(5) H. S. Rosenkranz and H. S. Carr, *Antimicrob. Agents Chemother.*, **2**, 367 (1972).
(6) S. M. Modak and C. L. Fox, *Biochem. Pharmacol.*, **22**, 2391 (1973).
(7) J. E. Coward, H. S. Carr, and H. S. Rosenkranz, *Antimicrob. Agents Chemother.*, **3**, 621 (1973).
(8) J. W. Stanford, B. W. Rappole, and C. L. Fox, *J. Trauma*, **9**, 377 (1969).
(9) G. J. Boelema, A. Bult, H. J. Metting, B. L. Bajema, and D. A. Doornbos, *Pharm. Weekblad Sci. Ed.*, **4**, 38 (1982).
(10) A. Bult and H. B. Klasen, *J. Pharm. Sci.*, **67**, 284 (1978).
(11) A. Bult and H. B. Klasen, *Arch. Pharm. (Weinheim)*, **311**, 855 (1978).
(12) J. J. M. van Saene, A. Bult, and C. F. Lerk, *Pharm. Weekblad, Sci. Ed.*, **5**, 67 (1983).

COMMUNICATIONS

Enhancement of Fluoride Concentration in Saliva after Topical Application of Fluoride Sustained-Release Dosage Form on Orthodontic Plates

Keyphrases ☐ Fluoride, sustained release—topical application, concentration in whole saliva

To the Editor: The beneficial role of fluoride topical applications for caries prevention is now well established. The effectiveness of a topical treatment resides in the amount of fluoride incorporated in apatitic form (1) and in the continuous supply and renewal of the fluoride content of tooth enamel (2–3). None of the topical dosage forms of fluoride marketed today (dentifrices, mouth rinses, and gels) are able to supply fluoride for a long period of time. A sustained-release dosage form of fluoride for topical application should provide conditions that will result in the major product being a stable fluoroapatite. The research effort expended to date on the development of a sustained-release delivery system for fluoride is minor compared with efforts expended in the areas of other drugs; however, significant progress has been made.

Three general approaches are being taken now to develop a sustained-release delivery system of fluoride: (*a*) matrix tables (4), (*b*) aerosol containing microcapsules for direct application on the tooth surface (5), and (*c*) intraoral system (6).

In our previous *in vitro* work (7, 8) it was shown that fluoride release could be sustained by embedding NaF or CaF_2 in ethylcellulose polymers. The aim of this work was to establish the fluoride level of saliva in children using orthodontic plates coated with a long-acting fluoride application.

A group of nine children aged 7–12 undergoing orthodontic treatment participated in the study. The subjects resided in the Jerusalem area, which had ~0.4 ppm fluoride in the water supply. None of the children had brushed their teeth with a fluoride dentifrice or received a fluoride supplement (including tea) 2 d before or during the experiment. The palatinale part of the upper orthodontic plates was coated by immersing the plates in a 10% NaF suspension in ethanol solution of ethylcellulose and allowing them to dry at room temperature (8).

The amount of the coating layer on the orthodontic plates was determined by weighing the difference between the uncoated and coated materials. The fluoride (F) concentration was calculated from the weight ratio of fluoride and polymer used and was in the range of 4.8–5.1 mg/plate. Whole saliva samples were collected by chewing paraffin wax, and the F concentration was determined in the centrifuged sample with a fluoride ion electrode (9). Statistical significance was determined by the paired *t* test.

F release resulted in a significant ($p < 0.005$) increase in the amount of fluoride in the saliva during the first 4 days of the study but returned to its initial level on the 5th day (Table I). By the use of fluoride dentifrices or ingestion of 1-mg fluoride tablets, similar increases in the F content in the saliva were reported (10). However, the increase was for a short period only, with the F concentration returning to the initial levels after 90 min.

A relationship between the natural fluoride content in water and the prevalence of dental caries is well established today.

In communities with a fluoride content of ≥1 ppm, the prevalence of dental caries was less than in those communities whose water supplies contained fluoride at a concentration ≤0.6 ppm.

It has been shown by Yao and Grøn (9) that the fluoride content in the saliva of children who consumed drinking water containing 1 ppm of fluoride was 0.01–0.05 ppm.

These values are similar to the fluoride concentration obtained in the saliva of the children using sustained release application of fluoride in this study.

In our previous work (7) it was shown that thickness of the coating applied on the orthodontic plate did not affect

Table I—F Content in Mixed Saliva of Nine Children after Fluoride Sustained Release Application [a]

	Day after Application				
	1	2	3	4	5
F, mean ± *SD*	0.015 ± 0.003	0.02 ± 0.003	0.016 ± 0.003	0.01 ± 0.002	0.007 ± 0.0002
P	<0.005	<0.005	<0.005	<0.005	NS[b]

[a] Control (F concentration in saliva before the experiment) 0.008 ± 0.002 ppm.
[b] NS = not significant.

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the release constant but determined the duration of fluoride release.

According to this it may be assumed that by an increase in the thickness of the coating applied to the plates, a prolonged continuous increase of F in saliva will be possible. The increase in the thickness of the coating may be easily achieved by adding additional layers of the coating solution.

The continuous presence of fluoride in saliva, achieved in this study, may favor the remineralization phase occurring between periods of enamel dissolution (2) and significantly increase the value of fluoride in caries prevention.

