THE USE OF SOFRAMYCIN (FRAMYCETIN SULPHATE) FOR INTESTINAL STERILIZATION

BY

N. E. STIDOLPH and J. M. ALSTON

From Whittington Hospital, London

From its known properties "soframycin" appears to be valuable for intestinal antisepsis since it has a broad spectrum. The intestinal bacteria are sensitive to it, it acts rapidly, is poorly absorbed from the gastrointestinal tract, and is well tolerated by mouth.

"Soframycin" (framycetin sulphate) is prepared from *Streptomyces decaris*. Its antibacterial spectrum is wide and it exerts both a bacteriostatic and bactericidal action on a number of Gram-positive and Gram-negative organisms (Massénat-Deroche, 1954). Staphylococci resistant to other antibiotics are highly sensitive to "soframycin" (Lutz and Hofferer, 1955a) and enterococci are sensitive in fairly low concentrations. The streptococcus requires relatively high bacteriostatic concentrations, especially for *Streptococcus viridans*, and Gram-negative organisms, especially coliform organisms, *Proteus* and *Pseudomonas pyocyanea*, are very vulnerable to "soframycin" (Lutz and Hofferer, 1955b), and the bactericidal potency of "soframycin" against *Proteus* is greater than that of the other usual antibiotics. Pathogenic coliforms, especially the well-defined antigenic strains occurring in infantile gastroenteritis, are very sensitive to the antibiotic (Connell and Rousselot, 1958; Louwette and Lambrechts, 1958).

"Soframycin" is readily absorbed when given parenterally, but because of toxicity it is not given therapeutically by this route. By contrast "soframycin" is but poorly absorbed when given orally because the intestinal barrier is almost impermeable to it and thus the antibiotic can exert a sustained effect on the intestinal flora.

It is necessary to reach a single oral dose of 4 g. of "soframycin" before blood concentrations become measurable (about 1 µg. per ml.) (Massénat-Deroche, *loc. cit.*). In therapeutic doses absorption is so poor that there are no systemic effects, as estimations of blood "soframycin" levels have repeatedly shown. The urinary levels are too low to cause any renal damage (Marquézy, Debray, Leveau, Grenier, and Lepage, 1955).

CLINICAL TRIALS

The clinical trial was conducted on 22 patients in the wards of Whittington or Hornsey Central Hospitals. All the patients to whom the drug was given were cases in which the bowel had to be divided for resection of a growth, for the establishment of a colostomy or ileostomy, or for the utilization of a portion of the bowel for another purpose, *e.g.*, ileal loop bladder or ureteroplasty. In all cases the patients were in hospital when the "soframycin" was administered. The drug was given in tablet form by mouth, 0.5 g. eight-hourly in the majority of cases, the total dosage varying from 2 g. to 4 g. The time and dose were recorded.

Patients were prepared for operation by the routine method used in the unit. No aperients were given but they had bowel washouts on the morning of the operation, on the evening preceding operation, and on the evening preceding that, *i.e.*, three in all. In the cases marked with a star in the Table, 250 mg. of "soframycin" in 60 ml. saline was instilled into the bowel after each washout and left to be passed by the patient as desired.

BACTERIOLOGICAL RESULTS

As far as possible, examination was made of (1) a specimen of stool passed recently before the first dose of "soframycin"; (2) a specimen passed after the last dose of "soframycin" and before operation; and (3) specimens of intestinal contents taken from the lumen of the portion of intestine removed at operation.

The specimens were examined on a quantitative basis, except in the case of small amounts of mucus or tissue, from the area of a malignant growth. The method was as follows:—

Weigh two equal portions of stool, approximately 1 g. Emulsify one portion in 100 ml. saline and dilute this emulsion 1 in 10, 1 in 100, and 1 in 1,000 in saline. Culture 0.1 ml. of each of these dilutions on desoxycholate citrate agar medium, on blood agar medium incubated aerobically, and on blood agar incubated anaerobically. After incubation, count the colonies on

