Unique Factors Influencing the Topical Absorption of Idoxuridine

Sir:

We have recently developed a procedure for the quantitative measurement of selected drugs in biological tissues, based upon X-ray emission spectroscopy. Speed, sensitivity, and applicability directly to tissue sections are among the advantages of this method. We have applied the method to measurements of the percutaneous and corneal absorption of idoxuridine, an antimetabolite effective against the herpes simplex virus. Some very interesting and unexpected findings regarding the factors influencing the topical absorption of idoxuridine have prompted this early reporting.

Measurements were made of idoxuridine in excised rabbit skin sections following topical applications of this drug at various concentrations in a variety of vehicle systems and after a variety of medication contact times. Drug contact times were controlled by maintaining drug solutions in reservoirs over the skin. Results are presented in Table I. *The data clearly show the existence of an inverse relationship between the concentration of idoxuridine in the vehicle and the amount of idoxuridine absorbed when the application is left for a sufficient period of time* (0.5 hr. or more). Differences in tissue uptake from solutions of different concentrations of drug become greater with increasing contact time.

TABLE I.—CONCENTRATIONS (mcg./cm.^{2}) OF IDOXURIDINE IN RABBIT SKIN FOLLOWING DIFFERENT IDOXURIDINE SOLUTION CONTACT TIMES

Solution Applied				
	IDU	Contact Time, min.		
Solvent System	Concn., %	15	30	45
Propylene glycol–water, 3:1	0.6	73.1	82.0	28.5
	0.4	57.5	...	48.1
	0.2	57.5	...	73.1
	0.1	45.5	57.5	118.1
1.4% Polyvinyl alcohol in water	0.4	66.9	59.7	90.9
	0.2	45.5	...	84.7
	0.1	41.9	70.4	90.9
Water	0.1	...	45.5	...
95% Polyethylene glycol 300–5% polysorb 80	1.0	...	30.3	...
	0.1	...	28.5	...
Dimethylsulfoxide	1.0	...	36.7	...
	0.1	...	19.2	...

If one assumes that tissue uptake of this drug is a function of cellular metabolism, the above findings for this antimetabolite appear reasonable. Other explanations can be postulated, but it is significant to point out that the clinical efficacy of idoxuridine formulations will very likely be influenced greatly by the drug concentration for a given vehicle and further that the maximum drug concentration is least ideal for maximum absorption. It appears safe to assume, considering the present generally accepted theory of idoxuridine action against the herpes virus, that higher *tissue* concentrations of drug are desirable for successful competition against thymidine.

The concentration of idoxuridine in rabbit corneas was determined following treatment by several dosage regimens as well as from application in different vehicles (0.1% in water, 0.1% in aqueous polyvinyl alcohol solution, and 0.5% in petrolatum ointment).

It was found that tissue levels of idoxuridine were sensitive to all of these variables, but it is considered significant, and therefore reported here, that the clinical regimen was uniquely important. The universally accepted regimen for all idoxuridine solutions in herpes simplex keratitis (one drop in the eye every hour through the day, every other hour through the night) was found to be greatly inferior to a new regimen suggested by Sears (1) for this antiviral drug (one drop every minute for 10 min., four times daily). This regimen, when followed using 0.1% idoxuridine in solution with 1.4% polyvinyl alcohol, produced maximum tissue levels which were about twice those from this vehicle or 0.5% ointment form administered by other regimens.

(1) Sears, M., Dept. of Ophthalmology, Yale University Medical School, private communication.

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Received April 5, 1965.
Accepted for publication July 12, 1965.