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Volume 5 Issue 4, Pages 426 - 464

Published Online: 12 Nov 2008

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Abstracts from the II International Symposium on Peritoneal Dialysis

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Abstracts from the

II International Symposium on Peritoneal Dialysis

Berlin, West Germany, June 16-19, 1981

• Oral Presentation, ▪ Oral Presentation, Nurse, ⁝ Poster Presentation

The Second International Symposium on Peritoneal Dialysis is an official Satellite Meeting to the VIII. International Congress of Nephrology, Athens, June 7–12, 1981.

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DIGITAL OBJECT IDENTIFIER (DOI)
10.1111/j.1525-1594.1981.tb04029.x About DOI

REASON FOR FAILURE OF SALINE-IODINE FLUSHES

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Despite improvements in technique, training procedure and rigid patient selection for continuous ambulatory peritoneal dialysis (CAPD), the incidence of peritonitis remains unacceptably high in many centres. The ineffectiveness and dangers of long-term prophylactic use of broad-spectrum antibiotics are universally appreciated. Understandably the concept of adding antiseptics to dialysis solutions has frequently been entertained as an alternate method of combatting infection.

In June 1979, Stephen et al. (7) reported on a clinical trial on peritoneal dialysis (PD) patients in which the incidence of peritonitis was reduced from 1 infection every 33 patient-weeks to 1 infection in 217 weeks. This excellent result was attributed to the use of saline-iodine flushes. These authors also described 4 patients in whom saline-iodine flushes appeared to be of value in treating established peritonitis. The procedure they recommended was to instil 1-2 litres normal saline intraperitoneally (IP) post-dialysis, drain immediately and follow with 1 litre saline containing 2 ppm iodine. This in turn was drained after a dwell time of 4 minutes. The purpose of the initial flush was to remove or dilute residual glucose which might convert the iodine to ineffectual iodide. The short dwell time and very dilute iodine was considered adequate for antibacterial activity.

The simplicity and apparent innocuous nature of this procedure was very appealing and routine use of saline-iodine flushes was instituted in many CAPD centres. However, the initial enthusiasm was not sustained and the procedure has to a large extent been discontinued in our own and other centres (6). There are an appreciable number of reports in the literature relating to beneficial use of more concentrated solutions of iodine and iodine containing compounds for peritoneal toilet and lavage in traumatic and surgical peritonitis (3,5,8), and the possibility exists that the ineffectiveness of the saline-iodine flushes in some patients might have been related to inadequate concentrations of iodine being present IP. To investigate the feasability of increasing the concentration of iodine in solutions for IP use we undertook a series of studies to ascertain the toxic effects, upper

limit of safety, rate of IP inactivation and antimicrobal efficacy of dilute iodine.

1. TOXICITY OF DILUTE INTRAPERITONEAL IODINE

METHOD AND MATERIALS

One hundred adult Sprague-Dawley rats (250-300 g) were divided into groups of five for each intended dose. The rats were anaesthetized with diethyl-ether and given a single IP injection of a dilute iodine solution with concentrations ranging from 2-1500 ppm available iodine in 40 ml isotonic saline/kg body mass. Survival for calculation of the LD50 was determined at 24 hours. Rats that survived beyond this period and appeared distressed in any way were sacrificed by excess ether. The remaining outwardly unaffected animals were similarly killed after 15 to 21 days for examination of the peritoneum and abdominal contents. Specimens of the peritoneum, omentum, liver and spleen were examined in histological sections stained with haematoxylin and eosin.

RESULTS

The LD50 of IP iodine in 23 rats that died within 24 hours was established as 900 ppm in 40 ml/kg saline. This is equivalent to 36 mg iodine/kg. The least fatal dose encountered at 24 hours was 600 ppm or 24 mg/kg. However all animals that had received IP iodine in concentrations greater than 400 ppm had to be killed off at 24 hours because of obvious distress with restricted movement and retraction of abdominal muscles due to pain. These rats were in a state of shock with marked fall in rectal temperature. It was quite obvious that they would also have died shortly were it not for the protocol to sacrifice them at 24 hours.

The post-mortem findings in the carcases of the acutely ill rats that died or were killed by 24 hours was similar in all the animals. There was blood-stained peritoneal effusion and acute fibrinous exudates mainly on the liver surfaces, causing the lobes to become adherent to each other and to the diaphragm. The liver lobes appeared swollen and congested and petechial haemorrhages were noted on the peritoneal surfaces of the bowel.

Microscopically there were numerous polymorphonuclear leucocytes between the strands of fibrin. In the liver sections early necrosis of the superficial hepatocytes underlying the fibrinous exudate was present. Scattered areas of fat necrosis could be seen in the omental tissue. In 3 rats this picture of acute chemical peritonitis was observed following IP injections of iodine in concentrations as low as 140 ppm.

