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THE TOXIC EFFECT OF A NEW LOCAL ANAESTHETIC OF ANILIDE TYPE (L 67)* ON THE TISSUES

by

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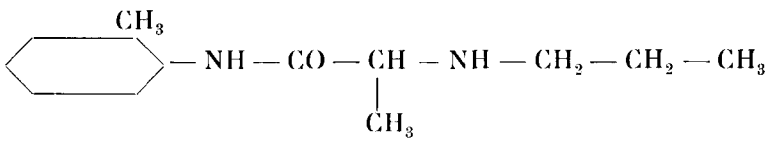
INTRODUCTION

Lidocaine (Xylocaine®), introduced in 1948, is now the most widely used local anaesthetic solution in dental practice in Sweden. A serious competitor is mepivacaine (Carbocaine®) introduced in 1959. One of the advantages of this latter preparation is that it produces good local anaesthesia of the soft tissues without any addition of epinephrine. If supplementary epinephrine is indicated, very small quantities are sufficient.

At Astra's Research Laboratories a new local anaesthetic solution has now been prepared. It is of anilide type, is called L 67 and has the following structural formula



The anaesthetic effect has been studied by *Eriksson & Gordh* (1959), *Åström & Persson* (1960) and others. They all appear to be satisfied with the anaesthetic effect of the preparation. L 67 has been examined for dental plexus anaesthesia by *Ber-*

* Introduced on the Swedish market under the name of Citanest.

ling & Björn (1960). They found that 2 % and 3 % solutions gave a high incidence and a good extent of anaesthesia and that the duration was satisfactory even with as low a concentration of epinephrine as 3.33 μg/ml solution.

The toxic effect of a local anaesthetic on the tissues should of course preferably be minimal. This toxicity can be judged from the irritating effect of the preparation on the cornea of rabbits, and from the effect of injection between the dermal layers of rabbits' ears. Using these two methods on rabbits *Wiedling* (1960) found the irritating effect of L 67 to be negligible. Irritating effects can also be judged from the influence of the solution on the tensile strength of healing wounds, inflicted in tissue infiltrated with the anaesthetic solution. This method has been used in the following investigation and is briefly described below (for details see *Björlin,* 1954).

The investigation was carried out on white rats weighing about 150—200 g. The animals were anaesthetised with ether. They were then shorn and shaved, after which four symmetrically disposed lines were marked in ink on their skin. The marks thus made denoted the sites at which the wounds were later to be inflicted. Two of the marks were always made about 1 cm caudal to the scapular ring, and two at a distance of at least 2 cm from the caudal end of the first two incisions. At each of two of the marks 0.5 ml of the solution to be tested was injected. After about 5 minutes, an incision about 1.5 cm long was carried through the entire thickness of the skin including the superficial muscle. The incisions were closed with three interrupted sutures placed 0.5 cm apart. The wounds were dressed with sterile gauze. After seven days the wounds were tested for tensile strength using an apparatus modified after that described by *Sandblom et al.* (1953).

The results have undergone statistical analysis and in the figures the following letters are used,

n = number of animals

m = mean value

σ = standard deviation

t = Students $t\left(m/\frac{\sigma}{n}\right)$

The following levels of significance were used,

o	$0.05 < P$ (not significant)	
x	$0.01 < P < 0.05$ (tendency)	
xx	$0.001 < P < 0.01$	significance.
xxx	$P < 0.001$	significance.

In each series M expresses the increase (positive values) or decrease (negative values) in tensile strength in per cent owing to the influence of the factor to be tested as compared to the control. M has been computed according to the formula

$$M = \frac{100\ m}{100 - \frac{m}{2}}.$$

RESULTS

In a first series, the effect of a 2 % L 67 solution without epinephrine was examined. As can be seen from Fig. 1 the tensile strength of wounds inflicted in tissue infiltrated with L 67 decreased by 40 % compared with that of the untreated control wounds. The difference was statistically significant ($t = 5.2^{xxx}$).

