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SOME PHARMACOLOGICAL PROPERTIES OF *o*-METHYL-α-PROPYLAMINOPROPIONANILIDE, A NEW LOCAL ANAESTHETIC

BY

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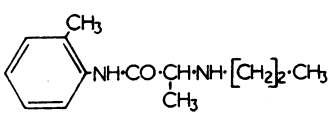
The anaesthetic action of *o*-methyl-α-propylaminopropionanilide (L 67, Astra) has been studied and compared with lignocaine in different *in vitro* and *in vivo* tests. Procaine and amethocaine (tetracaine) were also included in several of the comparisons. In nerve block on the isolated frog sciatic nerve L 67 is somewhat less effective than lignocaine. In all *in vivo* conditions, however, L 67 is quite comparable to lignocaine as to duration, latency and frequency of anaesthesia. As a spinal anaesthetic in rabbits 2 to 4% solutions of L 67 give a longer duration of anaesthesia than lignocaine. Toxicity in mice and rabbits and respiratory and circulatory effects in cats have also been evaluated. L 67 is almost twice as well tolerated as lignocaine. It is concluded that L 67 may prove to be a useful anaesthetic in certain clinical applications.

In recent years investigations of compounds chemically similar to lignocaine have been initiated because of the favourable clinical results obtained with this local anaesthetic. In collaboration with Löfgren and his associates a large number of lignocaine analogues have been synthesized and tested in our laboratories. One such compound is *o*-methyl-α-propylaminopropionanilide (L 67, Astra) (Löfgren & Tegnér, 1960), of which the chemical formula is:



Basic pharmacological data on this substance have been published by Wiedling (1960). In the study presented here the local anaesthetic properties of L 67 have been investigated *in vitro* (isolated frog nerve) and *in vivo* (nerve block, surface and spinal anaesthesia) in rats and rabbits. The action on the circulation and respiration and the toxicity of the drug have also been evaluated.

METHODS

Isolated nerve preparation. The sciatic nerve of the frog (Rana esculenta) and toad (Bufo vulgaris) was studied according to the method described by Mauro, Truant & McCawley (1948) and Truant (1957). The nerve was dissected out to include the tibial branch, and a 1.5 cm long portion of the nerve between the proximal stimulating and distal recording electrodes was immersed in a 4 ml. bath containing the local anaesthetic at 20° C. Supramaximal stimulation was performed with a Grass stimulator (Model S4E) including a stimulus isolation unit. The duration of the monophasic pulses was 0.05 msec and the voltage approximately 2.5 V.

A stimulation frequency of 30/sec was used and has been found to be preferable to single shock and higher frequencies in this type of studies. The compounds were dissolved as hydrochlorides in the modified Ringer solution used by Mauro *et al.* (1948) at *p*H 7.20.

The decrease in amplitude of the action potential (A-spike) was tested by applying the stimulus (30/sec) for 1 to 2 sec first every min while the test segment of the nerve was being bathed in the local anaesthetic solution and then every second min during washing out of the local anaesthetic. The action potential was recorded each time and 10 to 13 such recordings were obtained in the same picture by advancing the beginning of the sweep to the right between each exposure (see Fig. 1). The preparation was given 20 to 30 min rest after complete recovery. With this procedure the nerve could be used 6 to 8 times, alternately using test solutions of L 67 and lignocaine solutions as standards.

Nerve block in vivo. Female Sprague Dawley rats (150 to 200 g) were injected at the level of the mid-thigh using a 26 gauge 6 mm long needle and a volume of 0.2 ml. of the anaesthetic agent. For each compound half of the animals were injected in one leg with the test solution and, after recovery on this side, the other leg was injected with the standard (lignocaine) of corresponding concentration. In the remaining cases the reverse order of injection was used. Thus in this series each animal served as its own control. Six animals were injected in rapid succession and the motor paralysis was checked 3 min after the injection. If complete inability to make a foothold on a slanting net had developed, the symptom was checked every 5 min until complete recovery. Only complete paralysis was recorded as a positive result (block). The anaesthetics were used as hydrochlorides (*p*H 6.5 to 6.8). The method, described by Truant (1958), is similar to a previously developed technique for guinea-pigs (Shackell, 1935).

Test for topical anaesthetic action. The method of Nieschulz, Hoffman & Popendiker (1958), slightly modified, has been outlined elsewhere (Åström and Persson, 1961). One nostril of the rabbit was sprayed with 0.5 ml. of the anaesthetic agent while the other was used as control. The sneeze reflex was tested with a fine painter's brush. The reflex was considered blocked if it could be elicited neither at 1 nor at 3 min after the topical application of the local anaesthetic.

Spinal anaesthesia. Rabbits, weighing 2.0 to 2.5 kg, were used and 0.50 ml. of the anaesthetic solutions was injected through a 24 gauge needle between the 6th and 7th lumbar segments. The rabbits were restrained in a hammock. The method is essentially the same as that described by Bieter, Cunningham, Lenz & McNearney (1936). Anaesthesia was considered positive only if complete bilateral paralysis of the hind legs developed. The end-point of duration was determined by timing the first retraction response to pulling out of the legs while in the prone position.

