

EVALUATION OF NEOMYCIN-PHTHALYLSULFATHIAZOLE IN PREPARATION OF THE LARGE BOWEL FOR SURGERY

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THE NEED for an effective intestinal antiseptic was evidenced as early as 1874, by Billroth¹ in his work on intestinal antiseptics. But no significant advance in this direction occurred until Poth² introduced succinylsulfathiazole as an adjunct in the preparation of the large bowel for surgery. Despite the use of new antibiotics within the past five years, including streptomycin, chlortetracycline (Aureomycin), chloramphenicol, and oxytetracycline (Terramycin), no single agent has proved completely satisfactory for all cases. A variety of unfavorable reactions, including diarrhea, proctitis, pruritus ani, pseudomembranous colitis with fatalities,* and outgrowth of resistant organisms has been noted with the use of certain antibiotics as intestinal antiseptics.

For effective use in the preparation of the colon or rectum, Poth⁵ has set forth the properties of an ideal intestinal antiseptic. It is unlikely that any single antimicrobial drug will be found which fulfills all of these criteria, but it is possible that some combination of drugs may approach the ideal. Satisfactory results over a five-year period with the use of streptomycin and phthalylsulfathiazole (Sulfathalidine) as adjuncts in bowel surgery have been obtained, with relative freedom from untoward reactions such as overgrowth of fungi and pseudomembranous colitis reported with other antibiotics, by one of us (H.E.B.).

This method of intestinal antiseptics was initially reported by Rowe, Spaulding, Madajewski, and Bacon⁶ in 1948 and later⁷ described in more detail.

In 1950 Poth⁸ recommended neomycin as an intestinal antiseptic superior to those previously available. Because of the frequent appearance of resistant *Aerobacter* organisms, however, he subsequently⁹ adopted a combination of neomycin and phthalylsulfathiazole. The excellent results reported by him¹⁰ prompted the present study.

PROCEDURE

Clinical confirmation of the rapid bowel preparation was made in a series of patients undergoing surgery of the colon and rectum, with the administration of 10 gm. of neomycin and 15 gm. of phthalylsulfathiazole in divided doses over a 24-hour period, immediately prior to

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* References 3 and 4.

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surgery. The agents were orally administered in the form of a single combination tablet (neomycin-phthalylsulfathiazole [Neothalidine†]). The following dosage schedule was employed: 5 tablets, each containing 200 mg. of neomycin and 300 mg. of phthalylsulfathiazole, were given orally, at hourly intervals for four hours; thereafter 5 tablets were given orally every four hours until a total of 50 tablets had been administered, making a total of 10 gm. of neomycin and 15 gm. of phthalylsulfathiazole given in the 24-hour period immediately preceding large bowel surgery. The last dose was given approximately six hours before making the incision.

In addition to the combination tablets, mechanical cleansing of the bowel was achieved by the oral administration of 60 cc. of castor oil given 36 hours prior to surgery or in divided doses if partial obstruction was present. Cleansing enemas of isotonic sodium chloride solution were given daily for three days prior to surgery and on the morning of the surgery. No solid foods were permitted the day preceding the surgery, liquid feedings being substituted. The selection of patients for this regimen of castor oil, enemas, and neomycin-phthalylsulfathiazole preparation precluded any patient in whom obstruction was a permanent factor requiring management different from primary resection without complementary colostomy. All patients in this study were treated in the Philadelphia area, during the winter and early spring, receiving a high-protein, high-carbohydrate, low-residue diet with protein supplement. No other intestinal antiseptics were used.

Data on Neomycin-Phthalylsulfathiazole-Castor Oil Effect on Microbial Flora of Bowel in Sixteen Patients

Average Colony Counts (In Thousands)			
	Preliminary Stool	Operative Fecal Specimen	Final Postoperative Stool
"Total" aerobes	1,000,000	400	2,000,000
"Total" anaerobes	5,000,000	1,000	40,000
Coliform bacilli	6,500	0*	80
Spores	8	0†	10
Enterococci	60	0†	2.5
Yeasts	31	0.8	15

* Less than 5,000 per gram of wet fecal material, the smallest number detectable by test method.
 † Less than 100 per gram.

The patients receiving this preparation have been divided into two groups. Group I consists of those patients having comprehensive microbiologic study of all stool specimens preoperatively, at the time of surgery, and postoperatively, in order to determine precisely the effect of neomycin-phthalylsulfathiazole upon the microbial flora of the large intestine. Group II consists of those patients who received neomycin-phthalylsulfathiazole after the completion of the cases in Group I. Thus, Group II patients were studied for clinical results and toxicity, while Group I patients were studied mainly for the microbiologic effect.