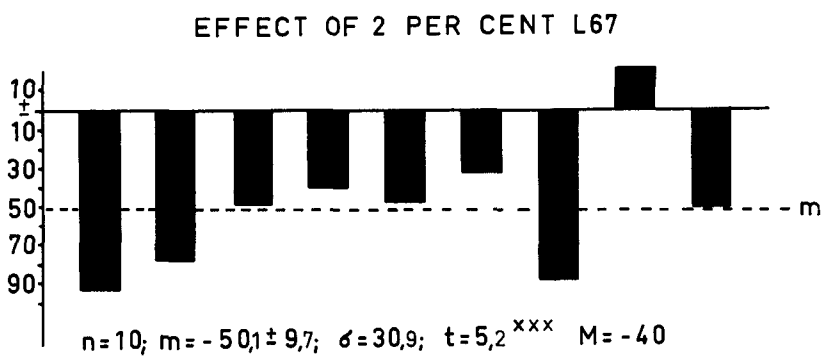


Fig. 1.

L 67 is intended to be used also in a 3 % solution and therefore it was considered worthwhile to perform some experiments with this solution. The results are given in Fig. 2. The tensile strength of the experimental wounds decreased in this series by 56.7 % compared with that of the control wounds. The difference was statistically significant ($t = 9.6^{xxx}$).

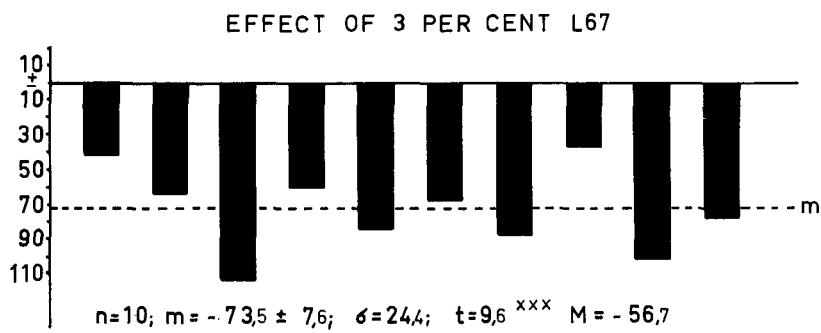


Fig. 2.

The effect on the tensile strength of the anaesthetic solution with supplementary epinephrine was investigated in two series. In the first series 12.5 μg/ml solution was added to a 2 % solution of L 67. This concentration of epinephrine was chosen because the most widely used local anaesthetic in Sweden (2 % lidocaine-epinephrine) has this epinephrine content, which has proved sufficient to produce good anaesthesia and ischemia for surgical procedures. The results of these experiments showed that the tensile strength of the experimental wounds decreased by 52.4 % compared with that of the control wounds (Fig. 3). The difference was statistically significant ($t = 4{,}8^{XXX}$). When 5 μg

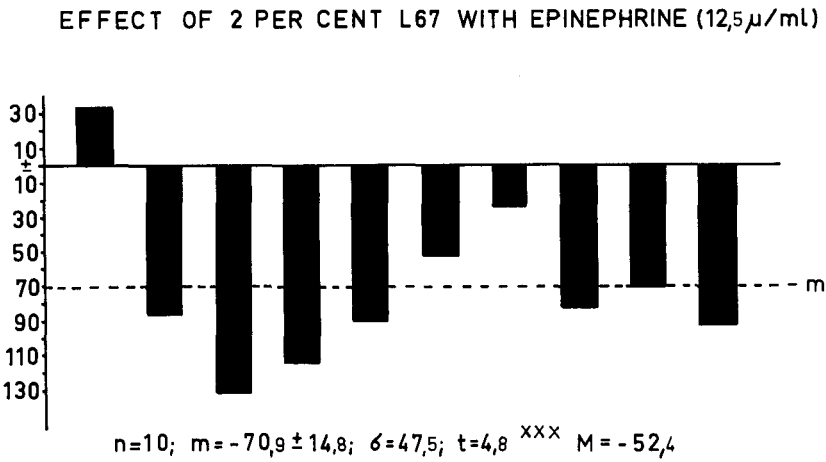


Fig. 3.