Respiratory and circulatory effects. The action of L 67 on the systemic circulation was studied in cats anaesthetized with pentobarbitone sodium, 35 mg/kg injected intraperitoneally, by recording (1) respiration (pneumotachogram), (2) systemic blood pressure, (3) heart rate (e.c.g.) and (4) changes in peripheral resistance (hind leg) by observing pressure changes distal to a constant flow rate pump (Model T-8, Sigmamotor, Inc., N.Y.). Strain gauge pressure transducers were used and recordings made on a direct-writing Grass oscillograph. The anaesthetics were given intravenously as rapid injections (10 sec) or as infusions by a machine for 5 to 10 min.

Acute toxicity and tolerance. In albino mice the lethal dose was determined by continuous intravenous infusion (Hint and Richter, 1958 ; Richter, 1958). Using a constant infusion rate of 0.067 ml./min, the lethal dose was determined in 10 animals for each of 6 concentrations. Almost continuous diuresis was observed during the infusion of the large volumes. When the animal had lost its righting reflex death was determined at the time when all regular e.c.g. complexes (lead I) ceased. If death did not ensue the infusion was stopped after 2 hr (8 ml.).

Rabbits were given a series of single injections into the marginal ear vein in 30 sec and the dose selected such that the first injection produced a loss of the righting reflex (LRR) for a few min. The injections were repeated at 10 or 15 min intervals. Different doses were tested in series of 5 animals and 5 or 9 consecutive injections were made in each animal.

The local anaesthetic agents were used as hydrochlorides. A stock solution of 100 mM was prepared with 0.35% NaCl and dilutions made with 0.85% NaCl solution.

The ± values which follow the means in the presentation of data represent standard error of the mean. Significance of differences observed was tested by Student's *t* test (Snedecor, 1956).

RESULTS

Nerve block in vitro. A measure of the local anaesthetic activity was obtained by observing the reduction in height of the action potential produced in 5 min with different concentrations of L 67 and lignocaine. The choice of the exposure time of 5 min was considered practical for the later comparison with the *in vivo* tests. Substances which require a longer time to produce a block in this preparation would, *in vivo*, probably be removed from the injection site by the circulation, unless a vasoconstrictor was used, before a blocking concentration could be reached in the nerve structure.

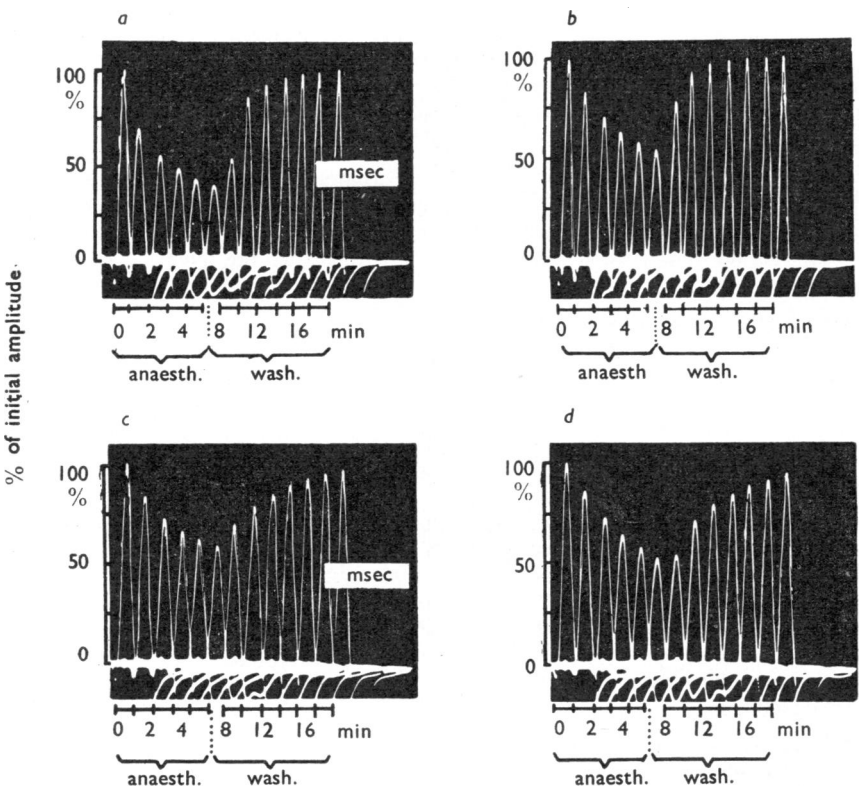


Fig. 1. Isolated frog sciatic nerve preparation. Decrease in amplitude of the action potential produced by (*a*) lignocaine, 5 mM, (*b*) L 67, 5 mM, (*c*) lignocaine, 5 mM, (*d*) L 67, 10 mM. The test segment (1.5 cm) of the nerve was immersed in the anaesthetic solution for 5 min and then washed with Ringer solution. The action potential was photographed each min while the agent was acting and every second min during washing. The beginning of the sweep was advanced to the right between each exposure. Stimulation frequency 30/sec. All solutions were *p*H 7.20.

