# A Study of Moniliasis in Aureomycin Therapy. (19209)

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Numerous reports have appeared in the literature describing the development of moniliasis following antibiotic therapy(1-3). Finally, in April 1951 the Council on Pharmacy and Chemistry of the American Medical Association decided that a warning statement should be added to the label of chloramphenicol, aureomycin, and terramycin(4). This Report of the Council pointed out that the overgrowth of monilia and other yeast-like organisms following the administration of antibiotics occurs most frequently in the large bowel and is of slight importance; however, it emphasized that deaths from pulmonary moniliasis can occur following therapy with these new preparations.

It was suggested to us that the addition of esters of paraben (parahydroxybenzoic acid) to aureomycin might prevent the development of moniliasis(5). These agents have been employed in foods and drugs as preservatives for many years(6,7). The methyl ester of paraben is effective against mold while the propyl ester is active against yeast(7). This paper is a report of the comparative incidence of moniliasis in patients receiving aureomycin and in those receiving aureomycin containing paraben.

*Experimental. In vitro* sensitivity studies using 4 strains of *C. albicans* and 1 strain of *C. krusei* established a definite inhibitory effect by mixed paraben esters. Eighty mg of methyl paraben and 20 mg of propyl paraben were added to 10 ml of physiological saline solution and serial dilutions were prepared. The paraben esters did not completely dissolve which made accurate interpretation of results difficult. The yeast was inoculated on Sabourand's medium containing various amounts of paraben ranging from 10 to 2500 $\mu$g per ml of medium. All control cultures having no paraben esters revealed yeast within 24 hours, but those containing 1000 to 2500 $\mu$g of paraben per ml of medium required (with a single exception) 96 hours. Following these studies capsules, powder and suppositories were prepared for us by the Lederle Laboratories Division of the American Cyanamid Company. Each of these preparations was supplied in 2 forms—one consisted of aureomycin alone and the other of aureomycin with paraben esters. This investigation involving 186 patients was divided into 3 sections: oral, vaginal and rectal studies.

*Oral studies.* Fifty-eight patients were selected who had no apparent gastrointestinal disease and had received no antibiotic or chemotherapeutic agent during the previous 72 hours. Thirty were given 500 mg of aureomycin orally every 6 hours, while 15 received the same medication except that each 250 mg capsule of aureomycin contained 142 mg of methyl paraben and 35.5 mg of propyl paraben. Inasmuch as these 45 patients had various infectious diseases, the duration of therapy ranged from 1 to 19 days with the average being 7 days. Thirteen additional patients were given 80 mg of methyl paraben and 20 mg of propyl paraben every 3 hours for 4 days. In each case efforts were made to obtain daily stool specimens; 1 to 3 control specimens were obtained in every instance before beginning therapy. Of the 15 patients who received aureomycin with paraben, 2 revealed *C. albicans* in the stool after treatment; though all had been negative originally. One of these patients noted mild nausea, while the other was asymptomatic. Two additional cases in this group noted nausea and vomiting; mild, painless diarrhea was observed by 2 others. In the group of 30 patients to whom aureomycin without paraben was administered, 21 were found to harbor *C. albicans* in the stools after treatment; though only 6 had revealed yeast prior to therapy. Five cases in this group noted nausea, vomiting or mild diarrhea; but only 1 of 3 patients who developed nausea and vomiting revealed *C. albicans* in the stool. However, yeast was demonstrated in the feces

TABLE I. The Effect of Paraben on the Occurrence of *C. albicans* in Aureomycin Therapy.

| | Type of treatment | No. of cases | Cases positive for *C. albicans* Before treatment | After treatment |
|---|---|---|---|---|
| Oral | A. Aureomycin alone | 30 | 6 | 21 |
| | B. Aureomycin with paraben | 15 | 0 | 2 |
| | C. Paraben alone | 13 | 8 | 3 |
| Vaginal | A. Aureomycin alone | 27 | 5 | 14 |
| | B. Aureomycin with paraben | 57 | 8 | 13 |
| | C. Paraben alone | 10 | 1 | 1 |
| | D. Aureomycin and Propion Gel | 15 | 4 | 7 |
| Rectal | A. Aureomycin alone | 9 | 1 | 2 |
| | B. Aureomycin with paraben | 10 | 2 | 1 |

of both cases that had diarrhea.

Thirteen patients received 800 mg of the methyl and propyl esters of paraben each day for 4 days. Initially 8 of these cases disclosed *C. albicans* in the stool. At the conclusion of therapy, however, this yeast was present in the feces in only 3 cases. It should be noted that 1 of these patients had not disclosed *C. albicans* prior to paraben therapy. No toxicity to treatment was observed. The results obtained in the oral studies are summarized in Table I.