(1) V. Caslavska, E. C. Moreno, and F. Brudeveld, *Arch. Oral Biol.*, **20**, 333 (1975).
(2) B. Houwink, D. O. Backer, and G. W. Kwant, *Caries Res.*, **8**, 27 (1974).
(3) C. W. Lemke, J. H. Doherty, and M. C. Arra, *J. Am. Dent. Assoc.*, **80**, 782 (1970).
(4) P. M. Meier, J. Dilou, and D. D. Marco, Final report on Contract NO1-DE-52448 to National Institutes of Health, Bethesda, 1976.
(5) D. L. Williams, P. M. Meier, T. J. Mullines, and K. R. St. John, 6th Report on Contract N01-DE-52448 to National Institutes of Health, Bethesda, 1977.
(6) D. M. Lewis, D. R. Cowsar, D. R. Miller, and L. Menaker, *J. Dent. Res.*, *56* 266 (1977) (Special issue).
(7) M. Friedman, *J. Dent. Res.*, **59**, 1392 (1980).
(8) M. Friedman, *Arch. Oral Biol.*, **26**, 131 (1981).
(9) K. Yao, and P. Grøn, *Caries Res.*, **4**, 321 (1970).
(10) P. Grøn, H. G. McCann, and F. Brudevold, *Arch. Oral Biol.*, **13**, 203 (1968).

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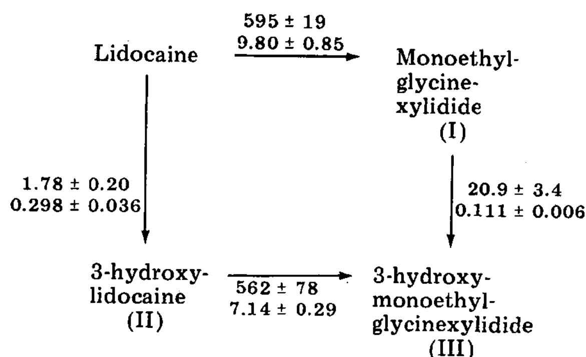
Precursor–Metabolite Interaction in the Metabolism of Lidocaine

Keyphrases □ Lidocaine—precursor–metabolite interaction, metabolism □ metabolites—interaction with precursor in metabolism of lidocaine □ metabolism—lidocaine in the liver

To the Editor:

Lidocaine is a local anesthetic and antiarrhythmic drug that has been known to be extracted exclusively by the liver with a high extraction ratio after oral administration (1–4). As shown in Scheme I (5), lidocaine is extensively metabolized in rats to monoethylglycinexylidide (I) and 3-hydroxylidocaine (II) by P_{450}-dependent *N*-deethylase and 3-hydroxylase activities. These primary metabolites are further 3-hydroxylated and *N*-deethylated, respectively, to form a common secondary metabolite, 3-hydroxymonoethylglycinexylidide (III). In common with other drugs highly cleared by the liver, the areas under the blood concentration *versus* time curve (AUC) obtained after portal vein infusion of lidocaine at a dose range of



Scheme I—Parallel metabolic pathways of lidocaine and the kinetic parameters. The figures are expressed as means ±SE (n = 3) μM for apparent Michaelis constants (top numbers) and nmol/min·mg microsomal protein for maximum velocities (lower numbers). Substrate concentration range: 200–2000 μM for N*-deethylation of lidocaine and 3-hydroxylidocaine (II); 1–100 μM for 3-hydroxylation of lidocaine and monoethylglycinexylidide (I).*

1–10 mg/kg were smaller (approximately one half) than those after peripheral vein infusion of equal doses in rats (6). However, of special interest is our preliminary finding that the AUC of I, a pharmacologically active lidocaine metabolite, obtained after portal vein infusion of lidocaine was ~10 times as large as that obtained after peripheral vein infusion (6). The AUC of metabolite II, on the other hand, did not differ significantly depending on the route of administration of lidocaine. If a drug and its metabolites are eliminated linearly and exclusively by hepatic metabolism, the AUC of the metabolites, or the ratios of AUC of any two metabolites, are independent of the route of administration (4). The unusually high AUC of I and also the difference in the AUC ratios of the two metabolites of lidocaine depending on the route of administration can be explained by the following possibilities: (*a*) the elimination of I itself is nonlinear; (*b*) 3-hydroxylation of lidocaine is saturable at lidocaine concentrations attained by portal vein infusion but *N*-deethylation is not, resulting in the formation of I in higher concentrations; (*c*) lidocaine inhibits the metabolism of I in the liver and the elimination of I decreases in the presence of high concentrations of liodcaine. The AUC of I (1.5–7.5 mg/kg) was found to increase in an apparently linear fashion with increasing intraportal dosage (6). Therefore, either the second or the third possibility or both of them may be operative in these phenomena.

Studies by von Bahr *et al.* (7) and from our laboratory (8) have indicated that the 3-hydroxylation and *N*-deethylation pathways of lidocaine are catalyzed by different P_{450} species. It is then of interest to test if the parallel hydroxylation pathways (3-hydroxylations of lidocaine and I) are catalyzed by the same P_{450} species or different. If they are catalyzed by the same P_{450} species, lidocaine and I would be mutually competitive inhibitors of their metabolism. Then this would partly explain the unusually high AUC of I obtained after portal vein infusion of lidocaine as described above. By the same token, it is also of interest to examine if the *N*-deethylation pathways of lidocaine and II share the same species of P_{450}. In this communication, we report *in vitro* metabolic kinetics of lidocaine and its metabolites in order to characterize the nature of lidocaine metabolism and to investigate the

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