed to calculate the diffusion coefficients. An estimation of the antibiotic concentrations in pancreatic tissue was obtained using a mathematical model. Efficacy factors (EF) were calculated and the stability of the antibiotic solutions were evaluated to optimize the dosing regimen.
Results: Piperacillin, vancomycin and metronidazole achieve high concentrations in the surrounding tissue very fast. Imipenem, ceftriaxone, ciprofloxacin, gentamicin, linezolid and cloxacillin achieve intermediate concentration values. Tigecycline, showed the lowest concentration values (<2 mg/L). Calculated EF is highest for piperacillin and imipenem short after administration and near to surface diffusion area (0.5 cm), but EF of imipenem is higher at deeper areas and longer time after administration.
Conclusions: Considering obtained results, some solutions are proposed using saline as diluent and 25 °C of temperature during administration. Imipenem has the best theoretical results in empiric local treatment. Linezolid and tigecycline solutions are not recommended.

Acute pancreatitis is a potentially severe disease leading to organ failure and local and systemic complications [1]. Local complications are acute peripancreatic fluid collections, pancreatic pseudocysts, acute necrotic collections and walled-off necrosis (WON) [1]. It is generally accepted that asymptomatic sterile collections do not require any specific therapy [2]. Infected acute necrotic collections may occasionally require early intervention, but attempts to debride pancreatic necrosis before three weeks increases the risk of complications such as bleeding or fistula [2]. Infected WON is a clear indication for step-up therapy, starting by systemic antibiotic therapy in those patients who are clinically stable and minimally symptomatic and stepping-up to minimally invasive drainage procedures and necrosectomy as required [1–3].

Procedures to drain and/or debride pancreatic and peripancreatic necrosis include open surgery, minimally invasive surgical procedures, and percutaneous or endoscopic techniques [4]. The best approach is often multimodal and must be adapted to individual patients and to specific settings. The use of less invasive techniques allows surgical debridement to be deferred or avoided [5–7] and, in addition, is associated with less systemic complications after intervention and a lower risk of developing new organ failure [8,9]. Current evidences favor endoscopic drainage followed by endoscopic necrosectomy if required, or percutaneous catheter drainage followed by minimally invasive laparoscopic necrosectomy if needed as the preferred routes for intervention for infected

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http://dx.doi.org/10.1016/j.pan.2016.05.396
1424-3903/

pancreatic necrosis [5,8].

The addition of a transmural nasocystic catheter to the endoscopic transmural drainage to provide irrigation as a method to treat infected WON was first described in 1996 [10]. This nasocystic catheter allows for continuous cyst irrigation with about 1 L of saline per day, and additional manual boluses of 100–200 mL depending on size and appearance of the cyst [11]. Interestingly, the nasocystic catheter can also be used for local infusion of antibiotics, although the evidence supporting this approach is scarce.

Failure of systemic antibiotics to treat infected WON should be explained by poor penetration in necrotic tissue [12,13]. In fact, tissue alterations due to necrosis and inflammation affect pancreatic perfusion. Together with the systemic treatment, local administration of antibiotics through transmural nasocystic or percutaneous catheter may allow increasing antibiotic concentrations in necrotic tissues and thus improving the efficacy of the therapy. After local administration, drug diffusion becomes the main factor influencing drug tissue penetration. Diffusion has been considered as the main factor because these antibiotics are small molecules, mostly. This characteristic favors molecular diffusion processes versus permeation. Furthermore, pancreatic tissue necrosis destroys the main structures responsible for convective processes and permeation: the microvasculature and endothelial cells [14–18].

One purpose of the study was to provide a rational framework to facilitate the design of schemes for local administration of antibiotics. The main goal was to increase concentrations inside the necrotic tissue. One type of tool to solve this problem are mathematical models. They can be used to assess drug concentration, consider the main forces that cause the movement of a drug from its administration to the target tissue as well as the most relevant factors that modify it. One type of models use biological parameters (blood flow, anatomic size … etc) to predict drug concentration evolution. Usually they are called physiology-based pharmacokinetic models (PBPK).

The construction of these models is complex and is a common strategy to divide the problem into smaller, simpler models. As an example, consider the following model: an artery irrigating an organ/tissue with a certain blood flow. This tissue is surrounded by a membrane with small pores and with a thick layer of lipids that limit the passage of large and polar molecules.

