LABORATORY AND CLINICAL EVALUATION OF A NEW TOPICAL ANESTHETIC

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Introduction

Topical anesthetics available to the dental profession have one major problem: The ointment does not adhere adequately to the oral mucosa. It tends to slide away from the area applied and thus preclude a profoundness of tissue anesthesia before the needle puncture. Numerous anesthetics have been combined with many vehicles in order to increase the adhesiveness of the product to the oral mucous membrane. However, once these ointments are subjected to the warmer temperature of the oral cavity and to the saliva, the topical anesthetic generally flows away from the area. Attempts to keep the area dry before applying the topical with the hope of retaining the ointment in the area long enough to derive some of the benefits of the anesthetic meet with inconstant results.

The purpose of this study was to evaluate the effectiveness of a new topical anesthetic base. The specific objective was to evaluate the tissue tolerance to the material in animals and to study the clinical effectiveness by means of a double blind experiment with patients in the Klahr Children's Clinic of Temple University School of Dentistry.

It was proposed that if a topical anesthetic were combined with a *base* that would adhere to the mucous membrane of the oral cavity, then a more efficient and predictable anesthetic would be available. Although, it was known that various anesthetics would give a satisfactory topical anesthesia if the conditions were ideal, there was the possibility that the combined ingredients may inactivate or reduce the shelf life activity of the topical anesthetic. In order to maintain its stability and effectiveness, a preservative was incorporated.

Thermal gelation is a phenomenon in which gelation of a product results from the application of heat. Ordinarily, when heat is applied to a product such as an ointment, it will tend to become liquefied and begin to soften. This results in "sliding" or "moving away" from a slippery mucosal surface. The Dow Chemical Company's product called Methocel Mc 4000 cps may be utilized in solving part of this problem. It provides an adequate base for cohesiveness to the oral mucosa. The temperature in the oral cavity enhances gel formation and adherance to the mucous membrane.

The material used as a base and the topical anesthetic itself were found to be safely tolerated by the oral tissues and to be effective in alleviating pain of the initial penetration of the needle for local anesthesia.

Review of The Literature

Few studies on topical anesthetics are available. Most of these have been confined to clinical evaluation. A ten year review of the literature, fails to reveal histopathological studies which tested the safety of topical anesthetics. Clinical evaluation of these materials was the primary criterion used by other investigators. Many combinations of anesthetics have been tried and several comparative potency methods have been developed to measure and standardize results.[1-7] No reported study of coordinated clinical double blind testing with extensive laboratory investigation was found.

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Methods and Materials

This study consisted of two parts; an animal study using 18 golden syrian hamsters and a human clinical study on 550 children from 3-6 years of age. The experimental materials were mixed in one batch and used over a period of nine months.

A. Animal Study

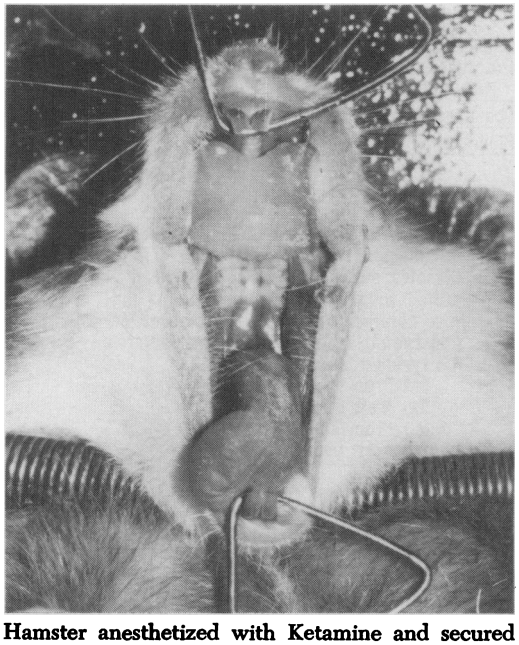
The hamsters were anesthetized using intramuscular ketamine (1 mg. per 4 Gms).[8 9] 10 week old hamsters ranged in weight from 85-100 Gms. and showed no apparent ill effects from the ketamine during the period of the study. Three materials (xylocaine ointment, methocel MC 4000, and the experimental topical anesthetic), were applied to the following areas:

1. palate
2. mandibular injection area
3. lower labial gingival mucobuccal fold area

At the intervals up to and including 15 minutes, the animals were kept under anesthesia in order not to disturb the agents used.

However, for the 24 hour interval, a modified Dachi appliance was used to keep the material in contact with the palate.[10] [See table 1 and figure 1.]