The 16 patients in Group I were observed for an average period of 11.7 days, and an average of nine specimens were examined from each patient. These included preliminary control stools, stools following castor oil, stools following neomycin-phthalylsulfathiazole tablets, fecal specimens taken at the time of surgery, and postoperative stools. The time at which the first postoperative stools were obtainable ranged from two to seven days after the operation.

Microbiologic examination consisted of "total" aerobic and anaerobic colony counts and of separate cultures on special media for coliform bacilli, micrococci (staphylococci), streptococci, yeasts, and spores. The predominating types of organisms were selected from the 20 culture plates routinely used and tested for neomycin susceptibility. In addition, the majority of stool specimens were assayed for the neomycin content.

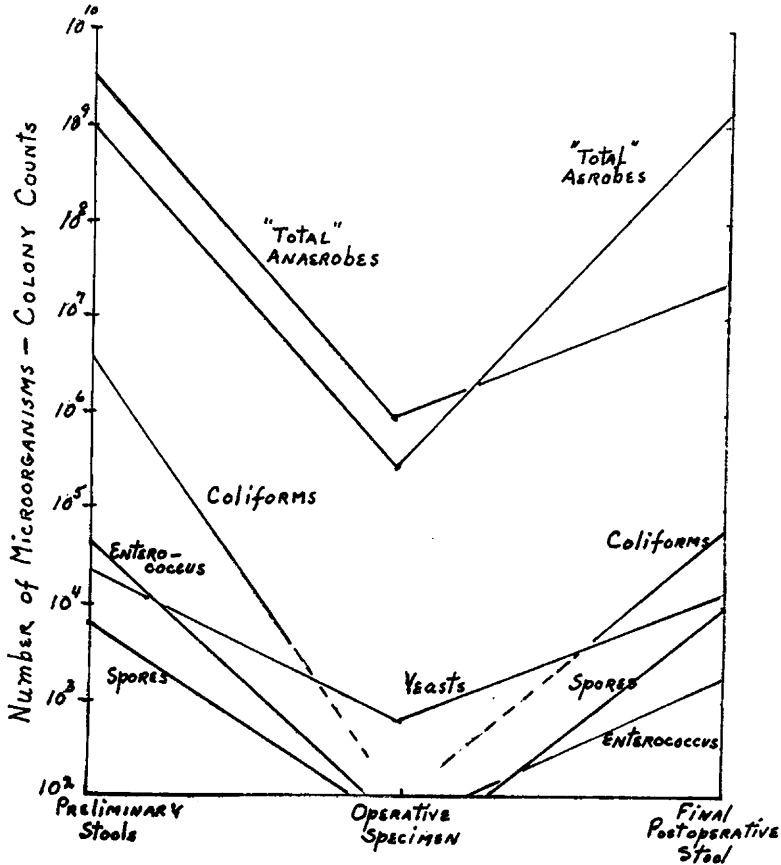
RESULTS

Group I.—A summary of the culture results appears in the Table. The number of coliform bacilli decreased rapidly, beginning with the first enema. In no

† The material used in this study was supplied by Sharp & Dohme, Inc., Philadelphia.

instance were coliforms detectable in the operative specimens; this means that the average number decreased from 6,500,000 in the preliminary specimens to less than 5,000 per gram of wet feces, which is the smallest number detectable by the culture method employed. In five cases these organisms were even absent from the post-operative specimen.

Spores and streptococci are normally present in relatively small numbers, 8,000 to 60,000 per gram. Therefore it is not surprising that these types were usually absent in the operative specimens. Because it is unlikely that neomycin-



Average colony counts with 16 patients receiving neomycin-phthalylsulfathiazole and castor oil in preparation for surgery.

phthalylsulfathiazole can bring about rapid destruction of spores, it is assumed that a disappearance of these resistant forms was the result of mechanical cleansing. The decrease in the number of streptococci can also be explained by the mechanical action of the castor oil and enemas.

On the other hand, yeast forms, which were present in all but two of the preliminary stools in approximately the same numbers as the streptococci, persisted in over half the cases. This fact suggests that the desirable results already mentioned with the coliforms were due to a combined purgation and drug effect.

