ACTIVITY OF TETROXOPRIM AGAINST R-FACTOR MEDIATED TRIMETHOPRIM RESISTANT BACTERIA

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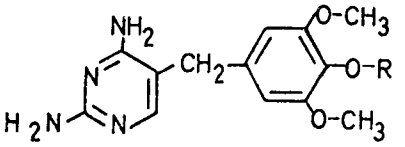
The enzyme Dihydrofolate reductase (DHFR) catalyzes the production of tetrahydrofolate (THF) from dihydro-folate (DHF) in both prokaryotes and eukaryotes. THF and its derivatives play a vital role in one carbon unit metabolism and are the sole source of reduction potential in thymidine biosynthesis. Inhibitors of DHFR hence have pronounced effects on DNA and other syntheses. Several such inhibitors exist although to be of use in antibacterial chemotherapy they must be considerably more active against bacterial than mammalian DHFR. Until recently only one such inhibitor, trimethoprim (Tm, R = $-CH_3$), which is 80,000 times more active against bacterial than mammalian DHFR (Burchall 1979), has been in clinical use. However, Heumann and Co. have now developed a new bacterial DHFR inhibitor, tetroxoprim (Tx, R = $-(CH_2)_2-O-CH_3$), which is at least 50,000 times more active against bacterial than mammalian DHFR (Aschhoff and Vergin 1979).



Bacteria have become resistant to Tm due to the possession of an R.factor which mediates the production of a DHFR which is 20,000 times more resistant to Tm than is the normal bacterial DHFR (Aymes and Smith 1974). The incidence of R.factor determined Tm resistance appears to be increasing (Aymes et al 1978) and it was therefore of interest to determine whether Tx could be significantly more active against bacteria possessing such R.factors. To investigate this a representative of each of the two known types of R.factor mediated Tm resistant DHFR were purified using ion-exchange chromatography and the IC50 and Ki for both Tm and Tx against these enzymes were determined as described by Aymes and Smith (1976). The normal Tm sensitive chromosomal DHFR of the host strain E.coli K12 J6.2 was also included for comparison.

E.coli Strain	IC 50(M)		Km(M)	Ki(M)		MIC($mg.l^{-1}$)	
	Tm	Tx	DHF	Tm	Tx	Tm	Tx
J6.2	$2.0x10^{-8}$	$1.5x10^{-7}$	$2.3x10^{-5}$	$8.3x10^{-9}$	$3.0x10^{-8}$	0.2	0.8
J6.2 (R483)	$3.0x10^{-4}$	$7.0x10^{-4}$	$2.7x10^{-6}$	$2.9x10^{-5}$	$4.8x10^{-5}$	1200	4400
J6.2 (R67bis)	$1.5x10^{-2}$	$4.0x10^{-2}$	$2.0x10^{-5}$	$1.1x10^{-2}$	$2.8x10^{-3}$	2000	4000

It can be seen that all three enzymes are slightly more resistant to Tx than to Tm and this increased resistance appears to be reflected in increased Minimum Inhibitory Concentrations (MIC) for each strain against Tx. Thus, although Tx is recommended as an alternative to Tm (Wise and Reeves 1979) it appears that it will be of no use in treating infections caused by bacteria which possess R.factors conferring Tm resistance.

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