INCREASED RESISTANCE OF TISSUE CULTURE CELLS TO THE TOXIC ACTION OF ANTIBIOTICS IN THE PRESENCE OF METACIL

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UDC 578.085.23:[615.779.9-015.25:615.754.3

The pyrimidine derivative metacil has been used to reduce the effects of the toxic action of large doses of the following antibiotics on the cell: the potassium salt of benzylpenicillin, oxacillin, bicillin-5, chloramphenicol, and dibiomycin.

EXPERIMENTAL METHOD

Transplantable strains of amniotic epithelium and strain SOTs were used. After cultivation at 37° the medium was replaced by a fresh sample containing, in the control series, one of the antibiotics used and, in the experimental series, the antibiotic with metacil. Some of the tubes with the cells were filled with a fresh sample of medium alone (group of intact cells). After 24 h the number of cells in all three groups was counted and their mitotic activity determined by the usual method.

Effect of Antibiotics and Their Combinations with Metacil on Number of Cells of Amniotic Epithelium and Its Mitotic Activity

Antibiotic	Dose (in units/ml)	Metacil	Dose (in μg/ml)	Mean No. of cells/ml after 24 h	P†	No. of mitoses per 1000 cells	P†
Potassium salt of benzylpenicillin	—	—	—	226 600		40	
	10 000	—	—	111 100		19	0,001
	10 000	+	10	190 200	0,01	36	0,1
	10 000	+	20	185 000	0,01	30	0,1
Bicillin-5	—	—	—	397 100		57	
	625	—	—	140 800		20	0,001
	625	+	10	231 000	0,05	40	0,1
	625	+	20	291 600	0,01	40	0,1
Dibiomycin*	—	—	—	386 100		42	
	100	—	—	148 500		19	0,001
	100	+	10	497 200		42	
	100	+	20	541 200		48	
Chloramphenicol	—	—	—	264 000			
	1 000	—	—	135 000			
	1 000	+	10	99 000	0,1	—	—
	1 000	+	20	78 000	0,1	—	—
Oxacillin	—	—	—	294 800			
	5 000	—	—	151 800			
	5 000	+	10	121 000	0,1	—	—
	5 000	+	20	110 000	0,1	—	—

Note: P in the experiments with a combination of dibiomycin with metacil was not determined because the indices in the experimental group were higher than in the control. The mitotic activity in the experiments with a combination of chloramphenicol and oxacillin with metacil was not determined because of the inefficacy of these combinations.

* In μg/ml.

† By comparison with the results in the group of intact cells.

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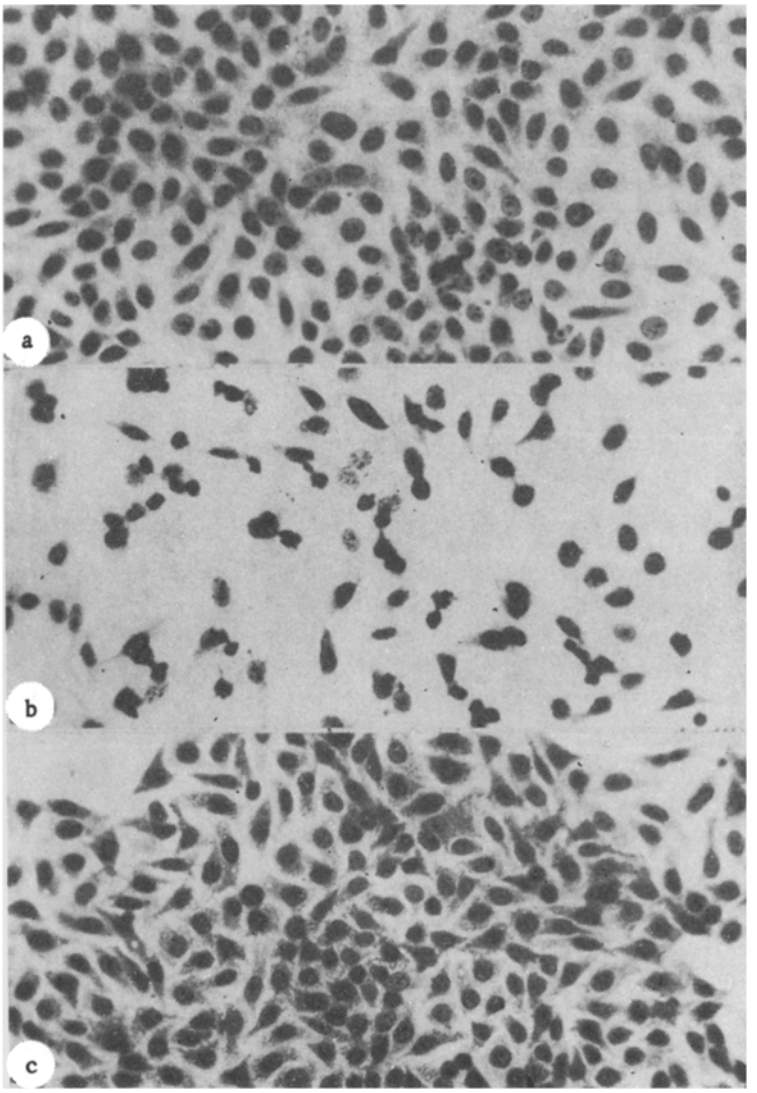

State of the cell layer in the group of intact cells (a), and subjected to the action of dibiomycin (b) and a combination of dibiomycin with metacil (c).

EXPERIMENTAL RESULTS

When benzylpenicillin or bicillin-5 was combined with metacil the number of amniotic epithelium cells was much greater than in the control series, i.e., the toxicity of both antibiotics toward the cells was lowered in the presence of metacil (see table). The combination of metacil with dibiomycin completely removed the toxicity of the antibiotic and the number of cells was greater in the experimental series than in the intact group. The mitotic activity was increased in the presence of metacil. Similar results were obtained in the experiments with the SOTs strain. The addition of metacil did not prevent a decrease in the number of cells under the influence of chloramphenicol and oxacillin.

Morphologically a marked weakening of the toxic action of dibiomycin, the potassium salt of benzylpenicillin, and bicillin-5 on the cell was observed in the presence of metacil (see figure). It was found by the serial dilution method that the addition of metacil did not affect the bacteriological activity of these three antibiotics in relation to various strains of staphylococci and to Escherichia coli.

Comparison of the results obtained with data concerning the stimulant action of metacil on cell proliferation [1, 2] suggests that the less marked toxic changes observed in the cells in the presence of metacil can evidently be attributed to the increase in resistance of the cells to the toxic action of high doses of the antibiotics used. It may

be concluded from the results of these experiments that it is desirable to use metacil in conjunction with penicillin and dibiomycin during the local application of these antibiotics to reduce or prevent completely their unwanted side-effects on the tissue cells.

SUMMARY

Combination of metacil with potassium salt of benzylpenicillin and bicillin-5 reduces, but combination of metacil with dibiomycin eliminates the toxic influence of the above-mentioned antibiotics on tissue culture cells. In these combinations there is a considerable decrease in the number of degenerating cells and the degree of their alteration, and the mitotic activity of cultures increases or even returns to normal. These findings are evidence that the less alteration of cells in the presence of metacil is due to an increase in the cell resistance to the toxic effect of large doses of the antibiotics applied. In combination of metacil with chloramphenicol or oxacillin their toxic effect on the cells is not reduced.

LITERATURE CITED

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