TABLE
RESULTS WITH SOFRAMYCIN SUMMARIZED

Initials	Sex	Age	Case No.	Condition for Operation	Dosage of "Soframycin" (g.)	Bacteria before "Soframycin"	Bacteria after "Soframycin"	Clinical Course
A.H.	♂	69	1	Resection of colostomy	1.0, 8-hourly (total 4)	Not recorded	No coliforms, haemolytic strep., staph. or yeast per g. dried weight	Good
V.A.	♀	56	2	Hemicolectomy for carcinoma of caecum	0.5, 8-hourly (total 2)	1.8 million/g. dried wt. mostly coliforms	Very little growth, only 118/500 enterococci g. dried wt.	Good
L.E.	♀	85	3*	Anterior resection, carcinoma of recto-sigmoid	0.5, 8-hourly, 1 instillation after each washout (total 2)	2,000 million coliforms/g. dried wt.	Proximal to neoplasm, very few coliforms; distal to neoplasm, very few coliforms	Good
C.H.	♀	54	4	Partial colectomy, carcinoma of ascending colon	0.5, 8-hourly (total 3)	Not recorded	Colon sterile, 12,000 coliforms/g. dried wt. in small intestine only	Good
E.P.	♀	56	5	Colectomy for ulcerative colitis; abdomino - perineal one-stage resection	0.5, 8-hourly (total 3.5)	Not recorded	Stool after 24 hours' treatment 160,000 enterococci/g. dried wt., after 48 hours, tissue and faeces from rectum, tissue and faeces from ileum, swab from ileum, all showed no coliforms but small numbers of enterococci and yeasts	Good
L.A.	♀	69	6	Resection of sigmoid colon and resection of 10 in. small bowel for colonic fistula after perforated diverticulitis	0.5, 8-hourly (total 3)	Not recorded	(1) Proximal end of colon, very few viable organisms; (2) distal end of colon, distal to colostomy, large numbers Gram + ve bacteria, chiefly enterococci; swab of ileum, no viable organism	Good
C.H.	♀	52	7	Resection of colostomy	0.5, 8-hourly (total 2)	Large growth 75 million/g. dried wt. almost all <i>E. coli</i>	(1) Proximal to colostomy, 1 million coliforms mostly <i>Proteus</i> (2) Culture of tissue, no growth	Good
E.H.	♀	42	8	Pelvic clearance with colostomy and ileal loop bladder	0.5, 8-hourly (total 2.5)	Not recorded	No coliforms, large number of Gram + ve bacteria, chiefly enterococci	Pelvic abscess
D.M.	♀	67	9	Resection of carcinoma of splenic flexure	0.5, 8-hourly (total 3.5)	230 million/g. dried wt. organisms of which at least 23 million <i>E. coli</i>	No growth or organisms on any media	Good
					0.5, 8-hourly (total 3.5)	58 million/g. dried wt. mixed bacteria including 25 million <i>E. coli</i>	30 million enterococci, no <i>E. coli</i>	Good
E.D.	♀	69	10	Resection of carcinoma of recto-sigmoid	0.5, 8-hourly (total 2)	27 million organisms/g. dried wt. of which 19 million <i>E. coli</i>	(1) Proximal end of specimen, 0.75 million <i>E. coli</i> /g. dried wt.; (2) distal end 0.66 million <i>E. coli</i> /g. dried wt.; (3) culture of tissue, no growth	Good
C.M.	♀	63	11	Colostomy for colovaginal fistula	0.5, 8-hourly (total 2)	192 million organisms, mostly coliforms	6,080 coliforms/g. dried wt.	Good
J.A.	♀	71	12	Abdomino - perineal resection for carcinoma of rectum	1.0, 8-hourly (total 4)	Not recorded	No coliforms, 14½ million enterococci/g. dried wt.	Good
E.F.	♂	63	13	Total cystectomy with ileal loop bladder	0.5, 8-hourly (total 2)	Not recorded	Not recorded	Good
W.U.	♂	76	14	(1) Uretero-colic anastomosis	0.5, 8-hourly (total 2)	127 million bacteria, mostly coliforms	2.13 million bacteria, mostly coliform and few enterococci	Good
				(2) Total cystectomy and uretero colic-anastomosis remaining ureter	0.5, 8-hourly (total 2)	400 million bacteria, mostly coliforms	6.4 million bacteria, mostly coliform; 1 day later, 2.4 million	Good
N.G.	♀	76	15	Resection for carcinoma of colon	0.5, 8-hourly (total 3)	930,000 organisms, mostly coliforms/g. dried wt.	No bacterial growth	Good
J.K.	♀	79	16*	Resection for carcinoma of recto-sigmoid	0.5, 8-hourly + 1 instillation after each washout (total 2)	100 million bacteria, mostly enterococci, with a few coliforms and <i>Cl. Welchii</i> g. dried wt.	No bacterial growth	Good
E.W.	♀	63	17	Ileal loop for ureteroplasty	0.5, 8-hourly (total 3)	62.4 million bacteria, mostly coliform and some enterococci	No bacterial growth	Good
R.B.	♂	32	18*	Ileal loop bladder and total cystectomy	0.5, 8-hourly + 1 instillation after each washout (total 3)	Not recorded	Not recorded	Good
F.P.	♂	67	19	Resection for carcinoma of sigmoid obstructing the bowel	1, 8-hourly (total 4)	400 million/g. dried wt. mostly coliform and enterococci	Proximal end of specimen, 126,000 organisms/g. dried wt., mostly enterococci; distal end sigmoid obstruction, 12.2 million/g. dried wt.	Good
A.P.	♂	54	20	Resection of benign ulcer of transverse colon	0.5, 8-hourly (total 2)	Not recorded	Not recorded	Good
A.	♂	52	21	Total cystectomy and ileal loop bladder	0.5, 8-hourly (total 2)	Not recorded	Not recorded	Good
F.S.	♂	71	22	Carcinoma of sigmoid, colon resected	0.5, 8-hourly (total 2)	Not recorded	Not recorded	Good

