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Intolerability to Lavasept® peritoneal lavage in experimentally induced peritonitis in the guinea pig

Summary

Background: Despite availability of antibiotics and advances in optimised surgical technique, faster decision for laparatomy and improved postsurgical intensive care and therapy, diffuse peritonitis still is a severe condition with high mortality. To reduce systemic side effects of antibiotics, an antimicrobial lavage of the peritoneum is desirable. For this, only Taurolidin is available, though the use of this compound is limited by the required long application time. The application of polihexanide has been shown beneficial for burns and chronic wound antisepsis. Therefore, the aim of the present study was to assess applicability of polihexanide for peritoneal lavage in an animal model.

Methods: In a guinea pig model, diffuse peritonitis was induced by inserting catethers (intraenteric and into the Douglas space) and by applying HCL (pH 2) followed by contamination with an *E. coli* suspension (ATCC 11229, 1,6x10^9 cfu/ml) after 4 hours. Peritoneal lavage was performed 6 hours after acetising using 0.05 % Lavasept® (0.0025 % polihexanide + macrogolum) and was continued for 5 days. In addition, Tarivid® (ofloxacin, 1.5 mg i.m.) was administered 2 times daily over 5 days. Main outcome criterion was survival rate after 11 days. Because of the intolerability of 0.05 % Lavasept® a second experiment was conducted using half of the initial concentration, whereby in one animal group diffuse peritonitis was experimentally induced, and one control group was included without peritonitis. Main outcome criterion again was survival rate within 11 days. Four animals of each group were observed for a total of 21 days. In all six groups, dead animals were dissected immediately, and swabs from peritoneal exsudate, samples from the parietal peritoneum together with subserosa, omentum maius and organs were obtained. Liver samples were examined microscopically and histologically using H.E. stain. The group receiving additionally Tarivid® was investigated for ofloxacin concentrations in exsudate, peritoneal tissue and blood obtained from the heart. Ofloxacin concentrations were measured using High Performance Liquid Chromatography (HPLC) technique.

Results: Without any therapy, 3/16 animals died after induction of peritonitis. When peritoneal lavage was performed using ringer solution and administering systemic antibiotics, all animals (0/18) survived. For ofloxacin, following concentrations were measured: peritoneal tissue 0.245 mg/kg, serum 0.137 mg/l and peritoneal exsudate 0.166 mg/l. Lavage using 0.05% Lavasept® resulted in death of 15/18 with and 16/18 animals without experimentally induced peritonitis, respectively. Using 0.0025% Lavasept® resulted in 1/14 dead animals with peritonitis, and no dead animal (0/14) without peritonitis. Administration of 0.05% Lavasept® resulted in opaque-whitish membranes on the serosa and a significantly reduced or completely stopped bowl peristaltic. Histologically, a sero-fibrinous inflammation of the peritoneum with regressive alterations of the subserous abdominal muscles with necrosis und calcification was observed. The liver showed a diffuse hyperaemia and steatosis hepatis. Animals included in additional experiments showed similar changes as the animals treated with Lavasept® lavage over 5 days. In the four animals which were followed over 21 days an increased intraperitoneal exudation with bloodly imbibitions was observable.

Discussion: Because of massive intolerability, Lavasept® using the tested concentrations of 0.05 and 0.025% can not be applied for peritoneal lavage. Because our animal model allowed only insuffi-

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ciently an intraperitobeal lavage, further studies should be performed using bigger test animals like e.g. pigs. This might then allow more detailed insights on mesothelial intolerability. By stepwise lowering the concentration of Lavasept® a dose finding for the lowest possible still antimicrobial concentration with above observed intolerabilities could possibly be assessed.