When a drug is administered intravenously, it is distributed according to the following factors (usually called forces): blood flow receiving the organ/tissue (convection), ability of the tissue to facilitate passage of the drug (permeability) through the membrane and finally, the ability of the drug to diffuse into the tissue in the absence of flow (diffusion). The three forces (convection, permeability and diffusion) are always present, but usually convection forces are greater than permeability. In addition, permeability forces are greater than diffusion forces. Therefore, the PBPK models for evaluating small biological scenarios (amount of drug that reaches the surface of a tissue, amount of drug that crosses the blood brain barrier, amount of drug within an abscess) typically consider only the main forces in each situations. In short, there are many different PBPK models and the key is to identify the main force in each scenario. In our case, we calculate the concentration of drug within a tissue, so that the main force was diffusion [16].

Mathematical modeling of diffusion processes with PBPK models, usually implemented in specific pharmacokinetic software [19–24]. However, several authors have used small versions for limited scenarios in the past [25–27].

No previous study has evaluated the efficacy of local antibiotics added to their systemic administration for the therapy of infected WON. Since the initial endoscopic or percutaneous drainage has become the standard of care, and since local irrigation through nasocystic or percutaneous catheter is frequently done, local administration of antibiotics is easy to do and evaluation of its efficacy deserves specific investigation. The present study aims at providing the rationale for the design of new research protocols evaluating the efficacy of local antibiotics for infected WON.

1. Material and methods

The study was divided into four steps: first, a review of microbiological data was performed to evaluate the most common organisms causing the infection of pancreatic necrosis, the antibiotic spectrum and the minimum inhibitory concentration (MIC) of different antibiotics. Second, a search of the physico-chemical properties of antibiotics was performed and the diffusion coefficient of each of them was calculated. Third, an estimation of the antibiotic concentrations in pancreatic tissue was obtained using a mathematical model. Finally, the expected efficacy of different antibiotics was quantified by calculating the efficacy factor (EF), as previously described [28].

The use of EF allow us to estímate the efficacy better than using drug concentrations only. Not all antibiotics have the same spectrum activity or need to reach the same concentrations. The efficiency factor (EF) is a theoretical parameter that incorporates pharmacokinetic and pharmacodynamic data (PK/PD). It is calculated for each antibiotic considering the following factors: type and frequency of the bacteria found in a determined infection, concentration at the site of infection and percentage of inhibition of bacterial growth. Therefore, using EF as a measure of efficacy in theoretical studies is more suitable than only analyzed concentrations values.

$$EF = \frac{(F \cdot PIS)_{E.\ coli} + (F \cdot PIS)_{Pseudomonas} + \ldots + (F \cdot PIS)_{Klebsiella}}{100}$$

F is the frequency of the bacteria, PIS is the percentage of inhibited bacteriologic strains, according with the literature, considering the antibiotic concentration present in each case.

In our study, we first selected microorganisms most frequently involved in infections of pancreatic necrosis and then we performed a literature search to obtain the percentages of inhibition of each bacteria, to different concentrations of each antibiotic [29–37].

The stability of different antibiotic solutions was also evaluated to define the appropriate administration schedules.

Common etiologies were reviewed through a literature search using PubMed database. “Pancreatic infection”, “necrotizing pancreatitis” and “acute pancreatitis bacteriology” terms were used (Medical Subject Headings: Acute [All Fields] AND (“pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“bacteriology”[MeSH Terms] OR “bacteriology”[All Fields]) [38–44].

To evaluate the efficacy of the selected antibiotics, eight types of microorganisms were chosen (Table 1). Then, we performed another search in PubMed and Google Scholar with the following terms: “minimal inhibitory concentration susceptibility” adding the international nonproprietary name (INN) of each antibiotic at the beginning of the search (“ceftriaxone, amikacin, linezolid … etc”). With these data, we could estimate the percentage of strains that had inhibited their growth at each concentration of antibiotic. However, local antibiotics sensitivities can alter this results significantly. Therefore, provided data must be interpreted in qualitative, not quantitative manner.

Physico-chemical properties of different antibiotics were collected from manufacturer's data sheet, ChemSpider, Chemicalize and LookChem databases [45–47].

Table 1
Frequency of analysed microorganism in pancreatic infections. Concentration to achieve at least 90% of inhibition of bacteriologic strains (PIS > 90%).