all plates where growth was not confluent. Dry the second portion of specimen in a desiccator and weigh the dried specimen in order to calculate the number of colonies per gram of dried specimen. From the appearance of colonies and from films of the colonies and of the original specimen, determine the approximate distribution of different bacterial species. Filter sufficient of the first (1 in 10) dilution of the original emulsion (equalling 1 in 1,000 of faeces) and test for the presence of free antibiotic by the disc technique.

RESULTS

In all cases the drug caused a marked reduction in the intestinal bacterial content, particularly in the coliform group of organisms and of *Cl. welchii*. Comparatively, enterococci were more resistant but they were much reduced in almost all patients. In several instances (Cases 15, 16, and 17) there was no growth of organisms at all in the stool after total dosages of 2 or 3 g. "Soframycin" was not detected by the disc technique in the specimens tested.

In only one case in which "soframycin" was used was there subsequent sepsis or complication of any kind, namely, in Case 8, a patient who had vesicovaginal and vaginocolic fistulae after previous radiotherapy for advanced carcinoma of the cervix, with gross sepsis before operation. One patient died from a pulmonary embolus on the sixth day after operation, and one, uraemic before operation, died in uraemia on the tenth post-operative day.

SIDE-EFFECTS

There were no side-effects attributable to the drug

in any of the cases treated. In addition to the above-mentioned patients a number of others were prepared for resection of bowel but no resection was done at operation nor did they show any evidence of side-effects from the administration of the drug.

SUMMARY

"Soframycin" was given in total dosage of 2 to 4 g. to 22 patients before operations involving division of the large intestine (18 cases) or small intestine (four cases). The drug led to a very great reduction or to the complete absence of viable bacteria in the stools or at the site of surgical operation. Post-operative infection of the peritoneum or intestinal or surface wounds was absent in all patients except one whose tissues were severely infected before operation. Undesirable side-effects from the drug were not found.

We acknowledge with thanks the assistance of ward sisters and nurses who helped in the work involved and of Miss E. Hutchinson in the Group Laboratory. We are indebted to Dr. E. W. Tapley for discussion on this clinical trial, and to him and Roussel Laboratories Ltd. for a supply of "soframycin" tablets.

REFERENCES

- Connell, J. F., and Rousselot, L. M. (1958). *Surgery*, 44, 447.
Louwette, R., and Lambrechts, A. (1958). *Brit. med. J.*, 1, 868.
Lutz, A., and Hofferer, M. J. (1955a). *Strasbourg méd.*, 6, 633.
—, — (1955b). *Rev. immunol.*, 19, 69.
Marquézy, R. A., Debray, P., Leveau, Grenier, and Lepage (1955). *Arch. franç. Pédiat.*, 12, 859.
Massénat-Deroche, B. (1954). Thesis, Paris.