Fig. 1



Hamster anesthetized with Ketamine and secured on operating wooden block.

In the case of the 24 hour samples applied to the palate, the following procedure was used:

The medication was placed into the recessed area of the acrylic modified Dachi appliance. (Fig. 2). The appliance was placed into position on the palate. Sutures were extended from the metal eye loops of the appliance to the buccal tissue. These sutures held the medication in contact with the palatal tissue for 24 hours. The animal was unable to remove the appliance. At the end of the designated time of application, the hamsters were re-anesthetized with intra-muscular Ketamine, and the appliance removed.

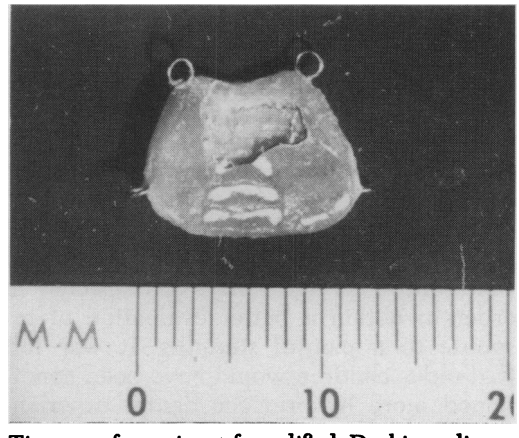
After the animals were asleep the three materials were applied and the animals killed at specified intervals of 1 minute, 3 minutes, 5 minutes, 10 minutes, 15 minutes, and 24 hours.

Tissues were examined for external signs of pathology as evidenced by redness, swelling, or sloughing. After the proper time intervals the tissue was biopsied and preserved in 10% formalin for sectioning. Biopsies were processed in paraffin and sectioned at 6 micron intervals and examined microscopically.

B. Clinical Human Study

1. This part of the experiment followed that of a double blind study: Neither the individual dispensing the samples nor the clinicians using the samples knew the identity of the sample used.

Fig. 2



Tissue surface view of modified Dachi appliance. Recess cut into acrylic for holding topical anesthetic for 24 hours.

TABLE I
Outline of Laboratory Investigation
18 Hamsters Used

Samples used	Areas	1 min.	3 min.	5 min.	10 min.	15 min.	*24 hrs.
Xylocaine oint. 5% (Astra)	Palate	X	X	X	X	X	X
	Mandibular	X	X	X	X	X	
	Gingivae	X	X	X	X	X	
Methocel MC 4000 (Dow Co.)	Palate	X	X	X	X	X	X
	Mandibular	X	X	X	X	X	
Base only	Gingivae	X	X	X	X	X	
Experimental Topical Anes. (Base & Xylocaine)	Palate	X	X	X	X	X	X
	Mandibular	X	X	X	X	X	
	Gingivae	X	X	X	X	X	

Note: Three "Dachi" acrylic palate plates were secured intra-orally to the palate of three hamsters for the 24 hour samples. The three medications remained on the palate for 24 hours after which, tissue biopsies were made for microscopic examinations.

2. There were five samples used as "topical anesthetics" in this part of the investigation.
   (a) Two inert substances were used (Tooth paste and petrolatum).
   (b) One sample of commercial Lidocaine.[11]
   (c) One sample of Methocel Mc 4000 (Dow Chemical Co.)[12]
   (d) One sample of "experimental topical anesthetic".
3. Five numbered jars were used and the contents were randomly dispensed by the supply assistant who was unaware of the nature of the contents. The number of the jar was recorded next to the patient's name on a chart.
4. Only the investigating recorder (The Clinical Observer) remained constant for every application of the medication and subsequent local block injection. At the end of the observing period, the recorder compared the clinical observations with the number of the jar and nature of the material used on the patient.
5. All clinical procedures performed in this study were done by junior and senior dental students.
6. All patients evaluated in this clinical study were within the age range of 3 to 6 years old. This age range was selected in order to obtain a better evaluation of response to a painful stimulus. It was felt that older children would have been conditioned more by previous dental experiences. There were a total of 550 children in this sample.
7. All patients in this phase of the study were evaluated by the following criteria:
   (a) "little or no pain"—no visable or audible response to injection
   (b) "pain on injection"—crying or other audible response
   (c) tissue at the site of the topical was examined for gross pathology such as redness or sloughing
   (d) any history of nausea following the application of experimental materials

See Table 2

TABLE II
Age Range of Patients 3 to 6 yrs. old

Medication Used	Number of Injections	Number of Patients That Didn't Cry	Percentage That Didn't Cry
Experimental Anesthetic	221	128	58%
Commercial Product	157	52	33%
Placebos (combined)	172	15	9%
Total	550		

