Intraperitoneal noxythiolin and povidone-iodine in experimental peritonitis*

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Summary

The efficacy of intraperitoneal noxythiolin and povidone-iodine was compared in mice and rats with induced Gram-negative peritonitis. Noxythiolin 1% solution reduced the mortality of mice from 65 to 41% ($P<0.1$) but was ineffective in rats. Povidone-iodine (6.0-7.5 mg available iodine/kg body weight) significantly reduced the mortality of both mice ($P<0.001$) and rats ($P<0.01$) in treated animals compared to matched controls. The mortality rate of rats treated with povidone-iodine was significantly less than those treated with noxythiolin ($P<0.01$).

Introduction

Any condition which releases bacteria into the peritoneal cavity is associated with much morbidity and mortality. The reason for this is readily appreciated when one realizes that diffuse peritonitis involves a mesothelial surface of 22 000 cm² and is equivalent to a heavily infected 75-100% body surface burn (McKenna *et al.*, 1970). The main cause of circulatory collapse and death in these patients is the absorption of Gram-negative organisms and their associated endotoxins. In order to reduce morbidity and mortality of peritonitis, as much as possible should be done to eliminate contaminant bacteria at the time of surgery.

To this end, numerous antibiotics have been used in the peritoneal cavity. But intraperitoneal antibiotics are liable to cause neuromuscular blockade in patients under general anaesthesia who are receiving muscle relaxants: motor paralyses, apnoea and death may follow (Hartshorn, 1971; McQuillen, Cantor and O'Rourke, 1968; Pittinger and Adamson, 1972). This acutely toxic phenomenon is particularly associated with the aminoglycosides, the most valuable antibiotics in Gram-negative peritonitis. Some intraperitoneal antibiotics also cause adhesions (Ellis, 1974; Shatten, 1956).

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If a surgeon wishes to add a safe antimicrobial to his lavage fluid to kill contaminant organisms he may either use an antibiotic with a limited spectrum and a slow action or an antiseptic. The advantages of using an antiseptic are its broad spectrum and rapid action without risk of neuromuscular blockade.

Noxythiolin is widely used in clinical peritonitis in Europe, but a recent study concluded that a search for more effective intraperitoneal antiseptics was necessary (Gilmore *et al.*, 1978a). Furthermore noxythiolin-resistant bacterial strains have recently emerged (Chattopadhyay, 1977).

Povidone-iodine has been shown significantly to reduce infection in a wide variety of abdominal wounds particularly those contaminated with Gram-negative organisms (Gilmore and Martin, 1974; Gilmore, Martin and Fletcher, 1973; Gilmore and Sanderson, 1975). It has been shown to be as effective as short-term systemic prophylaxis with tobramycin and lincomycin in acute abdominal surgery (Stokes *et al.*, 1978). It does not inhibit healing (Gilmore, Reid and Strokon, 1977). In addition, attempts to induce bacterial resistance to this agent completely failed (Gilmore and Sanderson, 1975; Houang *et al.*, 1976). In experimental peritonitis, intraperitoneal povidone-iodine (6.0-7.5 mg available iodine/kg body weight) significantly reduced the mortality of treated animals compared with untreated matched controls (Gilmore *et al.*, 1978b).

Because of the doubts regarding the effects of noxythiolin (Tolhurst *et al.*, 1974; King, Gurry and Brooke, 1975; Gilmore *et al.*, 1978a) it was decided to undertake controlled trials comparing the efficacy of this agent with povidone-iodine in experimentally-induced peritonitis in mice and rats.

Materials and methods

Mouse study

A controlled study was undertaken using 330

mice. Female Theiller Original (TO) mice, specific pathogen free, weighing 20–25 g were used exclusively. Peritonitis was induced by the injection of *Escherichia coli* 0141/K85/H4 (Gilmore, 1977). Known volumes and concentrations of *E. coli*, constant for each experiment, and ranging from 3 to 9×10^7 organisms per ml, were used as inocula for the induction of peritonitis. Following the induction of peritonitis the mice were randomly allocated to one of three treatment groups according to the intraperitoneal instillation which was injected one min after the induction of peritonitis.

The mice in Group A (control) received 0.2 ml Ringer solution, those in Group B received 0.2 ml noxythiolin 1% solution, and those in Group C received 0.2 ml of povidone-iodine solution containing 0.075% available iodine.

A sterile 1.0-ml disposable tuberculin syringe with a 16-mm 25-gauge disposable hypodermic needle was used for injecting. The injection site was in the midline, midway between the xiphisternum and pubis. The mortality rate in each group was recorded and all survivors were killed at one week. A post-mortem examination was performed on every animal shortly after death.