Bacteria	Frequency	Concentration to PIS >90%									
		Imipenem	Ciprofloxacin	Ceftriaxone	Cloxacillin*	Metronidazole	Piperacillin	Gentamicin	Linezolid	Vancomycin	Tigecycline
Escherichia coli	26%	0.5	50	0.25	–	–	8	0,5	–	–	0.25
Pseudomona spp	16%	4	25	64	–	–	90	3	–	–	–
Staphylococcus aureus	15%	0.12	1.5	16	1.4	–	4	0.75	1.9	1.6	0.25
Klebsiella spp	10%	1	1	0.25	–	–	32	0.5	–	–	0.85
Proteus spp	10%	8	0.03	2	–	–	7	1	–	–	3.9
Enterococcus faecalis	4%	0.06	47	–	0.5	–	16	110	1	0.25	0.16
Enterobacter spp	3%	0.064	0.016	16	–	–	70	0.5	–	–	1
Bacteroides fragilis	16%	0.5	–	90	–	1.25	16	–	–	–	–
TOTAL	**84%**										

Note: 16% caused by others microorganism and fungi are not included.
*Cloxacillin data were extrapolated from oxacillin.

Theoretical diffusion coefficients were estimated by Wilke-Chang method [48] considering water at 37 °C as diluent. Two theoretical behaviors, time- and distance-dependent, were simulated. The influence of time was assessed by considering the concentration of the antibiotic over time at 0.5 cm from the cyst surface. The influence of distance was assessed by considering the concentration of antibiotics at different distances from the cyst surface at 24 h from infusion start. For the theoretical model, a spherical cyst of 8 cm size (268.1 mL) was considered. Antibiotics were evaluated at the concentrations usually used for intravenous administration. It was assumed that the amount of drug infused is immediately diluted and that the protein binding rate in the cyst is similar to that observed after intravenous administration. Crank solution of Fick's second law was used as mathematical model for calculation [49] as follows:

$$C(x,t) = C_0 \cdot erfc \frac{x}{2\sqrt{D^* \cdot t}}$$

where C (x,t) is the drug tissue concentration at time t and distance x from the surface of the collection, Co is the initial concentration, D* is the corrected diffusion coefficient and erfc the complementary error function. D* depends on the drug diffusion coefficient in the media and the tortuosity factor, which can decrease the effective diffusion coefficient. Tortuosity factor of 1 for all antibiotics was considered to normalize the effect of the biological matrix. Crank equation allows thus estimating tissue concentrations at different times and distances according to antibiotic chemical properties such as diffusion coefficient and initial concentration.

Solution stability data were collected using manufacturer data sheet of each drug, Stabilis and Micromedex database [50].

The theoretical efficacy of the following antibiotics was evaluated: gentamicin, imipenem, linezolid, vancomycin, tigecycline, piperacillin, cloxacillin, metronidazole, ciprofloxacin and ceftriaxone.

2. Results

2.1. Microbiological data

Microorganisms infecting pancreatic necrosis are usually related to other intra-abdominal infections. *Enterobacteriaceae* group are involved in most of the infections, but other microorganisms such as anaerobes are frequently associated [38,40]. The presence of aerobic (*Escherichia coli*, *Klebsiella* and *Enterobacter*) and facultative aerobic microorganisms (Staphylococcus spp, Streptococcus spp, Listeria spp) is especially frequent in infected pancreatic necrosis [40]. Antibiotic therapy must particularly consider *Escherichia coli* and *Enterobacter aerogenes* because they are responsible of near the 30% of the infections [42] (Table 1).

Most microorganisms have a MIC below 8 mg/L for all antibiotics with the exception of *Pseudomonas aeruginosa* and *Enterococcus faecalis* which can reach 16 mg/L [51]. MIC values should be considered especially if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, since linezolid should be used if MIC for vancomycin is greater than 1.5 mg/L [29–37,52].

2.2. Tissue estimated concentrations

A dilution of the individual antibiotic dose in 100 mL saline was considered for local administration in the 8 cm size cavity. Larger dilution volumes were considered for linezolid (300 mL) and ciprofloxacin (200 mL) since they are commercialized prediluted in most countries. Plasma protein binding ratio was considered since only the free fraction diffuses. The resulting concentration was used to estimate the free fraction of drug (Table 2).