The striking pathological feature in the surviving rats killed between the 15th and 21st days was the develo-

pment of fibrous peritoneal adhesions between the omentum, lobes of the liver, diaphragm, spleen and loops of bowel (Fig. 1). Microscopic examination of the adhesions showed fibrous tissue infiltrated with lymphocytes and plasma cells. Adhesions were found in all rats that had received IP iodine greater than 80 ppm, in a few rats with lesser doses, and in 2 rats following only 33 ppm.

2. INTRAPERITONEAL INACTIVATION OF DILUTE IODINE

METHOD AND MATERIALS

Twenty rats were anaesthetized with diethyl-ether for insertion of short 16-guage flexible IP catheters. Iodine solutions ranging from 2 to 40 ppm in 40 ml normal-saline/kg body mass were injected IP via the catheters, following which 1 ml samples were aspirated at 20-second intervals. The presence of residual iodine in the aspirates was determined potentiometrically with sodium-thoisulphate using the method described in the 1980 edition of the British Pharmacopoea. The method is sensitive enough to determine the presence of 1 ppm iodine.

RESULTS

Through the entire range 2-40 ppm we were unable to detect free iodine in any of the aspirates collected at the end of the first 20-second period following injection of the iodine. This indicated almost immediate conversion of the iodine to iodide, with the $t_{\frac{1}{2}}$ of IP iodine being less than 20 seconds.

3. ANTIBACTERIAL EFFICACY OF DILUTE IODINE

METHOD AND MATERIALS

Stable broth cultures of Staph. epidermidis and E. coli were diluted with normal-saline to counts of 10^6/ml. 1 ml samples of the bacterial suspensions were placed in a series of test-tubes to each of which was added 9 ml of iodine in normal-saline to give a final iodine concentration of 4, 40, 100, 250, 500 or 1000 ppm. Bacterial suspensions were also added to control test-tubes of normal-saline without iodine. Precisely 10 minutes after adding the iodine, a loopful of each suspension was spread on nutrient agar plates and incubated for 12 hours at $37^{\circ}C$

RESULTS

There was complete inhibition in the growth of both organisms from the tubes containing 1000 ppm iodine. The Staph. epidermidis was only partially inhibited by 100, 250 and 500 ppm, while the growth from 4 and 40 ppm was

as luxuriant as that from the control tube without iodine. E. coli was partially inhibited by 500 ppm but totally unaffected by exposure to the lower concentrations of iodine.

Figure 1. Adhesions between loops of bowel, omentum and liver - IP iodine 100 ppm.

DISCUSSION

Acute inflammatory changes and adhesion formation have been well described in animal experiments following the use of relatively concentrated iodine solutions (3,4,5). In the present study we have shown that similar lesions can also be induced by dilute iodine under conditions that are more analagous to the PD procedure. From our investigations it is obvious that the upper limit for

safe dosage of IP iodine must be well below 33 ppm, the lowest concentration we noted to be followed by adhesion formation. Higher concentrations cannot be considered for PD because of the intense chemical peritonitis. These observations make one doubt whether the surgical practice of peritoneal irrigation with povidone-iodine and other standard iodine solutions is as innocuous as has been reported. The procedure may have a useful prophylactic effect from the mechanical removal of foreign material, but adhesion formation almost certainly follows (3,4), a complication that would be unacceptable for PD. To date there is no convincing evidence that established peritonitis has ever been cured as a result of iodine alone. The contrary would seem more likely to be true. Lagarde et al. (4) noted that the shock caused by IP iodine increased the mortality of dogs and rats in whom experimental peritonitis was induced by appendicular ligation. We made several attempts to assess the in-vivo antibacterial activity of dilute iodine in rats. However the results were always inconclusive because of inherent technical problems. The rat is particularly resistant to infection by Staph. epidermidis, and E. coli peritonitis was invariably fatal despite the administration of iodine or antibiotics in any dose or concentration.

The rationale for using only 2 ppm iodine in saline-iodine flushes was based on the experience of water engineers concerned with sanitation of swimming bath and drinking water that is relatively free of organic matter (1,2). Quite apart from the glucose content of dialysate solutions, the peritoneal cavity is never free of electron donating proteins, amino-acids and dextrose that is present in all extracellular fluid. Also the free surfaces of the mesothelial cells that line the peritoneal cavity form a rich source of electrons capable of rapidly converting this small amount of iodine to inactive iodide.