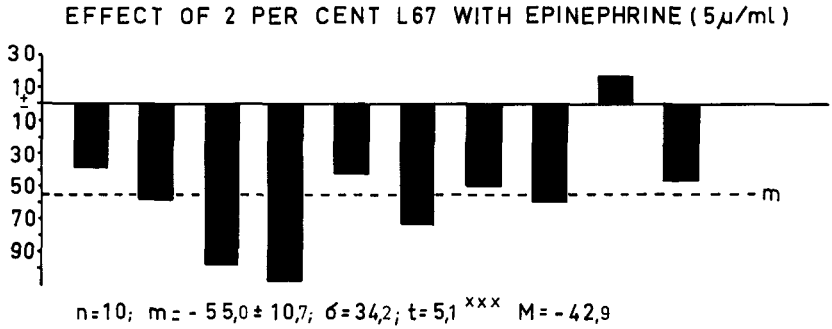


Fig. 4.

epinephrine per ml solution was added, the tensile strength decreased by 42.9 % (Fig. 4). This difference was also statistically significant ($t = 5.1^{xxx}$). As L 67 is also obtainable as a 3 % solution with epinephrine 3.33 μg/ml it was thought to be of interest to compare this solution with the more frequently used 2 % lidocaine-epinephrine solution. This was done in one series, the result of which can be seen in Fig. 5. The tensile strength of wounds inflicted in tissues infiltrated with 2 % lidocaine-epinephrine was 31.6 % lower than that of wounds inflicted in tissues infiltrated with 3 % L 67 having epinephrine 3.33 μg/ml. The difference was statistically significant ($t = 4.0^{xx}$).

Since lidocaine is widely used, followed closely by mepivacaine, it was considered justified to compare the effect on the tensile

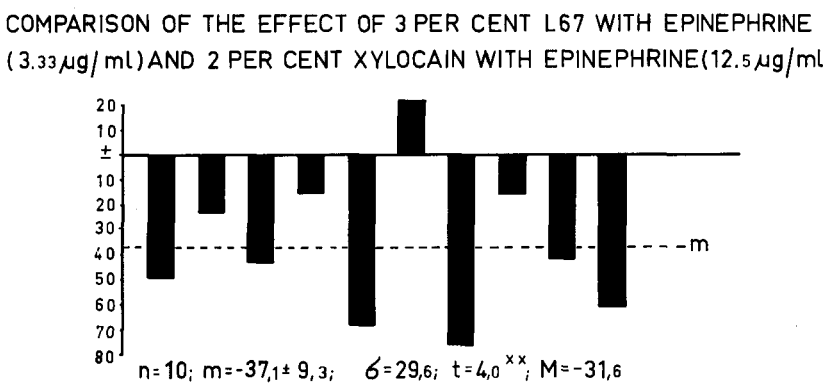


Fig. 5.

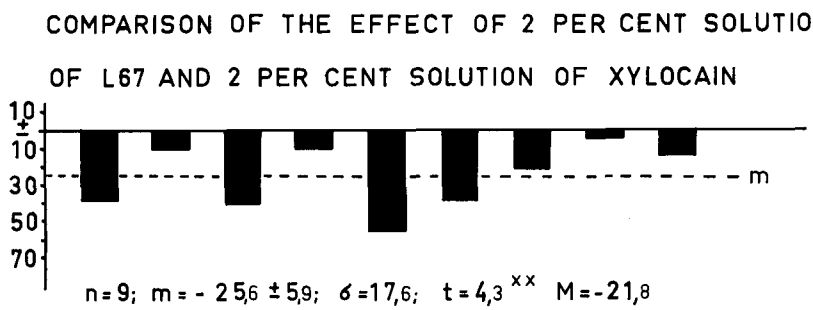


Fig. 6.

strength of these solutions with that of L 67. In one series, therefore, 0.5 ml of a 2 % lidocaine solution was injected at two of the marks where wounds were later to be inflicted and 0.5 ml of a 2 % L 67 solution at the other two marks. The wounds inflicted in tissue infiltrated with a 2 % lidocaine solution healed 21.8 % slower than did wounds inflicted in tissue infiltrated with a 2 % L 67 solution (Fig. 6). The difference was statistically significant ($t = 4.3^{xx}$).