On each nerve preparation the L 67 tests were always interposed between two lignocaine tests since the sensitivity of the nerve to the action of a local anaesthetic regularly increased during an experiment. The mean value of the bracketing lignocaine tests was used for comparison with the L 67 action. If tested in concentrations of 5 to 10 mM solutions L 67 was regularly less effective than lignocaine in reducing the height of the action potential (Fig. 1). On the basis of the results obtained in 12 nerve preparations it was concluded that in this preparation an 8 to 10 mM solution of L 67 is as effective as a 5 mM lignocaine solution.

L 67 and lignocaine were also studied with the same technique as in Fig. 1 on desheathed frog sciatic nerves. This preparation was about 5 times more sensitive than the intact nerve, but the relation between L 67 and lignocaine remained the same.

In similar experiments a 50% reduction of the amplitude of the action potential was produced by L 67 and lignocaine and the time for complete recovery was then measured. Using 5 mM lignocaine and 8 mM L 67 to produce the same degree of block, no difference in recovery time could be found. The recovery time of the action potential, during washing, from 50% to 100% of its original magnitude was 15 to 20 min for both agents. This is in sharp contrast to the recovery after amethocaine which under similar conditions is in excess of 1 hr as also found by Truant & Takman (1959).

Nerve block in vivo. 0.2 ml. of 0.5, 1.0 and 2.0% solutions of L 67 and lignocaine were injected in close proximity to the sciatic nerve in rats. The animals served as their own controls and the results (Table 1) show that the frequency and duration of

TABLE 1

NERVE BLOCK, SCIATIC NERVE IN RATS

Results from two series in which each animal received L 67 on one side and either lignocaine or procaine on the other

Compound	Concn. %	Duration of anaesthesia in min Mean±s.e.	Frequency of motor block out of 12
L 67	2	96±6	12
Lignocaine	2	92±5	12
L 67	1	80±5	12
Lignocaine	1	44±11	8
L 67	0·5	37±7	9
Lignocaine	0·5	28±7	8
L 67	2	105±5	12
Procaine	2	68±8	11
L 67	1	79±8	11
Procaine	1	6±2	6
L 67	0·5	52±8	10
Procaine	0·5	0±0	0

block were of the same order of magnitude for both local anaesthetics, although a slightly longer duration of anaesthesia was seen consistently with L 67 in these clinically relevant concentrations. The latent period for both substances is quite short (3 to 4 min). For purpose of comparison the results from a similar study with procaine have been included in Table 1.

Topical anaesthetic potency. The concentration needed of L 67 and lignocaine to block the sneeze reflex in 50% of the cases (EC50) was determined in rabbits. The EC50 for L 67 was $1.1 \pm 0.1\%$ (n=70) and for lignocaine $0.9 \pm 0.1\%$ (n=84). The EC50 and its standard error were estimated by the graphical method of Miller & Tainter (1944). No statistically significant difference in efficiency of L 67 and lignocaine was observed.

Spinal anaesthesia. The results at different concentrations are given in Table 2 and the relation between duration of anaesthesia and concentration of the anaesthetic

TABLE 2
SPINAL ANAESTHESIA IN RABBITS

Compound	Concn. %	*p*H	Duration of anaesthesia in min Mean±s.e.	Frequency of paralysis of hind legs
Lignocaine	4	6·6	44±5	10/10
	2	6·9	39±3	11/11
	1	6·8	31±6	11/11
	0·5	6·8	5±3	3/10
L 67	4	6·6	68±6	11/11
	2	6·6	46±4	10/10
	1	6·5	19±2	10/10
	0·5	7·0	5±2	6/10
Amethocaine	0·5	7·1	135±6	5/5
	0·25	7·0	76±16	5/5
	0·125	7·2	30±8	4/5

solutions presented in Fig. 2. At the lowest concentrations incomplete anaesthesias were noted with all agents and these cases were recorded as failures. At higher concentrations L 67 tended to produce anaesthesia of a longer duration than lignocaine. With 4% solutions this difference is statistically significant ($P<0.001$).

Both L 67 and lignocaine have a very short latent period and complete paralysis was generally seen as soon as the animals were removed from the hammock. The latent period of amethocaine was noticeably longer. In Fig. 2, for comparison, the dose-response curve for amethocaine is included, and the finding that it produces anaesthesia of a long duration at low concentrations is in agreement with previous investigations.

Action on circulation. In the cat under pentobarbitone anaesthesia, rapid intravenous injection of 1 to 3 mg/kg of L 67 produced a transitory fall in systemic blood pressure and usually some decrease in respiration of short duration. A fall in blood pressure has previously been observed in rabbits (Wiedling, 1960). The effects observed with L 67 on respiration and blood pressure were qualitatively the same as for lignocaine but less pronounced (Fig. 3A).