TABLE III
Formulation of 100 grams of 5% Methocel and 5% Lidocaine (W/W)

1. Dissolve small portions of powder in 40 grams of hot distilled water with constant stirring until a uniform mixture is obtained. (Powder = Methocel Mc 4000)
2. Add two ml. of the following preservative:
   A. Paraben Mixture:
      (a.) Propyl Paraben 15 ml.
      (b.) Methyl Paraben 25 ml.
      (c.) Propylene Glycol 1 ml.
3. Place cover over beaker and allow 24 hours for setting to occur.
4. Levigate 5 grams of glycerine (95%) into the base until a uniform base is obtained.
5. Dissolve 5 gm. of Lidocaine HCL into 2 gm. of distilled water and then levigate the Lidocaine into the base until a uniform base is obtained.
6. Flavoring agent — essential oil of peppermint = 1 ml.
7. The finished product is ready to be applied by cotton swab to soft tissue area.

Findings

A. Animal Study

There were no clinical signs of pathology such as redness, swelling, or sloughing of the tissues either in the experimental animals or in the controls.

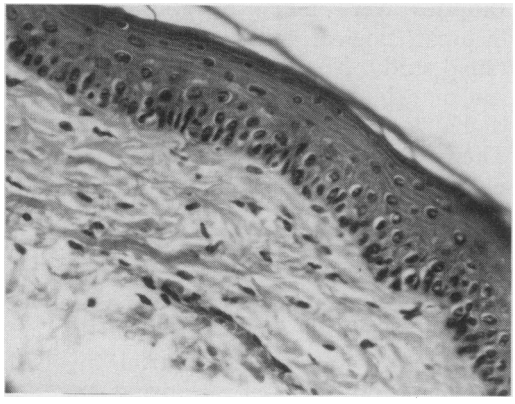
Histological study of the tissue sections revealed no microscopic pathology. In both the experimental animals and in the controls, tissues were essentially normal, with intact epithelium and no signs of inflammatory response, or tissue edema. (Fig. 3, 4, 5 and 6.)

Apparently, the topical materials used are kind to the oral tissues, and do not provoke adverse tissue responses even at the microscopic level.

B. Clinical Study – Humans

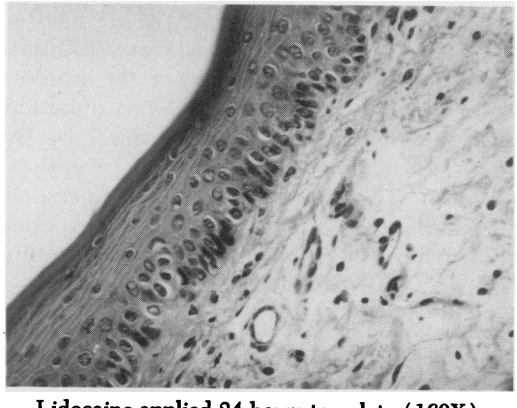
Evaluation of the tissues of the children paralleled that of the animal study. There was no swelling, redness, or sloughing seen at the site of topical application. About 10% of the sample was reexamined approximately two weeks after the application of the topical material. There was no pathology present in any of these children. Apparently there is little or no adverse tissue reaction to the topical materials either immediately or after a period of time. Questioning of the parents elicited no histories, in any case, of an allergic type of response. There was no history of fever, facial swelling, nausea, or itching. There was no diminution in effectiveness of the topical anesthetic over the period of the study (9 months). Apparently the preservative system in this formulation keeps the product highly stable. Therefore, a shelf life of at least 9 months is possible.

Fig. 3



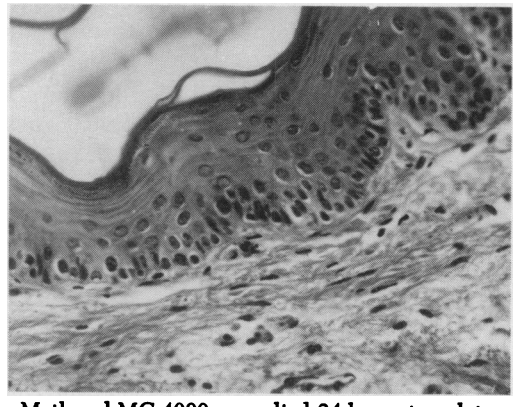
Control Animal – No Medication
Appliance applied 24 hours to palate (160X)