The brief $t_{\frac{1}{2}}$ of less than 20 seconds determined in the IP iodine inactivation study may be adequate to impart a fleeting antimicrobal effect. However this can hardly be considered as being useful prophylactic cover for the exchanges that take place during the ensuing 48 hours, the recommended time interval for successive saline-iodine flushes. Greater concentrations of iodine may well have a more prolonged $t_{\frac{1}{2}}$ than we had determined, but there was little purpose in extending our investigation to include iodine concentrations that are in the obvious toxic range.

The in-vitro antibacterial test with dilute iodine demonstrated that both E. coli and to a lesser extent Staph. epidermidis were still viable after exposure to concentrations up to 500 ppm for 10 minutes, i.e two-and-a-half times as long as the dwell time of the much more dilute iodine used in saline-iodine flushes.

It is appreciated that standard U.S.P. and B.P.

solutions of iodine such as the 2% tincture or 10% povidone-iodine are useful antiseptics for topical use on the skin and mucous membranes. However the toxicity of iodine is non-selective and not intended for internal administration. From our studies we can only conclude that 2 ppm iodine in saline-iodine flushes is a safe but totally ineffective intraperitoneal antimicrobal agent.

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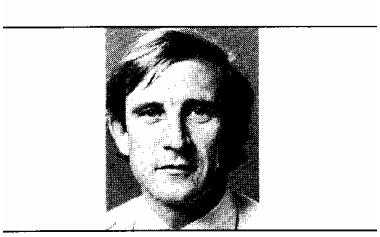

Peter C. Farrell

PERITONEAL MASS TRANSFER

Peter C. Farrell

The most fundamental parameter of the human peritoneum, as it relates to solute transport, is the overall mass transfer coefficient (MTC) .To some clinicians this term may sound as if it is not connected to clinical reality. In fact, it is of fundamental importance because it is the maximum achievable clearance, without the effect of ultrafiltration. Clearly, the latter can enhance clearance by solute-solvent coupling due to convection. However, to determine the capacity of a given peritoneum to remove solutes, be they drugs, waste metabolites or whatever, one would need to know the peritoneal MTC. Furthermore, serial measurements of the MTC provide the most accurate indicator of variations in the permeability of the peritoneum.

Even a rapid clearance measurement (45 minutes) would only provide a rough indication of changes in peritoneal permeability because even if adhesions were causing peritoneal area loss, or if fibrosis of the peritoneum was leading to peritoneal thickening, the reduction in diffusive capacity of the peritoneum is likely to be balanced by an improved convective removal of solute. The explanation is simple. A reduction in peritoneal MTC affects both outgoing (e.g. urea, creatinine) and ingoing (e.g. glucose) solutes in the same way. A reduction in the diffusive capacity for, say, urea means that the diffusion of glucose into the blood must also be compromised. As a consequence, for any given dialysate, there will be greater ultrafiltration due to the retention of glucose within the peritoneal cavity. The net result is improved convective solute removal overcoming, to a greater or lesser degree, the reduction in the peritoneum's diffusive mass transfer. In brief , the only way to be sure about subtle (as opposed to gross) changes in the peritoneum is to determine the mass transfer coefficient.

Various models of peritoneal mass transfer have been proposed (1-4) none of which are perfect but all of which, if correctly applied under appropriate exper

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imental conditions (4), can provide indications of any changes which may occur in the patient's dialysing surface.

We have used a model of the peritoneal mass transfer kinetics to follow patients' MTCs over periods of up to two years (4). Our initial observations (5) suggested that patients on intermittent peritoneal dialysis appeared to have a "tighter" membrane than patients who have been on CAPD for two weeks or more. In fact, the mean MTC for vitamin BIz (MW, 1355 Daltons) was 4.2 ± 1.5 ml/min in IPD patients compared to 7.4 ± 2.2 ml/min in CAPD patients. We could not readily explain these data except to suggest that perhaps the peritoneum, when bathed continuously in a hypertonic solution, became more solute permeable, whereas the peritoneum of patients on IPD is allowed to recover from the effects of lavage. As yet, this proposition is unproven but the observations are nonetheless of some interest (5). More recently, we have had an opportunity to follow variations in the MTCs of patients who have been on CAPD for periods up to two

years.

Briefly, the MTC is obtained from theoretical mass

transfer models, which are applied to experimentally obtained data based on serial dialysate concentration measurements. For urea and creatinine a single-pool model of the body is used, whereas a two-pool (intra/extracellular) is necessary for accurate determination of vitamin BIz MTCs. A variable dialysate volume is used and parameters such as net solute generation, ultrafiltration, convective flux, characterised by a sieving coefficient, and residual kidney function are taken into account. Complete details of models, experimental approach and methods of solution are outlined elsewhere (4, 6).