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Introduction

Despite the availability of antibiotic treatment, optimised surgical techniques, enhanced decision-making for laparotomy and improved postsurgical intensive care and treatment administered through central venous access routes, diffuse peritonitis continues to be a life-threatening condition with high mortality. The knowledge that it can culminate in systemic inflammatory response syndrome (SIRS) has spurred on research into new therapeutic approaches aimed at interrupting the myriad immunological cascades triggered here. Furthermore, the ongoing validity of Kirschner's postulates [1] for definitive eradication of the infection source and safe removal of the infectious peritoneal exudates is underscored, something that can be assured through effective local treatment of the inflamed peritoneum. To reduce the well-known side effects of systemic antibiotics (dose-related toxic effects, allergic reactions, pathogen- and drug-interaction-induced effects as well as resistance development), concomitant antiseptic peritoneal lavage continues to be a desirable option [2–6].

However, both chlorhexidine [7,8,9] and povidone (PVP) iodine [10] have in previous animal experiments proved unsuitable here because of their high cytotoxicity. Only Taurolin® is endowed with sufficient tissue compatibility for this indication [11,12,20], however, it has the disadvantage of onset of the antimicrobial effect, at least in vitro, only after 6 h [19].

Since the combination of polihexanide with macrogolum (Lavasept®) is much superior in terms of tissue compatibility to the wound antiseptics customarily used at present [12,13,14], as confirmed by clinical trials [15,16], the present study aimed at investigating its suitability for peritoneal lavage of experimentally induced Escherichia coli peritonitis in the guinea pig. In view of the fact that, despite their risks, antibiotics are the drugs of choice for treatment of peritonitis [17], ofloxacin (Tarivid®) was investigated by way of comparison.

Materials and Methods

In a guinea pig model (Harlan Winkelmann breed, held in animal holding cabinets at a constant temperature of 22 °C and air humidity of 80 %, Regulation Az. VI 522a-7221,31-1-014/98 as per authorisation of the animal experimental project by the Ministry for Agriculture and Nature Protection), diffuse peritonitis was induced by inserting two Braunüle® catheters (Vasofix-Braunüle® 16G2) intrerenterically and into the pouch of Douglas, while inducing standardised peritonitis by first applying 1 ml hydrochloric (HCL) acid at pH 2 followed by application of a 3 ml E. coli suspension ATCC 11229 of 1.6×10^9 cfu/ml 4 hours after HCL application via the interenteric Braunüle® catheter (model for perforation peritonitis). To that effect, the animals were placed in the dorsal position after inducing narcosis, with the extremities extended and manually secured. The puncture sites selected were the right hypochondrium and the border between the left hypochondrium and the middle abdomen. After placement, the catheters were secured to the abdominal wall using Mersilene® 230 single-button sutures and sealed with a cap. The Braunüle® catheters had been fitted with slits so that they could be used as drains. The experimental animals showed few adverse effects and moved around unhindered. At the end of treatment, the animals were killed under ether-induced narcosis with a seamless transition from the tolerance to the asphyxia stage and the excised tissue samples were examined histologically after staining with hematoxylin-eosin (HE).

The following were tested: Lavasept® (per 1 ml: 200 mg polihexanide, 10 mg macrogolum 4000, Aqua pur q.s., Fresenius Kabi Homburg, Germany) and Tarivid i.v. 200 (per 100 ml: 200 mg Ofloxacin-HCl, Aventis Pharma Frankfurt a.M., Germany).

In the main experiment four groups were formed with the same number of male and female animals in each group (Table 1).

Treatment was initiated 6 hours after HCL acid application for groups 1 to 3 and continued for 5 days.

Since administration of a 0.5 % Lavasept® concentration resulted in opaque-whitish membranes on the serosa (see Results), a further experiment was added whereby the Braunüle® catheters were inserted on day 1 but intraperitoneal Lavasept® irrigation with and without standardised peritonitis induction using a half Lavasept® concentration (0.025 %) was initiated only on day 2 (Table 2).

The main outcome criterion was survival rate for 11 days after beginning the experiments.

Only in groups 5 and 6 were four animals followed up in each group for 21 days.

In all groups animals dying during the experiments were dissected immediately and, in the same way as at the end of the experiments, microbiological and histological examination of the following specimens were carried out: of the swabs taken from the peritoneal exudates, of samples of the parietal peritoneum together with subserosa abdominal wall muscles as well as of samples from the greater omentum and liver.