Antibiotics can be classified into three groups according to the influence of time on their concentrations (Fig. 2). The first group (piperacillin, vancomycin and metronidazole) achieves high concentrations (>10 mg/L) in the surrounding tissue. The highest concentration is achieved with piperacillin, whereas a high concentration is fastest reached with metronidazole due to its high diffusion coefficient (1,44E-5 cm^2/s). The second group (imipenem, ceftriaxone, ciprofloxacin, gentamicin, linezolid and cloxacillin) achieves intermediate concentration values (2–10 mg/L). Finally, tigecycline reaches the lowest concentration values (<2 mg/L). Fig. 1 shows the estimated concentration of different antibiotics, at different times and at a distance of 0.5 cm.

Analysis of the influence of the distance on the concentration profile of different antibiotics shows that piperacillin has the highest diffusion capacity followed by cloxacillin up to a distance of 2 cm from diffusion surface (Fig. 2). Metronidazole concentrations are the least affected by distance due to its low protein binding.

2.3. Efficacy factors and antibiotic irrigation schedules

Table 3 shows the calculated EF (from 0 to 1) of different antibiotics for infected pancreatic necrosis at 6 and 24 h after local infusion, and at 0.5 and 3 cm respectively from diffusion surface. The closer the EF to 1.00 is, the higher the efficacy of the antibiotic is in terms of inhibition of the bacteria commonly found in infected pancreatic necrosis.

Taking into account all the above mentioned data and the stability of antibiotics in solution (Table 4), the appropriate administration schedules of the different antibiotics evaluated is shown in

Table 2
Antibiotic doses, volumes and initial free concentrations into the collection considering specific protein binding rates. D* is the corrected diffusion coefficient.

Drug	Molar volume (cm^3)	D* estimated (cm^2/s)	Dose (mg)	Protein binding rate (%)	C_0 unbound drug (mg/L)
Ceftriaxone	281.7	8.538E-06	2000	90%	7.46
Ciprofloxacin	228.8	9.673E-06	400	25%	5.60
Cloxacillin	279.3	8.582E-06	2000	94%	4.48
Gentamicin	366.8	7.287E-06	80	20%	2.39
Imipenem	183.9	1.103E-05	250	20%	7.46
Linezolid	259.0	8.979E-06	600	31%	5.15
Metronidazole	117.9	1.440E-05	500	20%	14.92
Piperacillin	340.5	7.620E-06	4000	21%	117.87
Tigecycline	402.5	6.892E-06	50	77%	0.43
Vancomycin	874.7	4.326E-06	1000	40%	22.38

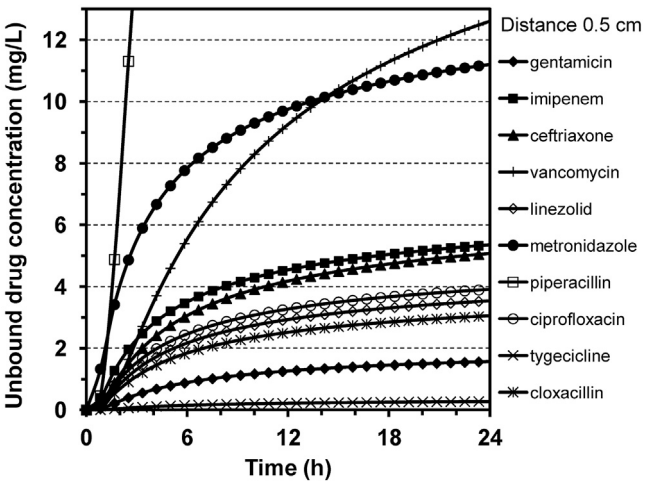

Fig. 1. Estimated unbound antibiotic concentration profiles at different times and at a distance of 0.5 cm from the diffusion surface.

Table 5.

3. Discussion

The present study provides the rationale for the appropriate local administration of antibiotics for infected pancreatic necrosis. This data are relevant for the design of clinical trials evaluating the efficacy of local administration of antibiotics for the treatment of infected WON.

The analysis of the concentration profiles at 0.5 cm from the diffusion surface shows that virtually no antibiotic reaches the steady state before 6 h. This time is even longer at greater distances. Antibiotics requiring high doses and having a low protein binding rate, such as piperacillin, quickly reach effective concentrations. However, if the dose used is low and the drug is widely linked to proteins, such as tigecycline, its initial concentration is low and probably it will never achieve effective concentrations.

