TITLE: LOCAL ANESTHETIC EFFICACY OF METHOXYFLURANE MICRODROPLETS IN MAN

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INTRODUCTION: Lecithin-coated methoxyflurane microdroplets (MOF) is a new local anesthetic capable of producing 25-hour local anesthesia in rats.[1] This report presents the results from our first studies in man. Lidocaine and phenol were used as reference compounds.

METHODS: The MOF preparations were made essentially as described in our previous communication.[1] The study satisfied the requirements of the Institutional Review Board for research on human subjects. Two of the authors (A.K. and D.H.) volunteered to have the various study drugs injected intradermally into the skin of the forearm or leg. An array of injection sites was delineated on the skin. Two electrode needles were inserted approximately 5 mm apart. A pulsatile output voltage was steadily increased at a frequency of 55 Hz with a pulse width of 1.5 ms. The threshold to sense an electrical pulse was taken as the end-point. Baseline voltage thresholds were determined and then 0.5ml of the study drug was infiltrated between the two stimulation electrodes. Post-treatment thresholds were determined at given time intervals. The electrodes were removed after the first two hours and were reinserted on subsequent days for the corresponding testing. In the initial experiments, the sequence of stimulus strength and the site stimulated were determined by random draw to which the subject was blinded. In subsequent experiments, the subject controlled the strength of the stimulus in order to increase the rate of data taking. However, the sites were still stimulated at random and the subject was blinded as to the site and study drug being tested.

RESULTS: Figure 1 shows the results following intradermal injection of 0.85% MOF. The threshold increases from 0.5 V to 1.6 V ($P<0.01$). Over the next 25 days the voltage threshold slowly returns to baseline values. The experiments with phenol and lidocaine were conducted in parallel with MOF. Although 0.375% phenol increased the threshold from 0.5 to 0.7 V; this change was not statistically significant. Figure 1 shows that 1% lidocaine caused the threshold to increase from 0.6 V to 1.8 V which returned to baseline values in 45 min. to 1 hr. There was no change in the color or in the integrity of the skin at any of the injection sites for MOF, phenol or lidocaine. In order to determine the safety and efficacy of MOF relative to phenol, the experiments in figure 1 were repeated by injecting the same volume at twice the concentration. At a concentration of 0.85% phenol, two out of three sites injected developed ulcers followed by necrosis of skin. In contrast, none of the nine sites injected with 1.7% MOF developed any change in the color or integrity of the skin. Figure 2 shows that phenol produced an increase in the threshold comparable to MOF during the first five minutes but by one hour the threshold of phenol had dropped to approximately half that of MOF.

DISCUSSION: Phenol is currently used in certain clinical settings when ultra - long local anesthesia is required by single injection. The present study shows that phenol is destructive to tissue at a concentration necessary to obtain a degree of local anesthesia comparable to MOF. In addition, a portion of the anesthetic effect produced by phenol at this "toxic" concentration is transient in nature. In summary, our initial clinical testing of MOF shows that it has a safety-efficacy profile superior to phenol. We believe that further clinical testing will reveal an important role for microdroplets in the management of pain.

REFERENCE: 1. Haynes DH, Kirkpatrick AF: Ultra-long-duration local anesthesia produced by injection of lecithin-coated methoxyflurane microdroplets. Anesthesiology 63:490-499, 1985.

Figure 1

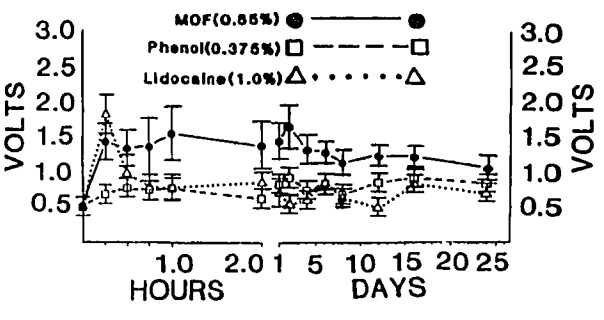

Figure 2