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A comparison of noxythiolin and povidone-iodine in experimentally induced peritoneal infection in mice

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SUMMARY

Noxythiolin (Noxyflex, Geistlich), given intraperitoneally as a 2·5 per cent solution, protected mice from the lethal effects of an intraperitoneal injection of Escherichia coli. Povidone-iodine (Pevidine, Berk), containing 0·075 per cent iodine, gave no protection.

GILMORE (1977) has compared the effects of noxythiolin and povidone-iodine given intraperitoneally to mice infected with an intraperitoneal suspension of *Escherichia coli*. In his experiments povidone-iodine was found to give significant protection at a dose of 0·2 ml of solution containing 0·075 per cent available iodine, while noxythiolin was shown not to produce a significant reduction in mortality. However, Gilmore used a dose of only 0·2 ml of 1 per cent noxythiolin while the clinically employed solution of noxythiolin contains 2·5 per cent. The concentration of noxythiolin is known to be critical, and it cannot, therefore, be inferred from Gilmore's report that noxythiolin is inferior to povidone-iodine in the protection of mice experimentally infected with *E. coli*.

We have now carried out a study in mice using 2·5 per cent noxythiolin (Noxyflex, Geistlich) and a povidone-iodine solution containing 0·075 per cent available iodine (Pevidine, Berk) to compare the protective effects of the two preparations at concentrations comparable to those employed clinically.

Materials and methods

Escherichia coli, serotype 044, were grown on nutrient agar plates and harvested after 24 h by scraping in 1 ml of 1 : 1 mixture of normal sterile saline and nutrient broth. A total of 60 plates was used and the bacterial suspensions were combined and the population of organisms estimated by comparison with Brown's opacity tubes. Two separate dilutions of the bacterial suspension were prepared and the mean of the two estimations was used as a count of the number of organisms present.

In pilot experiments, bacterial suspensions were injected intraperitoneally into groups of 10 male TO (Theiller Original) mice weighing between 20 and 24 g in order to determine the minimum number of organisms required to induce death within 24 h. This was found to be about 10^{10} organisms per mouse.

In the main experiment the organism was grown and harvested as before and was then diluted to give a suspension containing 10^{11} organisms/ml. Three groups of 60 TO male mice received 0·1 ml of this suspension intraperitoneally followed 1 min later by an intraperitoneal injection of 0·2 ml of 2·5 per cent noxythiolin or 0·2 ml of povidone-iodine containing 0·075 per cent available iodine or 0·2 ml of sterile saline.

The mice were maintained in groups of 5 in polythene boxes at an environmental temperature of 20–21 °C with a relative humidity of 45–55 per cent. They had constant access to water and to their normal diet pellets (Dixon's 41B).

Death times were recorded at 15-min intervals for 24 h and thereafter hourly for the following 12 h, after which there was no further mortality.

Results

The injection of the povidone-iodine solution appeared to cause acute discomfort. Povidone-iodine solution also accelerated death compared with the control group receiving sterile saline.

Noxythiolin appeared to cause no discomfort on dosing. It increased survival time and also reduced the mortality rate. The details of mortalities and survival time are shown in *Table I*.

Table I: GROUP MEAN SURVIVAL AND MORTALITY RATES

Treatment group	Mean survival time (h after infection ± s.d.)*	No. of animals dying within 36 h ($n = 60$)
Sterile saline (0·2 ml)	7·4 ± 3·2	60
2·5 per cent noxythiolin (0·2 ml)	12·9 ± 5·7**	42
Povidone-iodine with 0·075 per cent available iodine (0·2 ml)	4·3 ± 3·0**	60

* Group mean survival time omits animals not dying within 36 h.

** Significantly different from control group ($P = < 0·001$).

Discussion

There has been a growing disenchantment with antibiotics amongst surgeons as more resistant organisms emerge and toxic and allergic reactions are encountered. However, recent papers by Stewart and Matheson (1978a, b) reported a significant reduction in septic complications in appendicular peritonitis in children using peritoneal lavage with tetracycline and other antibiotics. Similar results have been achieved with metranidazole (Study Group, 1976), which is emerging as the treatment of choice in infections of colonic origin, where bacteroides is the most significant organism in residual sepsis. Other workers have been reinvestigating antiseptic compounds, especially where massive infection occurs in a body cavity, as is the case with peritonitis. The two main groups of compounds in use at the present time are the iodine antiseptics, where iodine is rendered water-soluble, stable and non-irritant by linkage to polyvinylpyrrolidone (PVP), and the formaldehyde-releasing compounds such as noxythiolin and taurolin.

The results of animal studies are not always strictly applicable to man and are difficult to compare owing to the wide variety of animal models used. Several authors (Browne and Leslie, 1976; Comber et al., 1976; Gilmore et al., 1978) have put forward a strong case for the standardization of techniques. These authors have all finally selected the mouse with peritonitis induced by the injection of a measured inoculation of standard bacteria as the best model. However, even with this standard model, different results are found by different workers, and the findings in the present experiments are in direct contrast to those reported by Gilmore (1977).