The present study shows that the key factor influencing antibiotic concentration at different distances is the diffusion coefficient. Thus, the initial concentration mainly determines the concentration reached near the diffusion surface and the diffusion coefficient determines the concentration at different distances. Piperacillin (D = 7.620E-06) reaches high initial concentrations, but at distances greater than 2.75 cm imipenem (D = 1.103E-05) reaches higher concentrations than piperacillin. Only metronidazole and imipenem have diffusion coefficients above 1E-6 due they low molecular weight (171.2 and 299.4 g/mol respectively). Molecular weight is closely related to diffusion capabilities. However, other factors also influence (solvent, temperature … etc). For that reason, better

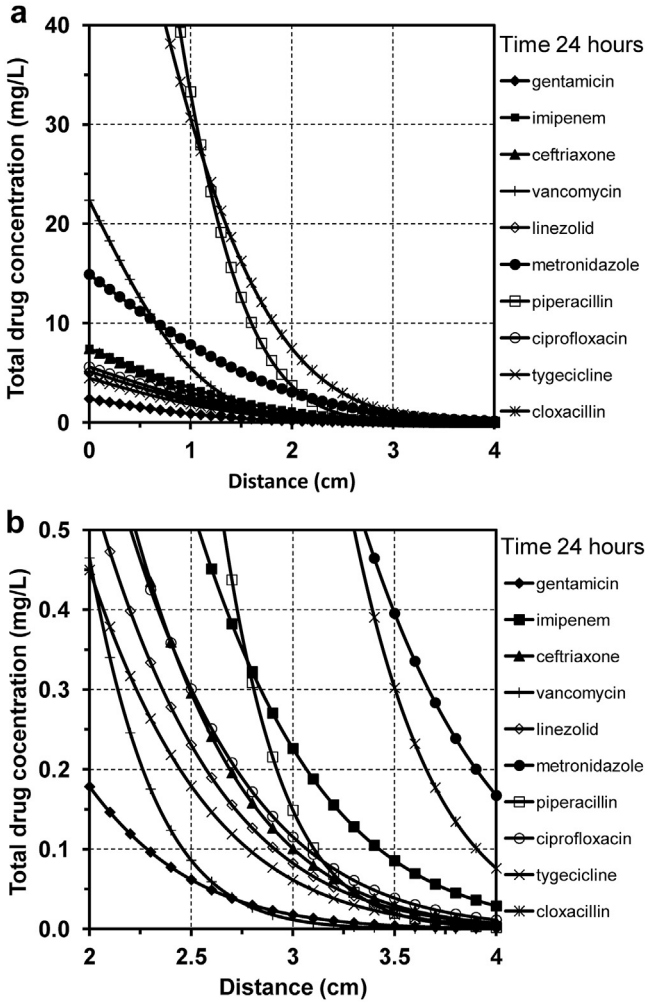

Fig. 2. Influence of distance from the diffusion surface in unbound drug concentrations. a) Concentration from 0 to 4 cm; b) Detailed concentrations from 2 to 4 cm.

estimates can be obtained using the diffusion coefficient (D) for mathematical calculations. However, this coefficient depends largely on the molecular weight, so molecules with low molecular weight like metronidazole and imipenem have higher diffusion coefficients.

These results agree with the calculated EF. Short time after infusion, piperacillin and imipenem have a high EF near the surface diffusion area (0.5 cm). However, at deeper distances (e.g. 3 cm) and longer times (e.g. over 24 h), the EF of piperacillin decreases more than it does the EF of imipenem. These results are consistent with the efficacy obtained with imipenem in some studies [53]. The

Table 3
Efficacy factor of antibiotics in infected pancreatic necrotic collections at different times from infusion start and at different distances from collection surface. Antibiotics are ordered according to their EF after 24 h at a distance of 3 cm. *Cloxacillin data were extrapolated from oxacillin.