Rat study

One hundred and fifty Wistar rats each weighing 200–250 g, were injected with 7.5 ml/kg body weight of a suspension of *E. coli* 0111/B4/H2 containing 10^9 organisms per ml, in 3.1% haemoglobin (Gilmore, 1977). Haemoglobin was added to enhance the virulence of *E. coli* (Rogers, 1973). Following the injection of this mixture the rats were randomly allocated to one of three different treatment groups. Those in Group A (control) received no additional instillation, those in Group B were injected intraperitoneally with 7.5 ml/kg body weight noxythiolin 1% solution and those in Group C with 7.5 ml/kg body weight of a povidone iodine solution containing 0.1% available iodine. The appropriate antiseptic was injected in the same manner as described in the mouse experiment one minute after the induction of peritonitis. The mortality rate of each group was recorded and all survivors were killed at one week. Again a post-mortem examination was performed shortly after death in every animal.

Statistical methods

For comparison of mortality rates in the different treatment groups a double sided Fisher's exact test was used. This involved the use of a computer programme written in FORTRAN and run on a time-sharing terminal to an IBM 370 computer.

Results

The mortality rates of the different groups of

mice are shown in Table 1. Treatment with either antiseptic administered one min after induction of peritonitis reduced the mortality of the mice. The reduction in mortality achieved by noxythiolin ($P < 0.1$) did not reach a level generally accepted as significant ($P < 0.1$). Treatment with povidone-iodine however, produced a statistically significant result ($P < 0.001$).

TABLE 1. Comparison of noxythiolin and povidone-iodine in the treatment of peritonitis in mice

Group	Total no. mice	Deaths	P
A Control (Ringer)	110	72	—
B Noxythiolin 1% solution	110	57	< 0.1
C Povidone-iodine (0.075% available iodine)	110	46	< 0.001

All mice with fatal peritonitis died within 4–18 hr of its induction, and the only abnormality found at post-mortem was peritoneal hyperaemia. At one week nothing abnormal was noted in any mouse. No mouse had peritoneal adhesions and there was no difference in the post-mortem findings between any group.

The results of the rat study are shown in Table 2. The mortality rate in the control and noxythiolin groups was identical, showing noxythiolin to be ineffective in this animal. Treatment with intraperitoneal povidone-iodine, however, significantly reduced mortality ($P < 0.01$). Of the control animals, 28% died compared with only 4% of those treated with povidone-iodine. At post-mortem all rats dying of peritonitis had a hyperaemic peritoneum and free intraperitoneal fluid, from which *E. coli* was cultured. No abnormality was found in any of the survivors, which were sacrificed at one week.

TABLE 2. Comparison of noxythiolin and povidone-iodine in the treatment of peritonitis in rats

Group	Total no. rats	Deaths	P
A Control (no instillation)	50	14	—
B Noxythiolin 1% solution	50	14	n.s.
C Povidone-iodine (0.1% available iodine)	50	2	< 0.01

Throughout both studies no adverse reaction was seen to either antiseptic in mice or rats at the time of injection or later.

Discussion

The intraperitoneal injection of povidone-iodine (6.0–7.5 mg available iodine/kg body weight) in

experimentally induced peritonitis significantly reduced the mortality of treated mice compared to matched controls ($P < 0.001$). Given a similar dose it also significantly reduced the mortality rate of rats with peritonitis ($P < 0.01$). Noxythiolin 1% solution, however, failed significantly to reduce mortality in either animal although it had some beneficial effect in mice. Perhaps a stronger solution may have been more effective.

The dose of povidone-iodine used in the experiments was almost ten times less than the intraperitoneal median lethal dose (LD_{50}) (Gilmore *et al.*, 1978b). This dosage is equivalent to giving a 70-kg man 500 mg of available iodine that is 50 ml of a standard 10% povidone-iodine solution (containing 1% available iodine). In fact, such a solution has subsequently been used by the authors in clinical peritonitis with apparent good effect and a controlled clinical trial is now proposed.

When the treatment-free interval in mice was increased from 1 to 15 min and later 30–60 min, the efficacy of povidone-iodine diminished (Gilmore, 1976). The probable reasons for this are several. The peritonitis induced in the mice was rapidly progressive and in fatal cases may have become irreversible shortly after induction. The short survival of the majority of mice dying of peritonitis indicates that bacteria and their toxins rapidly enter the blood stream. For an antiseptic to be effective in cases with septicaemia it would need to be given in conjunction with systemically active antibiotics as occurs in the clinical situation.

These studies have shown povidone-iodine to be superior to noxythiolin in the treatment of experimental peritonitis. They indicate that for povidone-iodine to be most effective it needs to be given early. The experiments in both animals suggest that this antiseptic may prove to be of greatest value in clinical practice at the time of operation in decontaminating the peritoneum following intestinal resections especially in an emergency.

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