*Vaginal studies.* Only patients who had not received an antibiotic or chemotherapeutic agent for 72 hours were included in this investigation. Vaginal cultures for yeast were obtained prior to treatment and then on the second, fifth and eighth days. In 7 cases a 250 mg gelatin capsule of aureomycin was inserted into the vagina each day for a week. In 6 additional patients, the same procedure was carried out except that Propion Gel (calcium propionate 9.5%, sodium propionate 9.5% and propionic acid 1%; Wyeth) was administered simultaneously with aureomycin. Fourteen other cases were subjected to the same regimen except that a 250 mg aureomycin suppository was employed which contained 280 mg of mixed paraben esters. In 19 cases, two 250 mg gelatin capsules of aureomycin were inserted intravaginally each day for a week. Aureomycin alone was employed in 10 patients, while in 9 it was administered concurrently with Propion Gel. Finally, 10 patients were subjected to the following regimen: 160 mg of methyl paraben and 40 mg of propyl paraben, in the form of a capsule, were inserted intravaginally each day for a week. Using a Holmes insufflator, powder consisting of 1 g of aureomycin in 3.95 g of talc was sprayed evenly over the cervix, vagina, introitus and vulva. In 10 cases this powder contained no paraben, in 14 cases it contained 1% paraben (.8% methyl paraben and .2% propyl paraben) and in 29 cases it contained 10% paraben (8% methyl paraben and 2% propyl paraben). To summarize: 109 patients were observed; 27 received aureomycin alone, 57 aureomycin containing paraben, 15 aureomycin with Propion Gel and 10 paraben alone. Results are represented in Table I.

*Rectal studies.* Nineteen patients were included in this study. Each patient was proctoscoped on the first, third and fifth day. At each proctoscopic examination the mucosa was observed, cultures for yeast were obtained and medication was inserted. On the second and fourth days, medication was inserted digitally. In 4 cases, two 250 mg gelatin capsules of aureomycin without paraben were administered each day. Five patients were subjected to the same regimen except that each 250 mg capsule of aureomycin contained 142 mg of methyl paraben and 35.5 mg of propyl paraben. A 250 mg wax suppository of aureomycin was employed in 5 instances; while 5 additional patients were treated in exactly the same manner except that each aureomycin suppository contained 224 mg of methyl paraben, and 56 mg of propyl paraben. Therefore, in this phase of the investigation 9 received aureomycin alone and 10 aureomycin containing paraben. The results are summarized in Table I.

*Discussion. In vitro* studies using 5 strains

of yeast isolated from patients complaining of moniliasis following antibiotic therapy established a definite inhibitory effect by the methyl and propyl esters of paraben. Oral, vaginal, and rectal studies involving 186 patients demonstrated that the addition of these agents to aureomycin was of value in preventing the development of moniliasis. This was especially obvious in the oral studies. When aureomycin alone was administered, 63% of those patients whose stools were initially free of *C. albicans* subsequently revealed these organisms. In contrast, when aureomycin containing paraben was employed, only 13% disclosed yeast. While the number of patients involved in the rectal studies was limited, results were consistent with those observed in the oral and vaginal cases. With 1 exception, *C. albicans* infections became more severe with aureomycin therapy; however, no alteration was observed when aureomycin containing paraben was administered. The combination of aureomycin and paraben caused the disappearance of *C. albicans* in only 2 cases. In 3 patients having monilial vaginitis the intravaginal insertion of 200 mg of paraben daily for 3 weeks resulted in an amelioration of symptoms but did not eradicate the yeast. It appears from these studies that methyl and propyl paraben exert only a weak or moderate inhibitory action on *C. albicans in vitro* and *in vivo* but are capable of preventing its overgrowth during aureomycin treatment.

Little variation was noted in the occurrence of nausea, vomiting and diarrhea in patients receiving aureomycin alone and in those given aureomycin containing paraben esters. No toxic effects to the esters of paraben were observed.

*Summary.* (1) *In vitro* sensitivity studies established a definite inhibitory effect by methyl and propyl paraben (para-hydroxybenzoic acid) on 5 strains of yeast. (2) Methyl and propyl paraben are essentially non-toxic when administered orally, vaginally or rectally. (3) Methyl and propyl paraben are of value in preventing the overgrowth of *C. albicans* associated with aureomycin therapy.

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Received September 25, 1951. P.S.E.B.M., 1951, v78.

## Comparison of Normal Blood Picture of Young Adults from 18 Inbred Strains of Mice. (19210)

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In this study of the formed elements of the blood of normal mice, a total of 18 inbred lines were investigated, including sublines of 10 major strains, a large proportion of those widely used in biological research(1-3). All are maintained together in the "inbred nucleus" of the Jackson Laboratory, where certain of the lines (marked with †) form the background of all mice sold to other institutions. Experimental mice were virgins, 2 to 3

* This work was done under a Grant-in-Aid to the Roscoe B. Jackson Memorial Laboratory from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council. It has also been aided by grants to the Jackson Laboratory from the Commonwealth Fund, Anna Fuller Fund, Jane Coffin Childs Memorial Fund, and the National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service.