Though the difference in wound healing was significant, one cannot exclude the possibility of a general influence on the animals by such relatively large doses of anaesthetic solutions as were used. In order to exclude this factor, one series was performed on rabbits weighing about 1.8 kg. In this series, the same

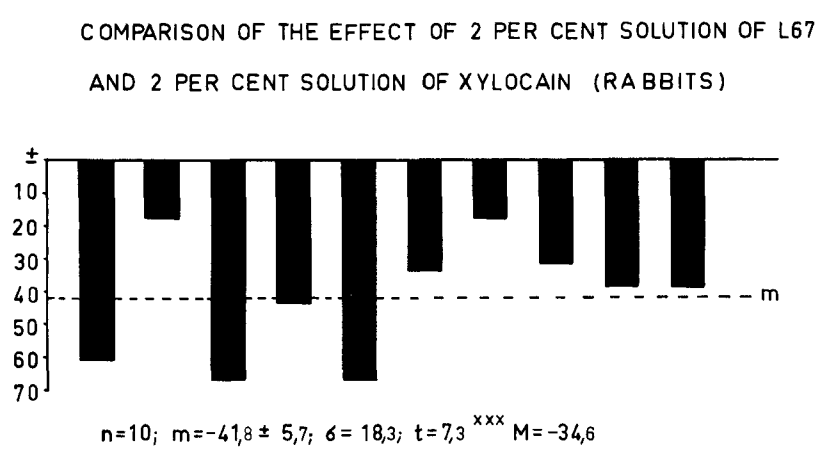


Fig. 7.

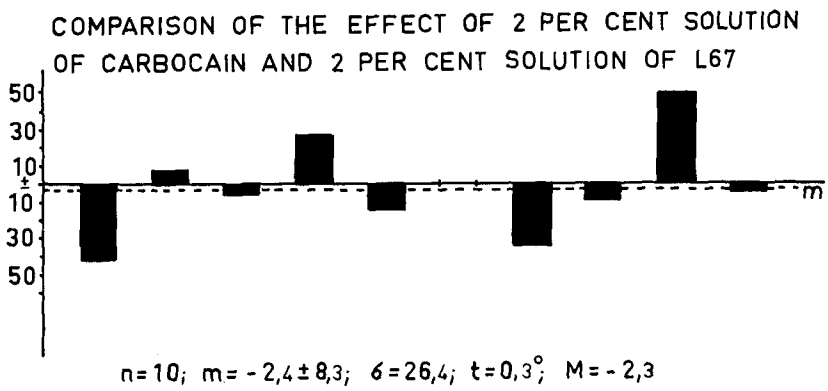


Fig. 8.

experimental conditions were used, *i.e.* 0.5 ml of one of the solutions (2 % lidocaine or 2 % L 67) was injected at the marks where wounds of 1.5 cm were later to be inflicted. In all, 1 ml of 2 % lidocaine and 1 ml of L 67 were injected into the same animal. Fig. 7 shows that the tensile strength of wounds inflicted in tissue infiltrated with 2 % lidocaine decreased, compared with the tensile strength of wounds inflicted in tissue infiltrated with L 67, with about 34 % ($M = -34.6$; $t = 7.3^{xxx}$).

In the last series a comparison was made between a 2 % mepivacaine solution and a 2 % L 67 solution. As can be seen from Fig. 8, there was practically no difference in tensile strength in these experiments between wounds inflicted in a tissue infiltrated with 2 % mepivacaine and wounds made in tissue infiltrated with 2 % L 67 ($M = -2.3$; $t = 0.3^{0}$).

DISCUSSION

These experiments show that L 67 seems to have a deleterious effect on wound healing in rats and rabbits, as judged by the tensile strength, both with and without addition of epinephrine. When epinephrine was added the decrease in tensile strength was larger than when epinephrine was not added. This confirms the results of earlier investigations in this field (*Björlin,* 1954), showing that epinephrine has a deleterious effect on wound healing, as judged by the tensile strength.