There was a marked variation in the total number of micro-organisms detectable at the time of operation. Since no single culture medium is capable of growing all of the numerous varieties of microbes in feces, the figures representing the number of colonies present on duplicate aerobic and anaerobic trypticase soy agar are referred to as "total" counts. In some cases the decrease was insignificant; in others the effect was so remarkable that only 1 organism in 6,000,000 persisted. The average figures for the 16 patients under study (Table) show that the "total" aerobes decreased by 99.96% and the "total" anaerobes by 99.98%. These results are presented graphically (Chart).

Group II.—This group included 39 patients, which, combined with those of Group I makes a total of 55 patients having neomycin-phthalylsulfathiazole preparation for large bowel surgery in whom no significant toxicity was encountered. There were five instances of gross peritoneal contamination inadvertently occurring at the time of open anastomosis or secondary to inadvertent escape of fecal content from the bowel. One of these patients died on the 11th postoperative day, as result of retroperitoneal sepsis; *Proteus* organisms were recovered from an abscess culture. No other mortality occurred on the basis of sepsis.

COMMENT

The results reported here agree with those of Poth ‡ to the extent that preparation of the bowel with large doses of neomycin and phthalylsulfathiazole combined with castor oil and enemas is highly effective. Coliform bacilli are absent at the time of operation, as in most instances also are spores and enterococci. In further agreement with that investigator, yeasts persist throughout such a regimen.

On the other hand, the present report fails to demonstrate the sterility state reported by Poth.¹⁰ Although completely negative cultures were obtained from one operative specimen, "total" counts in the range of 100,000 to 1,000,000 per gram were generally obtained. Because of the large doses of neomycin-phthalylsulfathiazole used in the bowel preparation described in this report, heavy concentrations of the drugs may be present in fecal specimens. These yielded assay values as high as 130 mg. per gram of feces, which are great enough to produce a bacteriostatic effect in the cultures made from low dilutions. When the proper technique was employed, however, it could be demonstrated that such specimens still contained many viable micro-organisms. Thus, we have been unable to demonstrate actual sterilization of feces.

The best results were obtained among the patients in Group I, in whom the response to castor oil was most marked. This observation emphasizes the comment made by Poth¹⁰ that the length of time required for the preoperative preparation of the bowel is determined by the degree of mechanical cleansing obtained. Furthermore, it raises the question as to whether the mechanical effect is not more important than the antimicrobial action of neomycin-phthalylsulfathiazole. Regardless of the actual roles played by the two agencies, a combination of castor oil, enemas, low-residue diet, and neomycin-phthalylsulfathiazole causes a marked reduction of the microbial population of the feces, provided a satisfactory emptying of the bowel occurs.

‡ References 9 and 10.

It must be emphasized that the microbial counts of the operative specimens are misleading. Sometimes a small bolus of fecal material was all that could be found at the time of resection, but this small specimen, when cultured, would often yield a comparatively high microbial count, in terms of the numbers of microorganisms per gram of feces. Although the figures thus obtained appear in the Table, it is apparent that they fail to reflect the fact that the bowel was practically empty at the time and actually contained comparatively few organisms.

Neomycin administered intramuscularly has been shown to cause both ototoxicity and nephrotoxicity, but when administered in large oral doses, up to 10 gm. a day as was done in this study, the amount absorbed from the intestine is negligible. The range of the urinary recoveries following the administration of 10 gm. of neomycin is usually less than 1% and has only occasionally been observed to be as high as 5% of the administered dose. Accordingly, neomycin administered orally is free of toxicity assigned to it following parenteral administration and by reason of nonabsorption remains in the gastrointestinal tract where it exerts a prolonged antimicrobial effect, an important property in the crucial period of relative ileus following bowel resection.

SUMMARY

A program of preoperative bowel preparation that combines mechanical cleansing with large doses of neomycin and phthalylsulfathiazole for 24 hours was carried out with 55 patients.

Extensive microbiologic studies were made in 16 cases. In confirmation of Poth's findings, coliform bacilli, spores, and streptococci were usually absent from the operative specimens.

Wide variation occurred, however, in the "total" microbial counts, depending upon the extent of the mechanical cleansing. The average reduction was 99.96% for aerobes and 99.98% for anaerobes. An occasional instance of apparent sterility was attributed to a false bactericidal effect produced by high concentrations of drugs carried over to the culture plates.

No significant toxicity was encountered after the oral administration of neomycin-phthalylsulfathiazole as described.

The regimen first suggested by Poth and followed in this study appears to be an effective method for bowel preparation. Because the drugs are administered for only 24 hours prior to surgery, there is little opportunity for overgrowth with yeasts and other resistant organisms before the time of operation.

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