We have examined urea, creatinine and BIz MTCs in 15 CAPD patients who have undergone from two to six evaluations for periods on CAPD ranging from six months to two years. Data on each patient were assessed by regression analysis and analysis of variance. There was good news and bad news. In three

patients there was a significant decrease in all solute MTCs. In two there was a steady decrease with time, in the third case there was a significant drop in MTCs between the first and second evaluations (five months apart) but no further deterioration over the next five months. The specific case reports are examined elsewhere in detail (6) but are summarized briefly below.

A 63-year-old woman with polycystic kidney disease had been on CAPD for 71 weeks before she ceased the treatment and died. She had had no previous dialysis and her MTCs were followed over the first year of her treatment. She had two episodes of peritonitis, which responded to treatment. Over the final six months of treatment her serum urea dropped from 23 to 8.4 mM/l, creatinine from 0.73 to 0.46 mM/l and albumin from 37 to 15 g/l, data indicating malnourishment and wasting. Concomitantly, her B 12 MTC fell from 4.9 to 2.7 ml/min and dietary protein intake (DPI) from 1.1 g/kg/24 h to 0.7 g/kg/24 h at the last evaluation, five months before she ceased CAPD. (DPI was assessed from net urea generation (7)) .N o autopsy report on the peritoneum was available.

The second patient, who was 13 years of age and had renal disease secondary to reflux nephropathy, was on HD for 20 months followed by seven months of IPD and approximately 20 months of CAPD with a subsequent return to HD. We followed the patient for 70 weeks of CAPD and conducted five MTC evaluations. MTCs fell consistently for all solutes (B12 from 7.5 to 2.5 ml/min over the 70 week period) with no accompanying increase in serum metabolites due to decreasing DPI, concomitant decreases in body weight, creatinine production and serum albumin level. After 20 months of CAPD, the patient had a laparotomy because of suspected subacute bowel obstruction. Both the large and small bowel were wrapped in a thick envelope of peritoneum which was resected. The patient was transferred to hemodialysis.

The third patient, a 47-year-old man, had chronic glomerulonephritis. Cardiovascular complications precluded HD and after four months of IPD the patient was put on CAPD, which continued for 16 months before the patient was admitted to hospital with generalized peritonitis, hypotension, and mitral incompetance. He subsequently died in hospital of a cardiac arrest. Three MTC evaluations were conducted on this patient and the results are shown in Table I.

The autopsy report revealed dense fibrous adhesions enveloping the anterior surface of the stomach, duodenum, and most of the small and large intestines.

In contrast, the good news is that the remaining 12 patients, four of whom had completed two years of CAPD, showed no deterioration whatsoever in their MTCs; this demonstrates that viability of the peritcneum can be maintained during continuous lavage with hypertonic solutions. The relevant data are shown in Table II.

In summary , CAPD is capable of supporting ESRD patients for extended periods with acceptable waste metabolite removal. However, complications due to peritoneal fibrosis and adhesion formation can result in deterioration of peritoneal mass transfer. Observed pathological changes may be related to conventional peritonitis or perhaps even to chemical peritonitis, an issue raised at the recent Berlin meeting by Furman *et al* (8) .However, out data are insufficient to implicate either factor. It should also be pointed out that serum urea and/or creatinine levels do not necessarily provide an acceptable indication of dialysance. The complications of anorexia and wasting, which are associated with inadequate dialysis, appear in patients adjusting to inadequate treatment, whether this be due to innate patient problems or insufficient daily lavage volume and may mask an increase in serum B ON and creatinine resulting from a decrease in dialysance. For this reason

TABLE I: *MTC values for patient number three*

PERIOD ON CAPD (WK)	9	30	47
Urea MTC (ml/min)	46.0	26.2	26.5
Creatinine MTC (ml/min)	31.6	12.4	13.2
Vitamin B_{12} MTC (ml/min)	23.1	4.8	5.5

TABLE II: *Variations in MTC with time on CAPD*

PERIOD ON CAPD* (n)	5±4 (12)	22±7 (12)	41±8 (7)	62±15 (6)	90±6 (4)
Urea, MTC (ml/min)	21.1±3.5	25.3±5.9	24.5±5.4	23.4±4.0	27.4±7.6
Creatinine MTC (ml/min)	11.1±3.0	14.0±5.1	14.7±2.4	14.7±3.1	19.8±5.1
Vitamin B_{12} MTC (ml/min)	4.8±2.4	5.2±3.3	4.7±0.7	5.8±3.1	7.4±1.9

*Mean ± SD (Weeks)

rapid clearance or, preferably, MTC measurements should be coupled with dietary assessment for complete definition of a patient's clinical status .

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