Drug	6 h–0.5 cm		24 h–3 cm	
	Concentration (mg/L)	Efficacy factor	Concentration (mg/L)	Efficacy factor
Imipenem	3.68	0.90	0.28	0.54
Ciprofloxacin	2.60	0.54	0.15	0.44
Ceftriaxone	3.24	0.51	1.01	0.49
Cloxacillin*	1.95	0.15	1.03	0.13
Metronidazole	8.17	0.16	1.07	0.16
Piperacillin	36.30	0.92	0.19	0.07
Gentamicin	0.95	0.67	0.02	0.00
Linezolid	2.30	0.19	0.12	0.00
Vancomycin	6.10	0.19	0.02	0.00
Tigecycline	0.16	0.37	0.01	0.00

Table 4
Stability data for different antibiotics in saline solution at 25 °C.

	Dose (mg)	Volume (mL)	Concentration (mg/mL)	Stability	Protected of light
Ceftriaxone	2000	100	20	5 days	Unknown
Ciprofloxacin	400	200	2	28 days	Unknown
Cloxacillin	2000	100	20	30 days	Unknown
Gentamicin	200	100	2	7 days	Unknown
Imipenem	250	100	2.5	6 h	Unknown
Linezolid	600	300	2	2 h	Yes
Metronidazole	500	100	5	24 h	Yes
Piperacillin/tazobactam	4000/500	100	40	4 days	No
Tigecycline	50	100	0.5	–	Unknown
Vancomycin	1000	100	10	62 h	Yes

Table 5
Proposed local antibiotic irrigation schedules.

Drug	Intravenous	Local		
	Schedule	Schedule	Volume per dose (mL)	Concentration (mg/mL)
Ceftriaxone	2 g c/24 h	1000 mg c/24 h	1000	1
Ciprofloxacin	400 mg c/12 h	400 mg c/24 h	200	2 (0.4)
Cloxacillin	1 g c/8 h	1000 mg c/24 h	1000	1
Gentamicin	240 mg c/24 h	80 mg c/24 h	1000	0.08
Imipenem	1 g c/8 h	250 mg c/6 h	250	1
Linezolid	600 mg c/12 h	Not recommended		
Metronidazole	1.5 g c/24 h	Not recommended		
Piperacillin/tazobactam	4/0.5 g c/8 h	4/0.5 g c/24 h	1000	4/0.5
Tigecycline	50 mg c/12 h	Not recommended		
Vancomycin	1 g c/12 h	1 g c/24 h	1000	1

EF of ceftriaxone, ciprofloxacin and metronidazole remain high at 24 h as well. On the contrary, gentamicin and tigecycline do not reach a high EF in any case.

Comparing our results with those previously published [54], several similarities can be observed. Pancreatic tissue concentrations of ten different antibiotics were determined by Büchler et al. in 89 patients undergoing pancreatic surgery [28]. Three groups of antibiotics were established as a function of tissue concentration and relative MIC. Bassi et al. studied pancreatic tissue penetration of different antibiotics intravenously administered in patients with necrotizing pancreatitis [13]. Their results showed that a high degree of penetration is achieved with metronidazole, piperacillin and imipenem. Both studies concluded that aminoglycosides have a poor tissue penetration, whereas quinolones, piperacillin or imipenem have a better penetration in the pancreatic tissue. These results are consistent with those found in our study.

In other similar infectious clinical situations, normally when abscesses has a small diameter (<3–5 cm) they are treated only with intravenous antibiotics. However, when they are larger, drainage is used. The concentration of the antimicrobial is inversely proportional to the distance to the centre of the abscess and therefore, in many cases, no adequate antibiotic concentration is reached when intravenous administration is used. The usual treatment is directed toward controlling the focus of infection, usually a surgical or percutaneous approach is performed. Local administration of antibiotics has been tested successfully in some clinical situations such as hepatic and pelvic abscesses [17,55–59].

However, it should be noted that the objective of this local therapy is to increase the effectiveness of treatment, never replace the primary control over the focus of infection. Debride infected necrotic tissue, and drainage is necessary for clearance of an abscess. In a large number of infected lesions (superficial abscesses, abscesses with abundant peripheral vasculature), antibiotic therapy intravenously is sufficient to achieve sufficient concentrations of drug in the infected area. So it is not necessary to apply in all cases a local administration. This technique should be considered as a tool when antibiotic access to the necrotic area is difficult. Especially in large abscesses and infected lesions related with high mortality.