It seems that L 67 is a good local anaesthetic solution: it produces a good anaesthetic effect, and its toxic effect on the tissues is much less than that of lidocaine, as judged by the tensile strength of healing wounds. This effect appeared in rats as well as in rabbits.

SUMMARY

The tissue irritating effect of a new local anaesthetic of anilide type (L 67)* in rats was judged from the tensile strength of healing wounds in tissue infiltrated with 0.5 ml of the solution.

A 2 % L 67 solution decreased the tensile strength by about 40 % and a 3 % L 67 solution by 56.7 %.

When a 2 % L 67 solution and a 2 % lidocaine solution were used the results showed that the lidocaine solution decreased the tensile strength by 21.8 % compared to the L 67 solution.

A comparison between a 2 % lidocaine-epinephrine solution and a 3 % L 67 solution with epinephrine 3.33 μg/ml showed that the tensile strength decreased with 31.6 % in wounds inflicted in tissues infiltrated with 2 % lidocaine-epinephrine solution. A comparison between L 67 and mepivacaine showed practically no difference in their effect on the tensile strength of the wounds.

*Citanest.

RÉSUMÉ

EFFET TOXIQUE SUR LES TISSUS D'UN NOUVEL ANESTHÉSIQUE LOCAL DU TYPE ANILIDE (L 67)*

L'effet d'irritation tissulaire d'un nouvel anesthésique local du type anilide (L 67) sur des rats a tét apprécié en se basant sur la résistance à la traction de plaies en voie de cicatrisation dans des tissus où 0,5 ml de la solution avait été infiltré.

Une solution de L 67 à 2 % diminuait la résistance à la traction d'environ 40 %, et une solution de L 67 à 3 % la diminuait de 56,7 %.

Lorsqu'on utilisait une solution de L 67 à 2 % et une solution de lidocaïne à 2 %, les résultats montraient que la solution de lidocaïne résuisait la résistance à la traction de 21,8 % par rapport à la solution de L 67.

Une comparaison entre une solution de lidocaïne-adrénaline à 2 % et une solution de L 67 à 3 % avec 3,33 μg/ml d'adrénaline a montré que la résistance à la traction diminuait de 31,6 % dans les plaies infligées aux tissus où la solution de lidocaine-adrénaline à 2 % avait été infiltrée. Une comparaison entre L 67 et la scandicaïne® n'a pratiquement pas révélé de différence dans leur effet sur la résistance à la traction des plaies.

*Citanest.

ZUSAMMENFASSUNG

DER TOXISCHE EFFEKT EINES NEUEN LOKALANÄSTHETICUS VOM ANILIDTYP (L 67)* AUF DAS GEWEBE

Der toxische Effekt eines neuen Lokalanästheticums (L 67) vom Anilidtyp wurde nach Infiltrierung von 0,5 ml der Lösung auf die Zugfestigkeit heilender Wunden an Ratten beurteilt.

Eine zweiprozentig Lösung von L 67 senkte die Festigkeit mit 40 % und eine dreiprozentige Lösung mit 56,7 %.

Wenn eine zweiprozentige Lösung von L 67 und eine zweiprozentige Lösung von Lidocain geprüft wurden, zeigte das Resultat, dass die Lidocainlösung die Festigkeit mit 21,8 % senkte, verglichen mit der L 67 Lösung.

Beim Vergleich einer zweiprozentigen Lidocain-Epinephrinlösung mit einer dreiprozentigen Lösung von L 67 mit Epinephrin 3,33 μg/ml erwies es sich, dass die Festigkeit der mit der zweiprozentigen Lösung von Lidocain-Epinephrin behandelten Wunden 31,6 % niedriger war. Beim Vergleich des L 67 mit Mepivacain bezüglich ihrer Wirkung auf die Festigkeit der Wunden fand man keinen wesentlichen Unterschied.

* Citanest.

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