DYCLONINE—A NEW LOCAL ANESTHETIC AGENT: CLINICAL EVALUATION

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ENDOSCOPIC examination of the respiratory and upper gastrointestinal tracts is usually carried out under topical anesthesia. Surgeons and anesthesiologists have the general impression that these procedures are more safely done this way than under general anesthesia. Topical anesthesia is not entirely free from ill effects, however, which is evident from numerous reports in the literature (1–5). Reactions have been attributed to the local effect of the drug, such as urticaria, dermatitis, eczematoid lesions, and edema. Systemic reactions, consisting of central nervous system stimulation and convulsions or cardiovascular depression and acute collapse, have also been frequently documented. Most anesthesiologists are familiar with several severe reactions that have not been reported in the literature.

Four severe reactions, with two deaths, following the application of a local anesthetic have occurred in our institution during the past two years. There is now general agreement that the systemic reactions to local anesthetics are due to the quantity and rapidity of absorption rather than to any degree of hypersensitivity to the drug. Few physicians appreciate the rapidity with which absorption of these drugs may occur, and fewer realize the difference in rate of absorption of the different drugs from various sites. Steinhaus (6) has carried out an excellent study of this subject on experimental animals. Several authors (7, 8, 9) have emphasized the importance of using small doses of these topical anesthetic agents and have devised techniques for limiting the amount of agent used. Such techniques are either time consuming, tedious, or both, and most anesthesiologists and surgeons have been reluctant to adopt them. More reliance is being placed upon the development of a topical anesthetic which is both effective and nontoxic. Several have received favorable reports (10, 11).

DYCLONINE

A new chemical compound having local anesthetic properties was recently brought to our attention. This drug has the chemical name 4-n-butoxy-β-(1-piperidyl)propiophenone hydrochloride and the generic

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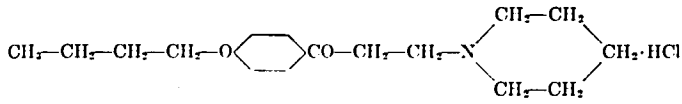
name "dyclonine." It has the trade name of Dyclone® and its structural formula is:



It differs chemically from any of the local anesthetics in use today.

Pharmacologic studies in animals have shown this drug to be a potent surface anesthetic when applied to the cornea of the rabbit and to be free of acute or chronic toxic effects (12). Dyclonine has no parasympatholytic actions and no effect upon the sympathetic nervous system. When administered intravenously to dogs (5 mg./kg.) the drug causes no significant effects upon the blood pressure or heart rate. This drug has been given to adult human beings by intravenous injection in doses of from 200 to 500 mg. over a five minute period. No change in blood pressure or heart rate has occurred and there was no evidence of central nervous system stimulation. Nausea and dizziness were the only effects except for the production of vomiting in one case (13). In view of the apparent minimal toxicity of this drug, it was considered worthwhile to attempt a clinical evaluation of its usefulness as a topical anesthetic for endoscopic procedures. Dyclonine was supplied in a 1 per cent solution and this was used throughout the study.

A preliminary evaluation of this drug for use in infiltration and block anesthesia was carried out by the intradermal injection technique. Concentrations of 0.25, 0.5, and 1 per cent were used. All concentrations of the drug were quite painful on injection and the 1 per cent solution caused definite local edema lasting one to three hours. Because of these local irritating effects, the drug was not used for other than topical anesthesia in further studies.

Methods and Results

The evaluation of dyclonine was performed by three different techniques.

Topical Anesthesia of the Mucous Membranes of the Mouth and Pharynx.—Fifteen healthy volunteers were used for this study. The subject was given 10 cc. of 1 per cent dyclonine to hold in his mouth and gargle for one minute. The subject was then asked to check for onset, intensity, and duration of anesthesia.

This method of evaluating a topical anesthetic is purely subjective and the results may be expected to vary from subject to subject. Probably partially owing to the selection of subjects (interns and residents), who knew what to expect and how to test for anesthesia, the results were surprisingly consistent. All reported beginning anesthesia within 2 minutes, with anesthesia reaching a maximum intensity in

from 4 to 6 minutes. This intense anesthesia lasted from 20 to 25 minutes, and the anesthesia of decreasing intensity lasted an additional 15 to 20 minutes. No subjective side effects were noted and no local reaction occurred. All subjects agreed that the drug was extremely bitter.

Topical Anesthesia of the Larynx.—Twenty-five unselected patients who were to receive inhalation anesthesia were utilized for this study. Patients were maintained in first plane cyclopropane anesthesia and evaluation of laryngeal activity was carried out before and following topical anesthetization of the larynx with 4 cc. of 1 per cent dyclonine.