If high doses were given rapidly intravenously a secondary rise in blood pressure was sometimes observed. For lignocaine (6 to 8 mg/kg) this secondary rise was seen more clearly than with L 67 (Fig. 3B) and seems to result, at least in part, from changes in peripheral resistance. The respiratory changes in such cases are very pronounced, and the long-lasting apnoea in Fig. 3B suggested that the decrease in respiration might be the cause of the secondary increase in blood pressure and

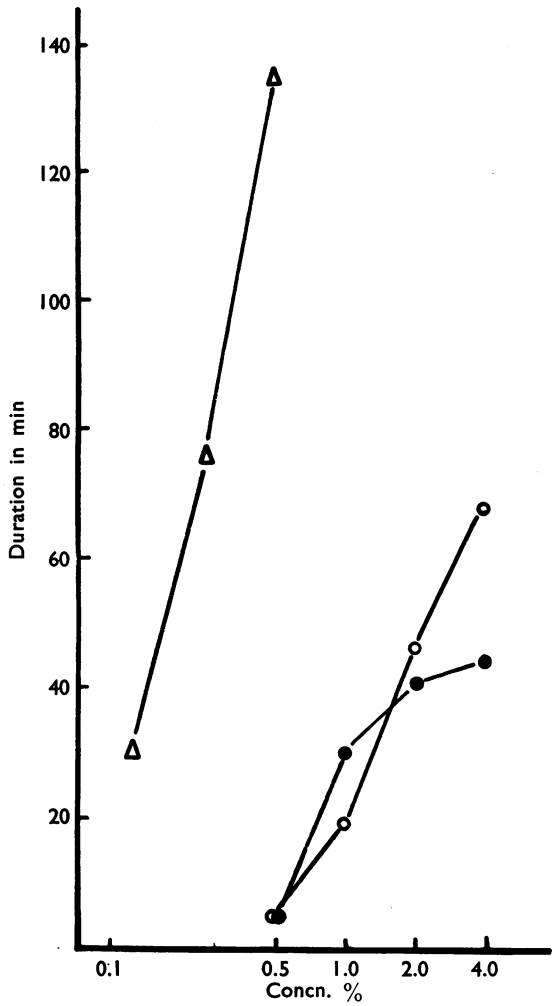


Fig. 2. Spinal anaesthesia in rabbits. Mean duration of anaesthesia at different concentrations. At high concentrations L 67 (○——○) produces anaesthesia of a significantly longer duration than lignocaine (●——●) ($P<0.001$ at 4%). △—— △=amethocaine. See also Table 2.

peripheral resistance. This assumption is supported by the results in Fig. 3C which shows that when hypoxia was prevented by artificial respiration the same high doses of lignocaine and L 67 produce predominantly a fall in blood pressure and peripheral resistance.

The effects of rapid intravenous injections of L 67 were compared with those of lignocaine in 5 cats, 2% solutions being given in different orders. From these studies it was concluded that in the dose range 2 to 5 mg/kg the depressor action of L 67 on (1) respiration is about half and (2) on blood pressure about half that of lignocaine. When hypoxia was prevented by artificial respiration the vasodilator effect of lignocaine, as measured in the hind leg, was about twice that of L 67.

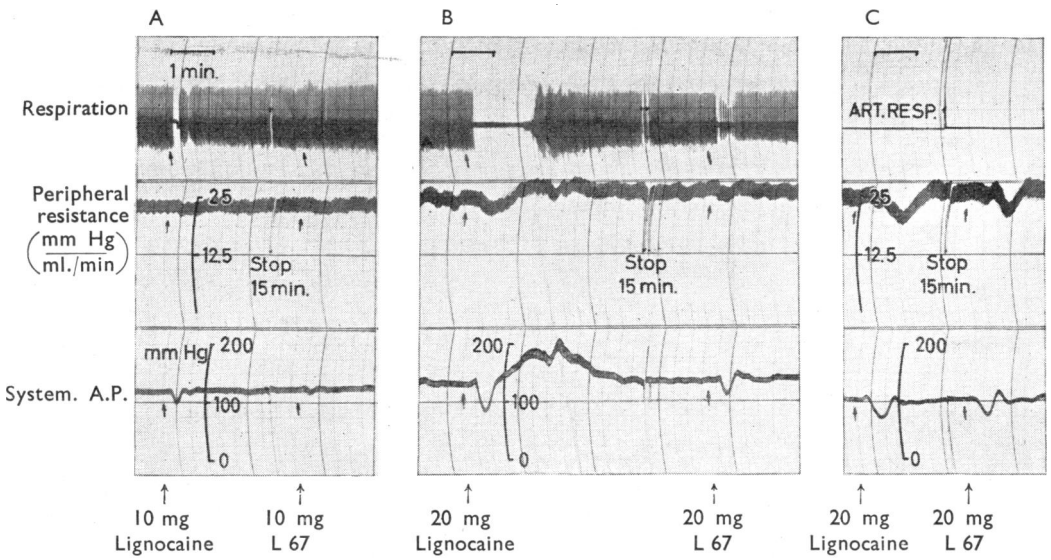


Fig. 3. Cat, 2.5 kg, pentobarbitone sodium anaesthesia. Effect of rapid intravenous injections of different doses of L 67 and lignocaine. Upper tracing, respiration; middle tracing, peripheral resistance in a hind limb measured by recording pressure changes distal to a constant flow rate pump; lower tracing, arterial blood pressure. Between A and B and B and C was a 30 min recovery period.

