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Molecular mechanism of the wound-healing action of Betamecil

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6-Methyluracil can undergo stereostructural changes during controlled synthesis and crystallization which are reflected in altered physicochemical properties and consequent altered biological activities. Previous investigations have shown that the β-modification of methyluracil, designated Betamecil, possesses marked wound-healing properties for linear and surface skin wounds in the rat, and in the cornea of the rabbit, and at thermal damages as well (Leonidov 1993, 1996). Betamecil is now widely used in medical practice as a stimulator of reparative process (Leonidov 1996). The work reported here deals with the comparative analysis of the activities of the modified compound - Betamecil - and the unmodified compound, methyluracil.

Standard methods were used to evaluate mitotic index of rabbit cornea epithelia, RNA-polymerase and DNA-methyltransferase activity, [3H]thymidine uptake, connective tissue cicatrix strength of cornea linear wounds, and free D cathepsin levels (Tata 1978; Smith & Berezny 1982).

Table 1. Wound-healing comparison of Betamecil and methyluracil.

Parameters	Test system	Betamecil	Methyluracil
Epithelization time (min, n = 12))	Rabbit cornea[a]	83.0 ±2.8*	100 ± 3.5
Time to loss of crust (days, n = 8)	Rat skin	8.6 ± 0.7	9.6 ± 0.5
Time to complete healing (days, n = 8)	Rat skin	17.7 ± 1.6	18.4 ± 1.6
Cicatrix breaking stress (g min^{-1}, n = 8)	Rat skin[b]	57.3 ± 9.0	40.1 ± 5.0
Mechanical damage (mitotic index, ‰)	Rabbit cornea		
	Day 4[a]	4.9*	3.8
	Day 7[a]	4.6*	3.4

[a]Betamecil ointment was compared with methyluracil 10% ointment. [b]Betamecil 0.25% solution was compared with methyluracil 1% solution. *Significantly different from corresponding values for methyluracil.

Table 1 summarizes the comparison of the wound-healing efficacy of Betamecil and methyluracil, and indicates that Betamecil is at least as active, if not more so, than the standard preparations. It should be noted that in these experiments, the Betamecil concentrations were lower than those of methyluracil while maintaining comparable activity.

Table 2 summarizes the comparison of the two preparations in the key biochemical tests which are indicative of stimulation of reparative processes. In these cases, Betamecil again proved more active than the unmodified compound. We conclude that the superior healing effect of Betamecil is due to its enhanced effect in these biochemical properties.

Table 2. Biological comparison of Betamecil and methyluracil.

Test	Control	Betamecil	Methyluracil
[a]RNA-polymerase (impulses (μg protein)$^{-1}$, n = 4-5)	1550 ± 165	2449 ± 107*	2079 ± 203
[b]DNA-methyltransferase (impulses (μg protein)$^{-1}$, n = 4-5)	1400 ± 45	3000 ± 65* **	2200 ± 38*
[a][^{3}H]Thymidine uptake by DNA odf rat liver (impulses (μg protein)$^{-1}$, n = 4-5)	10.5 ± 0.7	18.5 ± 0.6* **	14.7 ± 0.6*
[c]Free cathepsin D in rat derma in experimental dermatitis (% total activity, n = 8)	71.0 ± 0.4	38.0 ± 0.5* **	46.0 ± 0.8*

[a]Determination in rat liver 3 h after intraperitoneal administration of 20 mg kg^{-1} of test substances. [b]Determined 6-24 h after administration of test substances. [c]Determination 60 min after intraperitoneal administration of 10 mg kg^{-1} of the test substances. *Significantly different from control, **significantly different from methyluracil.

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