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Theoretical approach to local infusion of antibiotics for infected pancreatic necrosis

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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 physico-chemical 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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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].

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