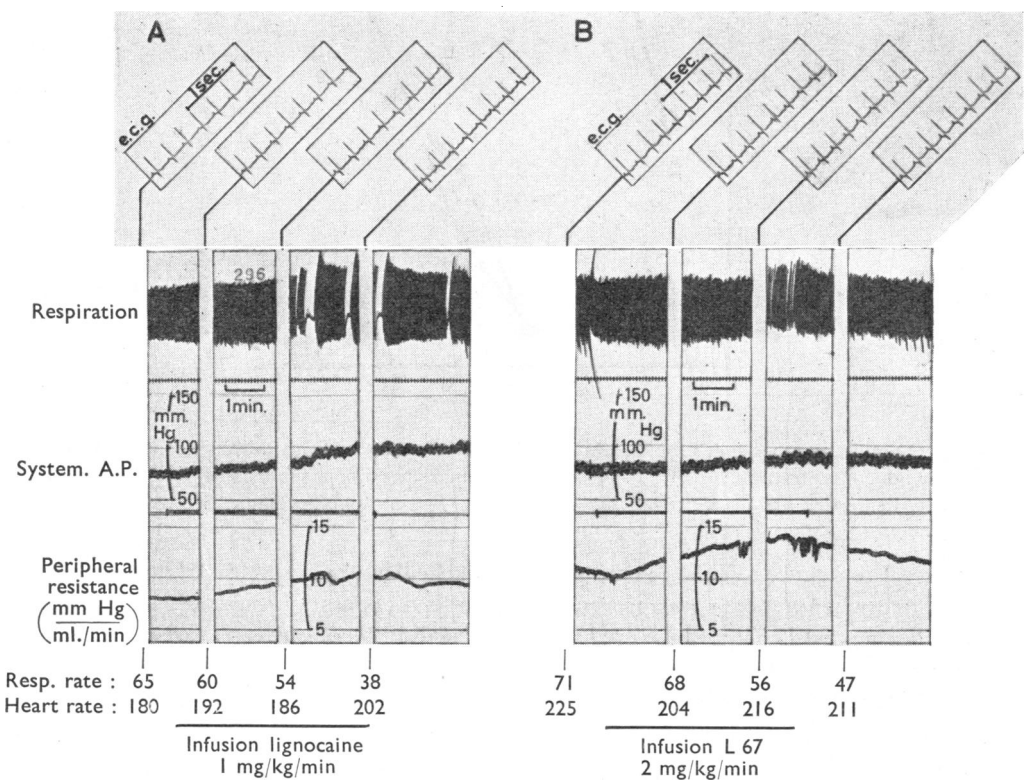


Fig. 4. Cat, 4.2 kg, pentobarbitone sodium anaesthesia. Effect on respiration, systemic blood pressure and peripheral resistance of intravenous infusions for 5 min of L 67 and lignocaine. The e.c.g. recording (top) and the respiratory frequency and heart rate/min (below) are given for each 5 sec period during which the speed of the polygraph was increased. Between A and B 45 min recovery.

In contrast to the results obtained with rapid intravenous injections an infusion of L 67 for several min usually produced a moderate increase in systemic blood pressure and peripheral resistance (Fig. 4B). At a rate of 2 to 3 mg/kg/min respiration is only moderately depressed. Lignocaine at only half this rate of administration produced a more marked depression of respiration and often produced repeated episodes of apnoea (Fig. 4A). As in the case of rapid injections of large doses the elevation in blood pressure seemed to follow largely as a consequence of respiratory depression and could be counteracted by artificial respiration. Other factors may, however, also contribute to the pressor effect on blood pressure. An elevation of blood pressure and cardiac output due primarily to a central effect has previously been demonstrated in dogs (Kao & Jalar, 1959). At infusion rates used in the type of experiments illustrated in Fig. 4 no definite changes were observed in the electroencephalogram for either L 67 or lignocaine.

Since in the cat experiments L 67 was found to produce less vasodilatation than lignocaine, it seemed possible that L 67 would enhance local circulation at an

TABLE 3

LETHAL DOSE DETERMINED BY CONTINUOUS INTRAVENOUS INFUSION

Solutions of different concentrations were infused at 0·067 ml./min until death occurred up to a maximum of 2 hr. With the lowest concentration of L 67 and amethocaine 1 of the 5 animals did not die within 2 hr

