REASON FOR FAILURE OF SALINE-IODINE FLUSHES

K.I. Furman, H. Kündig, D.T. Ninin and J.D. Block.

Department of Experimental and Clinical Pharmacology, Department of Pathology, University of the Witwatersrand and the Witwatersrand Technikon, Johannesburg, South Africa.

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.

REFERENCES

1. Black, A.P., Kinman, R.N., Keirn, M.A. et al. (1970): Amer. J. Public Health, 60, 535
2. Black, A.P., Thomas, W.C., Jr., Kinman, R.N. et al. (1968) : J. Amer. Water Works Assoc., 60, 69.
3. Gilmore, O.J.A. (1978) : In: Proceedings, World Congress on Antiseptics, p. 117. Editor: H. Reber, H.P. Publishing Co., New York.
4. Lagarde, M.C., Bolton, J.S. and Cohn, I. (1978) : Ann. Surg., 187, 613.
5. Lavigne, J.E., Brown, C.S., Machiedo, G.W., Blackwood, J.M. and Rush, B.F. (1974) : J. Surg. Res. 16, 307.
6. Nolph, K.D. (1980) : In: Proceedings, International Symposium, Continuous Ambulatory Peritoneal Dialysis, p. 272. Editor: M. Legrain, Excerpta Medica, Amsterdam.
7. Stephen, R.L., Kablitz, C., Kitahara, M., Nelson, J.A., Duffy, D.P. and Kolff, W.J. (1979) : Dial. Transplant., 8, 589.
8. Weissenhofer, W., Meissner, K. and Metka, W. (1978) : In: Proceedings, World Congress on Antiseptics, p. 120. Editor: H. Reber, H.P. Publishing Co., New York.