In group 3 of the main experiment, exudates, peritoneal tissue and heart blood were taken in addition for measurement of the Tarivid® concentration.

The ofloxacin concentrations were measured using High Performance Liquid Chromatography (HPLC) technique. To that effect, the serum was calibrated with the international standard moxifloxacin, with protein being removed by means of trifluoroacetic acid and centrifugation. A constant temperature of 20 °C was assured. Fluorescence examination was carried out at 504 nm [18].

Results

Mortality

In the main experiment three animals died following induced peritonitis without treatment (group 4) (Table 3).

All animals survived following irrigation with Ringer® solution and administration of systemic antibiotics. For ofloxacin the following concentrations were measured: peritoneal tissue 0.245 mg/kg, serum 0.137 mg/l and abdominal cavity exudates 0.166 mg/l.

Following irrigation with 0.05 % Lavasept®, 15 animals died without induction of peritonitis (group 1), 16 after

Table 1: Group formation in the main experiment.

Group	Number of animals (n)	Body mass (g) Arithmetic. mean (min-max)	Drainage	Peritonitis	Therapie (5d)	Mittlere Tagesdosis (mg/kg)
1	18	392.8 (330-480)	with	none	3×10 ml 0.05 % Lavasept® ip	0.038
2	18	401.4 (320-440)	with	induced	3×10 ml 0.05 % Lavasept® ip	0.037
3	18	427.2 (360-490)	with	induced	3×10 ml Ringer® ip; 2×1.5 mg Tarivid® im	7.025
4	16	392.5 (235-480)	without	induced	none	–

Table 2: Group formation in the subequently added experimental groups.

Group	Number of animals (n)	Body mass (g) Arithmetic. mean (min-max)	Drainage	Peritonitis	Therapie (5d)	Mittlere Tagesdosis (mg/kg)
5	14	375 (345-395)	with	none	3×10 ml 0.025% Lavasept® ip	0.02
6	14	337.5 (305-455)	with	induced	3×10 ml 0.025% Lavasept® ip	0.022

induction of peritonitis, whereby in the case of peritonitis induction the time of death had already taken place during the treatment phase, i.e. in group 1 no animal died in the treatment phase, 15 died in the follow-up phase, while in group 2 four animals died during lavage and 12 in the follow-up phase.

In the subsequent experiment with administration of half the Lavasept® concentration (group 6), one animal died in the group with peritonitis induction, but no animal died in group 5 with no peritonitis induction.

Clinical / pathological and histological findings as well as pathogens detected

Similar findings were seen for groups 1 and 2. Opaque-whitish membranes were seen on the serosa which greatly impaired or impeded peristalsis. On removal of these, the shiny serous surface was exposed. The livers were often pale. Histologically, a sero-fibrinous inflammation of the peritoneum with regressive alterations of the subserous abdominal wall muscles with necroses and calcifications was observed. Similar findings were noted for the greater omentum. Virtually all livers showed diffuse hyperaemia and hepatic steatosis. In group 2 granulocytic infiltration of the peritoneum was seen in 11 animals. In group 1 the post mortem abdominal cavity swab revealed 12 × *Proteus spp*., 1 × *Pseudomonas spp*., 1 × *E. coli*, 2 × Gram-positive, 2 × Gram-negative and 1 × Gram-labile rods.

In group 2, 5 cases of resolved peritonitis with extensive fibrin formation and 3 cases of acute inflammation were observed. In the abdominal cavity swabs taken at post mortem the following were noted: 5 × *E. coli* were detected, 4 swabs were negative, 5 swabs were positive without microbial differentiation. In six cases a change in the microbial pattern was seen following Lavasept® lavage: 2 × *Proteus spp*., 3 × *Pseudomonas spp*. and 1 × Gram-positive rods were isolated.