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The method in the present study was intended to mimic that used by Gilmore, although it is appreciated that injection of the test substance 1 min after the dose of organisms is unrealistic and bears little relation to the clinical situation.

Unlike antibiotics, the quantity of antiseptic formaldehyde-transmitter (such as noxythiolin or taurolin) required depends on the number of infecting organisms, there being a direct relationship between the two. Too small a dose of antiseptic will diminish the infection but allow bacteria to survive to produce residual abscesses or infection at a later stage, while an effective antiseptic in adequate dosage can result in a massive release of endotoxin which may in itself be fatal. Formaldehyde-releasing compounds also neutralize endo- and exotoxins (Wright and McAllister, 1967; Leslie and Pfirrman, 1978) and so should be administered in excess so that both their antibacterial and anti-endotoxin effects can be utilized. This anti-endotoxin property has not been demonstrated for povidone-iodine compounds, although PVP itself has some weak ability to fix toxins and allow their excretion through the kidney.

The recommended concentration of noxythiolin is 2·5 per cent (Browne, 1967; Stoller, 1967; Browne and Stoller, 1970; Leger et al., 1972; Pickard, 1972; Gue, 1974), and since there is a stoichoimetric relationship between the dose of antiseptic and the number of organisms present, it seems likely that the disparity between our results and those of Gilmore (1977) and Cleaver et al. (1974) is due to the fact that the latter workers used doses well below the recommended levels. The same criticism also applies to the results reported by Stewart and Matheson (1978a, b), where the dose of noxythiolin used was less than half the recommended level while the dose of tetracycline was very high.

The injection of povidone-iodine caused discomfort in the injected animals and accelerated death. At autopsy, however, all the animals showed diffuse purulent peritonitis with no difference detectable between the groups. It is therefore not possible to postulate a direct toxic effect of povidone-iodine from these results.

References

BROWNE M. K. (1967) Intraperitoneal noxythiolin in faecal peritonitis. *Clin. Trials J.* **4**, 673–678.

BROWNE M. K. and LESLIE G. B. (1976) Animal models of peritonitis. *Surg. Gynecol. Obstet.* **143**, 738–740.

BROWNE M. K. and STOLLER J. (1970) Intraperitoneal noxythiolin in faecal peritonitis. *Br. J. Surg.* **57**, 525–528.

CLEAVER C. L. T., HOPKINS A. D., KEE KWONG K. C. N. G. et al. (1974) The effect of postoperative peritoneal lavage on survival, peritoneal wound healing and adhesion formation following faecal peritonitis: an experimental study in the rat. *Br. J. Surg.* **61**, 601–604.

COMBER K. R., OSBORNE C. D. and SUTHERLAND R. (1976) Intraperitoneal challenge. In: WILLIAMS I. D. and GEDDES A. M. (ed.) *Chemotherapy*, Vol. 2. New York, Plenum.

GILMORE O. J. A. (1977) A reappraisal of the use of antiseptics in surgical practice. *Ann. R. Coll. Surg. Engl.* **59**, 93–102.

GILMORE O. J. A., HONANG E. T., REID C. et al. (1977) Noxythiolin in peritonitis. *Postgrad. Med. J.* **54**, 33–35.

GUE S. (1974) Intraperitoneal noxythiolin in faecal and purulent peritonitis. *Aust. NZ J. Surg.* **44**, 375–378.

LEGER L., MOULLE P. and DELAITRE B. (1972) Noxythiolin intraperitonéale dans les péritonités généralisées. *Chirurgie* **98**, 539–542.

LESLIE G. B. and PFIRRMAN R. W. (1978) The anti-endotoxin actions of taurolin. (In preparation.)

PICKARD R. G. (1972) Treatment of peritonitis with pre- and postoperative irrigation of the peritoneal cavity with noxythiolin solution. *Br. J. Surg.* **59**, 642–648.

STEWART D. J. and MATHESON N. A. (1978a) Peritoneal lavage in appendicular peritonitis. *Br. J. Surg.* **65**, 54–56.

STEWART D. J. and MATHESON N. A. (1978b) Peritoneal lavage in faecal peritonitis in the rat. *Br. J. Surg.* **65**, 57–59.

STUDY GROUP (1976) Metronidazole in prevention and treatment of Bacteroides infections after appendicectomy. *Br. Med. J.* **1**, 318–319.

STOLLER J. L. (1967) Faecal peritonitis. *Clin. Trials J.* **4**, 670–671.

WRIGHT C. J. and MCALLISTER T. A. (1967) Protective action of noxythiolin in experimental endotoxaemia. *Clin. Trials J.* **4**, 680–681.

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