Fig. 4



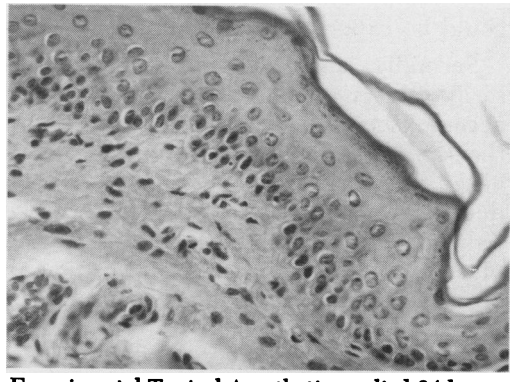
Lidocaine applied 24 hours to palate (160X)

Fig. 5



Methocel MC 4000 – applied 24 hours to palate
(160 X)

Fig. 6



Experimental Topical Anesthetic applied 24 hours
to palate (160 X)

Discussion

The safety of the experimental material was well established by this study, for in *no* case was any pathology found. Even at the microscopic level there was no evidence of pathology. The fact that large numbers of children were treated (550) without any untoward results indicates a high level of safety and a material that the dentist may use with confidence in the treatment of children.

Since this topical anesthetic was so effective in relieving the pain of injection compared to a commercial product, we may conclude that the thermal gelation base is an effective mechanism for keeping the anesthetic material itself localized on the tissues for longer periods of time. The clinical impression of the investigator was that the material seemed to be better localized than the commercial product and to give a greater physical depth of anesthesia. Also it seemed that the threshold of pain was raised considerably over that of the commercial product.

This may be attributed to the thermal gelation effect which kept the topical anesthetic base better localized making a greater concentration of anesthetic available to the tissues. It is also possible that there is a synergistic action between the base material and the topical material, potentiating a more profound anesthesia.

The limitations of this study were several. First, the placebo effect is operating on perhaps as high as 9% of this population. It is generally conceded, however, that the placebo effect grows proportionately with age so that at this low age level (3-6 years) the effect was not as high as could be expected in the adult population.

Secondly, the observations were necessarily subject to some variation even when accomplished by the same observer, but the size of the sample (550) would tend to offset this bias. Since this study was conducted as a double blind and the observer did not give the injections himself, nor apply the topical material, the variations in observations would tend to level out. Due to availability of topical anesthetic material and due to the difficulty in compounding the thermal gelation base, only lidocaine was evaluated. Since lidocaine ranks fifth in effectiveness as a topical anesthetic, it might be well to test other topical anesthetics with the new base.

Summary

This study was conducted to test the safety and the efficacy of a topical anesthetic using a thermal gelation base. The safety was proven without question by backing up clinical observations with a histopathological study in animals. In no case was there any pathological reaction. The new product called Methocel Mc 4000 gives promise to the development of a better topical anesthetic.

The product tested in this project was the final result of many combinations of drugs. It was tested topically in hamsters over a wide range of time applications. The clinical appearance of the soft tissue of the oral cavity showed no evidence of surface damage even after 24 hours of continuous tissue contact with the new product. Biopsies were taken of all animals and histopathological slides were made for detailed study. No evidence of connective tissue or cell damage was found in the epithelial layers or in the submucosal layers. There was no evidence of inflamation, necrosis or degeneration that could be detected microscopically after a 24 hour period. A control biopsy was taken and slides made for direct comparison of animal tissues where no medication was applied. No significant differences were noted.

A double blind clinical trial involving 550 children was set up using the new experimental anesthetic against a commercial product and against a placebo. Its effectiveness was high (58% against 33% for a commercial product and against 9% for the placebo). The parents of all children who took part in the study were informed of the experimental nature of the product and written consent forms were obtained. A series of observations were made by the same observer and the results were recorded. The observer made a personal evaluation as to whether the child cried during the injection from a painful stimulus or from fear of the needle.

Conclusions

1. The experimental topical anesthetic was safe, as there were no adverse effects found either clinically or histologically.

2. The experimental material is very effective as a topical anesthetic.

3. The thermal gelation base tends to keep the topical anesthetic material localized for a longer period of time, thus giving a more profound topical anesthesia.

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The authors wish to acknowledge the help of Dr. Calvin Leifer for his review of the histopathological slides. We further extend our thanks to Mr. Alex Mucha for his part in preparing all photographs for this paper.

Finally, we wish to acknowledge that this research project received its financial support from the Faculty Research Committee of Temple University.

CORRECTION

The abstract entitled "Althesin in Africa", published in the May-June, 1974 issue of *Anesthesia Progress* on page 85 incorrectly identified Althesin as propanidid. Althesin is a mixture of alphadolone acetate and alphaxolone; both of these compounds are steroids.