In group 3 status post lower and middle abdominal peritonitis with fibrin adhesions was observed in every animal. The parenchymatous organs were unremarkable and the serosa were shiny in all cases. Active peristalsis was assured. The following were isolated from the post mortem abdominal cavity exudates: 9 × *Pseudomonas spp*., 3 × Gram-positive cocci, 2 × Gram-positive rods und 2 × *E. coli*. In one case, there was positive microbial detection but without differentiation, in another case the swab did not give rise to any growth. Fibroproductive inflammation was seen on microscopy, with 5 cases of bloody imbibitions, and 7 of granulocytic infiltrations. One case of abdominal wall phlegmona in the form of purulent myositis was seen. The subserous musculature was inflamed in 3 cases. The uniform manifestation of muscle fibre regression seen in groups 1 and 2 was not present. Seventeen cases of liver diffuse hyperaemia and 4 of steatosis were observed.

In two animals of group 4, which died on day 2, there was acute peritonitis. In one weakened animal that was killed on day 3, resolved local peritonitis was observed. After 11 days the remaining animals revealed healed lower abdominal peritonitis with fibrin adhesions but otherwise unremarkable organs and shiny serosa. The abdominal cavity swab revealed 1 × *E. coli*, 2 × Gram-negative rods, 1 × Gram-positive coccus and no growth was seen in 2 × cases.

Histologically, signs of fibroproductive peritonitis were seen in nine cases, previous serous inflammation in 4, normal findings in 2, connective tissue was seen in the mesothelium in 1 case and pronounced adhesions in 2 cases. The subserous musculature was implicated in the inflammatory process in 5 cases. Regression of muscle fibres was seen in 1 case with concomitant regeneration of necroses. In 12 cases, the liver preparation revealed hyperaemia and steatosis in 1 case.

The peritoneum of group 5 animals appeared paler and the intestinal serosa were also brighter. However, peristalsis was assured – albeit slow – in all cases. The intestinal convolute appeared "dry", but was not fixed. One animal's liver showed slight formation of deposits and there was one case of steatosis. The abdominal cavity swabs taken at post mortem showed *E. coli* contamination in 3 cases but no other microbes were isolated. Histologically, there was slight fibroproductive inflammation, but this was mainly of a discrete nature. In 7 cases, the subserous musculature was implicated in the inflammatory process with focal overlapping. There was one case of isolated regressive muscle fibres. No calcifications were seen. There were 6 cases of liver diffuse hyperaemia and 4 of slight steatosis.

Acute purulent peritonitis with lower abdominal fibrin formation was seen in the group 6 animal that died on day 4. In the animals killed on day 11, resolved lower abdominal peritonitis with adhe-

sions was observed in 4 cases. The peritoneum was paler, the intestinal serosa brighter but not fixed. Peristalsis was assured – albeit slow – in all cases. The abdominal cavity swabs taken at post mortem showed *E. coli* contamination in 3 cases but no other findings were noted. Fine-tissue examination showed varying degrees of fibroproductive inflammation in six animals. There was one case of purulent / granulocytic inflammation and one case of serous peritonitis. The subserous musculature was implicated in the inflammatory process in 3 cases. Regressive alterations were no longer seen. Nine cases of diffuse hyperaemia of the liver and four of hepatic steatosis were seen.

In both the experimental groups that were added at a later stage, four animals underwent late evaluation only after a long observation period of 21 days. These revealed the macro- and microscopic findings characteristic of the respective group. One conspicuous finding was, however, a discernible tendency towards increased amounts of intraperitoneal exudates with a bloody tincture.

Table 3: Mortality during treatment and the follow-up phase.

Experimental group	Number of animals dying on the respective test day										Total
	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	
1					1	6	5		2	1	15
2	1	3	1		7		1	1		2	16
3											0
4	2	1									3
5											0
6			1								1

Discussion

In this animal model cavity perforation (ventricular ulcer) with "chemical" peritonitis and subsequent inoculation with *E. coli* was carried out. Other possibilities for onset of secondary peritonitis were ruled out as per the model specifications. Artificial infection was restricted to a typical prototype (*E. coli*). "Desirable" was local inflammation prior to diffuse spread or systemic perpetuation of the clinical manifestations.