Compound	Concn. mM	No. of mice	Amount infused 10^{-6} mole/min/20 g body weight	Lethal dose mg (base)/kg Mean±s.e.
Lignocaine	100	10	6·70	190±22
	50	10	3·35	139±9
	25	10	1·67	167±17
	12·5	10	0·83	225±23
	6·25	5	0·42	266±14
L 67	100	10	6·70	190±34
	50	10	3·35	155±9
	25	10	1·67	222±19
	12·5	10	0·83	342±10
	6·25	5	0·42	>450
Amethocaine	6·25	10	0·42	28±1·3
	3·125	10	0·21	27±1·7
	1·563	10	0·11	50±3·3
	0·782	5	0·05	>75
Procaine	50	10	3·35	246±9
	25	10	1·67	180±6
	12·5	10	0·83	185±12
	6·25	10	0·42	236±35

injection site less than lignocaine. We are very grateful to Mr. Walde of this laboratory, who tested this possibility. He prepared 1% solutions of the agents with partially radioactive 0.85% NaCl solution and studied the clearance of ^{24}Na from the immediate surroundings of the sciatic nerve in rabbits. In two series of 6 animals it was found that ^{24}Na rose more slowly in the blood in the L 67 series than in the lignocaine series.

Toxicity and tolerance. The results from the infusion studies in mice are given in Table 3 and Fig. 5, in which the LD has been plotted against rate of infusion. The figure shows that with all anaesthetics the lethal dose decreases with increasing

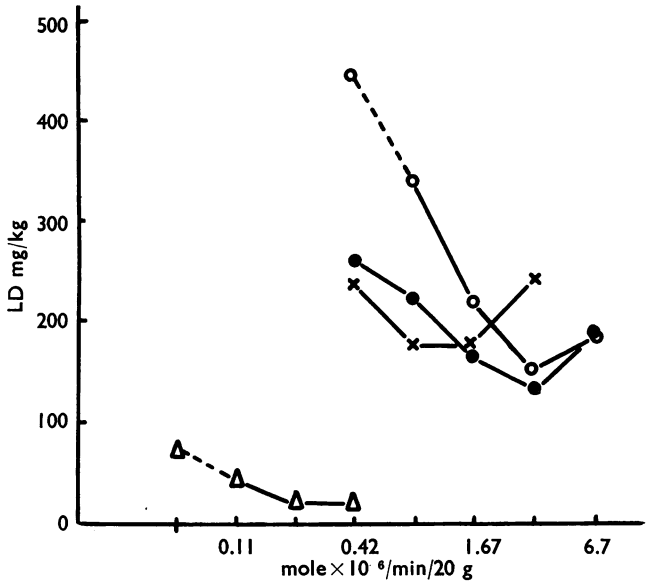


Fig. 5. Mice, 18 to 23 g. The lethal dose (LD), expressed in mg of the base, determined for L 67 (○——○), lignocaine (●—— ●), procaine (X——X) and amethocaine (△—— △) at different rates of intravenous administration. Infusions with different concentrations made at a constant volume rate of 0.067 ml./min. At 0.42×10^{-6} mole/min/20 g 1 of 5 animals receiving L 67 survived the 2 hr infusion of a total volume of 8 ml. With lignocaine and procaine survivals during the 2 hr started to occur at 0.21×10^{-6} mole/min/20 g and a valid estimate of LD was therefore not obtained at this rate of administration.

amount infused/unit time. Using 50 mM solutions (3.35×10^{-6} mole/min), the ratio LD lignocaine/LD L 67 was 0.9, while with 6.25 mM solution (0.42×10^{-6} mole/min) the ratio was about 0.6. At this latter concentration death occurred with L 67 in 4 of 5 cases. The animal which survived was infused with a total of 8 ml. in 2 hr, the others in this group died within 71 to 103 min. With lignocaine at the same rate of infusion all 5 animals died within 38 to 78 min, and with procaine all 5 died within 30 to 52 min. Since death was not observed within 2 hr L 67 could not be tested in the lowest concentration. With lignocaine and procaine survivals for 2 hr started to occur at the infusion rate of 0.21×10^{-6} mole/min. A valid estimate of LD was therefore not obtained at this rate of administration although a tendency for the procaine and lignocaine lines to cross was obvious. When 100 mM solutions were used the lethal doses were higher than those observed with 50 mM solutions of L 67 and lignocaine. Because these doses are very high and above the dose-response range, the results are not considered relevant here.

In the rabbit, tolerance for L 67 was compared with that for lignocaine. The study was performed by injecting intravenously at 10 and 15 min intervals a dose of each anaesthetic which on the first injection caused a loss of righting reflex (LRR). After preliminary trials two doses of 2% solutions were selected for the comparison, 9 and 12 mg/kg of lignocaine and 12 and 16 mg/kg of L 67. The injections were repeated if the animals had recovered from the preceding injection ; if no recovery occurred, then the test on this animal was terminated. Fig. 6 summarizes the results obtained.