The technique of evaluation of the topical anesthetic was essentially that described by Clark, Orkin, and Rovenstine (14). This consisted of performing direct laryngoscopy and touching the vocal cords lightly to stimulate laryngeal activity. Any patient in whom severe laryngospasm was not initiated was not used for this study. The adducted cords were then sprayed with 4 cc. of 1 per cent dyclonine and after 10 to 15 seconds any excess solution was aspirated from the pharynx. First plane anesthesia was then reestablished. At five-minute intervals following the initial observation, laryngoscopy was done and the degree of laryngeal activity noted. This procedure was continued until the original degree of laryngeal activity had returned.

The results of this study were quite consistent. All subjects developed excellent anesthesia of the larynx within 5 minutes, showing minimal or no laryngeal activity at the time of the first testing. Twelve subjects showed laryngeal anesthesia at 20 minutes but had some laryngeal activity at 25 minutes. Thirteen subjects had anesthesia at 25 minutes and showed laryngeal activity at 30 minutes. None of the subjects had good laryngeal anesthesia at 30 minutes. No significant changes of blood pressure or heart rate were noted and no evidence of central nervous system stimulation was seen. No local reactions to the topical anesthetic were observed and no postoperative sequelae related to the laryngeal anesthesia occurred.

Topical Anesthesia of the Pharynx, Larynx, and Trachea for Endotracheal Intubation.—Seventy-five unselected patients receiving general anesthesia were utilized for this study. Ten conscious patients undergoing either bronchoscopy or esophagoscopy were included in this series. The anesthetic agent or technique was not restricted in this group of patients except as to the depth of anesthesia, first plane in all cases, and no relaxant drug was used. Thiamylal-nitrous oxide-oxygen and cyclopropane-oxygen with the circle absorption technique were the most frequent types of anesthesia used. When the patient was in first plane anesthesia, direct laryngoscopy was performed and the activity of the laryngeal reflex noted. Any patient not showing severe laryngospasm was not used for this study. The adducted cords were then thoroughly sprayed with 1 per cent dyclonine for 10 to 15 seconds, excess solution was aspirated from the pharynx, and first

plane anesthesia was reestablished. Five minutes after the initial spraying of the larynx, a second direct laryngoscopy was performed and laryngeal activity noted. If no laryngospasm occurred, endotracheal intubation was done. If the laryngeal reflex was still present, the cords were again sprayed with 1 per cent dyclonine and the above procedure was repeated. In no case was more than two applications of the topical anesthetic required.

The results of this study were very gratifying. Anesthesia of the larynx and trachea was good to excellent in all cases, and endotracheal intubation was performed with ease in the majority of cases. (Difficult intubations were due to technical difficulty of exposing the larynx, not to laryngospasm.) Purposeful repeated sprayings of the larynx and trachea were carried out in a number of patients, using a total of 20 cc. of the 1 per cent dyclonine, to determine the safety of large amounts of the anesthetic. Again there was no effect upon the blood pressure and heart rate, and no evidence of local reactions was seen. Dyclonine gave very satisfactory anesthesia for bronchoscopy and esophagoscopy in the conscious patient.

Discussion

A topical anesthetic which produces good anesthesia and which has no local or systemic toxicity would be very desirable. Many excellent topical anesthetics are available, but most of them have one or more undesirable properties. The rather small, safe dosage of several of these makes their use either technically difficult, because of the limitation in volume necessary, or dangerous because of the rapid absorption that occurs from the tracheobronchial tree. Several produce satisfactory anesthesia and are reasonably safe but do not give adequate duration of anesthesia. A 1 per cent solution of dyclonine has been found to produce good topical anesthesia of about 20 to 25 minutes' duration. This drug has also been given intravenously to man in doses of 200 to 500 mg. without major toxic effects. If the lower dosage is accepted as the maximum to be used, this would allow 20 cc. of the 1 per cent solution to be used for topical anesthesia. This volume should be ample for any endoscopic procedure. Assuming that absorption from the tracheobronchial tree approached that of intravenous injection, one would still not expect to see any major toxic effects. Our studies with this drug suggest that it produces no toxic reactions in the dose ranges (4–20 cc. of a 1 per cent solution) used. The absence of any central nervous system stimulation or cardiovascular depression was a constant observation.

Summary

Dyclonine in a 1 per cent solution has been found to produce good anesthesia, of 20 to 25 minutes' duration, of the mucous membranes of

the pharynx, larynx, and trachea. No local or systemic reactions were noted in the dosages used. If this proves to be true when dyclonine is used for a large number of cases, then it should be a valuable topical anesthetic for endoscopic procedures. The minimal toxicity allows the amount used to be uncritical, which should be of value to the endoscopist.

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