Whereas in humans several access or target drains can be placed, in the present animal model only insertion of two 2 Braunüle® catheters was possible so as not to overly challenge the animals' general condition. As such, there were problems with the efficiency of the experimental design since it was not possible to fully drain the irrigation solution, i.e. to achieve a zero balance.

The interpretation of the abdominal cavity as a "wound cavity" also proved to be a problem under the comparatively miniaturised test conditions. The stomato of von Recklinghausen, provide for rapid transport of microbial particles into the thoracic duct so that the number of i.p. inoculated bacteria can already decline before the influx of phatocytic cells is triggered. One aspect to be discussed is whether in certain individual cases spontaneous remission will already have occurred before initiation of peritonitis treatment because of rapid transdiaphragmal bacterial absorption. The low mortality seen in experimental peritonitis without treatment lends credence to that belief. Pronounced peritonitis-induced changes were observed in the experimental groups in which, due to regular irrigation procedures, repeated manipulations had been performed on the parietal peritoneum with the potential introduction of microbes via the inserted flexules. This would also explain the change in the microbial spectrum frequently observed or microbial detection in the groups in which peritonitis had not been induced. Accordingly, the peritonitis-related findings could be attributable more to the sequelae of irrigation manipulation than to peritonitis induction.

Furthermore, quite apart from the infection challenge, the animals also faced hyperhydration and cardiac challenge. Intraabdominal microbial elimination was effected in more a diluted than a reliable manner. Based on Dunn et al. [3], the effects caused by intraabdominal *E. coli* inoculate are determined by the total amount of fluid administered. A microbial suspension in 30 ml instead of in 1ml solution resulted in significantly higher 48 h mortality and quicker bacterial proliferation. Accordingly, the essential requirements of surgical peritonitis treatment as per Kirschner's postulates were only insufficiently met.

The second treatment mainstay, systemic antibiotics, was assured by measurement of effective concentrations of the antibiotic in all relevant compartments.

The third treatment pillar, intensive-medicine monitoring of vital functions, could be assured only to a certain extent since a zerobalance could not be achieved and in view of the lack of central venous access under the given miniaturised anatomic conditions.

Based on the mortality and, in particular, because of the histological findings, the polihexanide intolerability could be observed in the main experiment. Credence is lent to the belief that this is really a side effect of polihexanide by the fact that on halving the Lavasept® concentration, there was a decline in the incompatibility manifestations seen on serous membranes. Although there was no evidence of "Lavasept® deposits", the serous lining appeared to be "dry" and peristalsis was impaired. Moreover, a conspicuous finding in all animals observed at a late stage was the increasing amount of abdominal cavity exudates with bloody imbibations. There was no further evidence of regression of the submesothelial musculature, thus confirming that mesothelial compatibility is dependent on the polihexanide concentration.

It can thus be concluded that Lavasept® in the tested concentrations of 0.05 and 0.025 % cannot be contemplated for peritonitis irrigation treatment because of local intolerability. In further investigations the Lavasept® threshold with regard to mesothelial compatibility should be elucidated by gradually reducing the active substance concentration within the microbicidal concentration range.

If, at the same time, one bears in mind the possibility that provision can be made for appropriate irrigation and drainage systems as well as the facilities for assuring intensive and therapeutic balance levels in humans, which was not assured under the comparatively miniaturised

conditions in the animal model used, following this study it remains unresolved whether Lavasept® lavage with a low polihexanide concentration is not after all suitable for treatment of peritonitis. The still just about effective concentration that could be contemplated, and would still be tolerated by the cartilaginous tissues, would be 0.005 % [13].

Should it prove to be possible in future studies carried out on a more suitable experimental animal species to optimise the efficacy of local treatment for peritonitis based on a polihexanide concentration that is both microbicidally effective and tolerated by the local serosa, possibly while dispensing with macrogolum, this would represent a promising therapy. This notwithstanding, after generalisation of peritonitis parenteral administration of antibiotics continues to the indispensable treatment mainstay.

Conflict of Interest

The authors declare that there is no conflict of interest as understood by the International Committee of Medical Journal Editors.

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