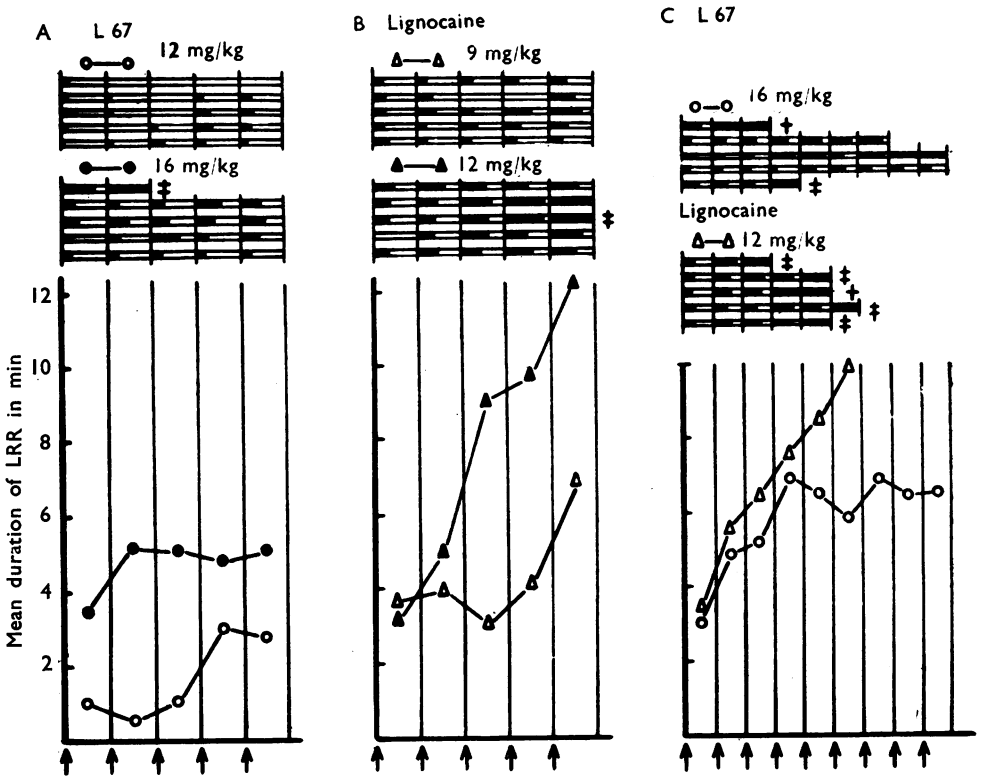


Fig. 6. Rabbits. Duration of loss of the righting reflex (LRR) indicated for each individual animal by black parts of the horizontal bars and the mean duration for each interval shown by the curves. Injections at 15 (A and B) and 10 (C) min intervals. † Death. ‡ Continued LRR.

The horizontal bars represent the duration of loss of the righting reflex (LRR) for each animal while the curves represent the mean duration for each group of 5 animals. In the cases when recovery had not taken place the duration of LRR for that interval was taken as either 10 or 15 min depending upon the intervals used. This tolerance study indicates that when lignocaine, 9 and 12 mg/kg, is injected at 15 min intervals (Fig. 6B) the duration of the LRR becomes progressively longer with each subsequent injection. Such an additive effect is not seen with L 67 (Fig. 6A) even at the high dose of 16 mg/kg. This difference between L 67 and lignocaine is well brought out in Fig. 6C in which 12 mg/kg of lignocaine and 16 mg/kg of L 67 are injected at 10 min intervals. Since the injected doses used are quite high and not much lower than the LD50 values for both anaesthetics some deaths were observed.

DISCUSSION

The methods used in this study were selected to determine certain pharmacological properties of L 67, which were thought to be related to important parameters in clinical anaesthesia. The investigation therefore includes (1) different methods of determining local anaesthetic activity, (2) various methods of evaluating systemic tolerance when administered intravenously at different rates, and (3) an evaluation of the effect on circulation and respiration.

Local anaesthetic action. The local anaesthetic action has been studied in a "semistatic" *in vitro* model, as well as in various dynamic *in vivo* conditions.

By the *in vitro* technique the efficiency of L 67 has been determined in relation to standard (lignocaine) by alternate tests on the same nerve preparation. The efficiency of a local anaesthetic determined by this method will largely be determined by its physico-chemical properties such as pK_a, lipid solubility and ability of the base to penetrate to the site of action in the nerve. The importance of these factors for the local anaesthetic effect has been discussed by Trevan & Boock (1927) and later by Ehrenberg (1948), Brown & Luduena (1953), Skou (1954) and Rud (1957). Determinations of certain physico-chemical properties of L 67 and lignocaine would therefore possibly offer an explanation for the lower activity of L 67 as observed on the isolated nerve preparation.

The dynamic *in vivo* conditions used were (1) nerve block, (2) topical anaesthesia of the nasal mucosa and (3) spinal anaesthesia. The experiments evaluating the ability of L 67 to block motor nerve fibres of the sciatic nerve in rats have shown that, at concentrations of 0.5 to 2.0%, L 67 is as effective as lignocaine in producing motor block. In these experiments it thus seems as if L 67 at the site of action reaches a sufficiently high concentration to make possible the same effective block in spite of its lower efficiency as determined on the isolated nerve.