The proposed local administration of antibiotics requires

prolonged administration times. For this reason, assessing the physico-chemical stability under conditions of common use (25 °C, saline solvent) is a key factor. Some antibiotics are particularly unstable (Table 4). Stability of most molecules with beta-lactam ring (penicillin, cephalosporin and carbapenems) is dependent on temperature, time and concentration. Furthermore, many of them are incompatible with diluents containing dextrose or a basic pH. Carbapenems stability is highly influenced by concentration, and a high concentration is associated with degradation products without antimicrobial activity. Recently, the stability of meropenem and doripenem has been studied for extended administration schedules confirming these results [60,61]. Other drugs such as quinolones or aminoglycosides are more stable, and have no apparent degradation over 24 h. The lack of stability studies involving longer periods of time than those recommended by the manufacturer limits the use of antibiotics such as metronidazole, linezolid and tigecycline. Vancomycin has been widely studied and its stability can be ensured for more than 24 h [62].

Considering the obtained results, some administration schedules for different antibiotics are proposed (Table 5). When the microorganism infecting WON is unknown, the best results are expected with the local administration of imipenem. Metronidazole, linezolid and tigecycline solutions are not recommended because of their narrow spectrum, lack of data on maximum dose, and solution instability. Specifically, linezolid use is not recommended because of the lack of stability data. They are currently no data available to infusion times over 2 h and protected from light (Table 4) [63,64].

Once the microorganism and its antibiotic sensitivity are known, the optimal antibiotic can be infused at the proposed infusion schedules. Note that ciprofloxacin is usually available as pre-diluted drug (400 mg/200 mL). Administration should be completed with 800 mL of saline to a total volume of 1 L. Therefore, concentrated ciprofloxacin (2 mg/mL) is diluted in the infusion system to 0.4 mg/mL. Piperacillin is commercialized in vials with 4 g of piperacillin and 0.5 g tazobactam. Dilution with 1 L of saline results in 4/0.5 mg/mL.

Some factors were not considered in the theoretical model to simplify calculations, among them cyst volume variations, electrical interactions, pH, time of administration and drug loss by degradation or elimination. The proposed model is deterministic, not stochastic type. We do not consider neither random effects. This issue is a limitation of the model, so we consider very interesting to add this information in future models. Furthermore, add uncertainty to the model allow performing a sensitivity analysis to identify more accurately the most influential factors in the results. Therefore, these results should be interpreted in a qualitative manner. Despite these limitations, some interesting conclusions can be extracted by the qualitative assessment.

Another limitation of the model is to assume that the main force that moves the antibiotic is diffusion. It would be of great interest the physico-chemical (density, polarity, pH … etc), histological and anatomic characterization (degree of endothelial desquamation, patterns microcirculation … etc) of necrotic pancreatic tissue to develop more accurate models.

Our results provide theoretical rationale for the local antibiotic administration in patients with infected WON. Strictly, the antibiotic solution concentration and the administration schedule can be calculated according to the size of the pancreatic collection. Although we used a mathematical model to approach a dynamic and variable situation, the use of the proposed fixed concentration solutions of antibiotics provides a simple and feasible approach for clinical research and clinical practice. In order to maintain the mechanical effect produced by continuous washing of the necrotic tissue, it is advisable to maintain a total infused volume of about 1 L/day of the antibiotic solution through the nasocystic or percutaneous catheter. In this way, the proposed schedules are optimized for a local administration rate of 42 mL/h of any antibiotic. The only exception is ciprofloxacin, which should be administered at a rate of 8.3 mL/h; in this case 750–800 mL saline should be administered in parallel (Y administration) to achieve the proposed total volume of 1 L/day. It is recommended to check residual volume and remove it through the same catheter if necessary before each antibiotic administration.

The aim of this study is to provide a theoretical framework to rationally apply the technique of local administration of antibiotics. Without a theoretical framework, clinical application of the technique and evaluation of its efficacy and safety would not be possible. Outcome assessment in clinical practice would be the second step.

In conclusion, the present study provides the theoretical rationale for the local antibiotic therapy of infected necrotic pancreatic collections. Our results are of help both for the correct use of local antibiotics in clinical practice and for the appropriate design of specific clinical trials.

Conflict of interest

The authors have no conflicts of interest.

Authorship statement

All the authors (Jaime Gonzalez-Lopez, Fernando Macías-García, J. Enrique Domínguez-Muñoz and José Lariño Noia) performed the research including conception, design, analysis and interpretation. All of them revising and accepting the final version of the article.

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