The study of the topical anaesthetic potency of the two compounds on the nasal mucosa of the rabbit has also shown that L 67 and lignocaine are equally active. 2% solutions of L 67 and lignocaine produce topical anaesthesia of the same duration and in this respect both agents are comparable to 1% amethocaine on the nasal mucosa of the rabbit (Åström & Persson, 1961). Thus in this *in vivo* test, too, L 67 is as effective as lignocaine.

In both these physiological conditions (nerve block and topical anaesthesia) the effect of the agents upon local circulation is, in all probability, a significant factor. As shown in this study the vasodilatation produced in cats by lignocaine is greater than that of L 67. The difference in action on the local circulation has been illustrated by the finding that ^{24}Na is cleared more rapidly from a local site of injection when mixed with lignocaine than when mixed with L 67. If lignocaine is removed from the local site by the circulation more rapidly than L 67, this would explain why L 67 in these *in vivo* conditions is as effective as lignocaine in spite of its lower efficiency in the isolated nerve preparation.

The third dynamic *in vivo* situation studied was spinal anaesthesia. The dynamic situation here differs from the other *in vivo* conditions in that an injected compound can be expected to be slowly transported away from the site of application in the cerebrospinal canal. The results (Fig. 4) have shown that at higher concentrations L 67 gives an anaesthesia of a significantly longer duration than lignocaine. A consideration of the results by this *in vivo* test for the three anaesthetics leads to the following conclusions: Amethocaine penetrates slowly to the site of action (long latency observed here), but since transport from the spinal fluid is relatively slow the drug will stay locally long enough to make possible a sufficiently high concentration at the site of action. Once at the site, it is slowly removed and hence produces anaesthesia of long duration. Lignocaine penetrates rapidly (short latency), but, since it also can leave its site readily, its duration will

be limited by a relatively rapid transport away by the circulation in the nervous tissue. L 67, finally, also penetrates rapidly (short latency), and, even if it is not retained at the site of action any more firmly than lignocaine, its weaker enhancing action upon local circulation in the nervous tissue may retard its elimination by this route. The duration of anaesthesia by L 67 is therefore longer than for lignocaine in concentrations high enough to compensate for its lower efficiency as seen in the isolated nerve preparation.

Toxicity and tolerance. The methods selected to evaluate the toxicity of L 67 were designed to yield data which, if possible, should give some insight about the tolerance to L 67 to be expected under clinical conditions. For the clinical tolerance of a local anaesthetic in most applications and excluding intravenous usage, the usually determined intravenous toxicity would be of direct interest mostly in the rare instances of accidental intravascular injection. Normally the rate of absorption from an injection site is relatively slow and varies with the vascularity of the region and the effect of the anaesthetic upon local circulation. By the method used in this investigation with intravenous infusions at different rates, the conditions at the lowest rates of administration will simulate those when an agent is injected, for example, subcutaneously or intramuscularly, while at the highest rates the conditions are more like those of an ordinary intravenous toxicity study. The results (Fig. 5) have shown that if solutions of a high concentration are infused the lethal doses of L 67 and lignocaine in mice are quite similar. At lower rates of administration, however, mice tolerated L 67 much better than lignocaine. It may be added that due to the difference in action on peripheral vessels the rate of absorption of L 67 from an injection site can be expected to be slower than that of lignocaine in most clinical applications, if both agents are used without a vasoconstrictor and injected in the same concentration and volume.

A similar conclusion as to tolerance for L 67 was obtained by multiple intravenous single injections at 10 and 15 min intervals in rabbits. As shown in Fig. 6, L 67 was better tolerated than lignocaine. A more rapid destruction of L 67 than lignocaine would seem to be the most plausible explanation for this difference in tolerance. The experiments with rapid intravenous injections as well as infusions in cats have further illustrated that L 67 is well tolerated (Figs. 3 and 4) and the action of L 67 upon respiration and systemic blood pressure is regularly less pronounced than that of lignocaine.

With the appropriate caution with which experimental results on animals always should be regarded when used to predict clinical usefulness of a compound, we would like to conclude that due to its favourable local anaesthetic activity and tolerance L 67 may prove to be a useful anaesthetic in certain clinical applications. On the mucous membranes in the respiratory tract and probably elsewhere its effectiveness may be expected to be of the same order of magnitude as that of lignocaine. Like lignocaine it is less rapidly absorbed than amethocaine from mucous membranes in the rabbit (Åström & Persson, 1961). In the case of the anaesthetics without the addition of a vasoconstrictor it may be expected that L 67 for infiltration anaesthesia and nerve block (in sites comparable to the mid-thigh sciatic nerve preparation in the rat) will be as effective as lignocaine. This has been found to be true in finger nerve blocks (Eriksson & Gordh, 1959).

It remains to be determined, however, if the lower relative efficiency of L 67 in comparison with lignocaine, as found on the isolated nerve preparation, will make it inferior to lignocaine in sites where a more extensive and profound action is required. For certain clinical applications it should also be considered that the action of L 67 cannot be prolonged by the addition of adrenaline to the same degree as lignocaine. This difference was first observed by Berling & Björn (to be published) in their studies of dental infiltration (terminal) anaesthesia in man and has been confirmed in our laboratory on sciatic nerve block in rats.

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