CONTROLLED CLINICAL STUDY OF THE CARDIOVASCULAR EFFECTS OF THE NEW LOCAL ANAESTHETIC MY 33–7, USING A SYSTEM OF MULTIPLE SIMULTANEOUS RECORDINGS

BY

B. ALLARIA, A. CITRO, G. MALAVASI AND F. PERRARO

SUMMARY

With the aid of a non-invasive system of multiple simultaneous recordings a study was carried out in two groups of ten patients free from circulatory disorders, to compare the effects on the circulatory system of MY 33–7, a new local anaesthetic, with those of lignocaine. The two drugs were administered subcutaneously in 20-ml doses and in equi-active concentrations, 0.5 per cent for MY 33–7 and 2 per cent for lignocaine. The multiple records were read before and 30 minutes after administration of the anaesthetics. It is concluded that: (1) The stroke volume is lowered by both anaesthetics. (2) Lignocaine reduces the voltage of the T wave in the electrocardiogram, and depresses the conduction mechanisms of the heart; this does not occur with MY 33–7. (3) MY 33–7 might therefore be safer than lignocaine for use in patients suffering from disorders of conduction.

The effect of local anaesthetics on the cardiovascular system and, in particular, the possibility of their causing arrhythmias both in animals and in man, has been known for some time (Huley and Wilburne, 1948; Foldes et al., 1960; Jerome et al., 1963; Cerciello, 1963; Zuccaro et al., 1969). Local anaesthetics are also known to have an anti-arrhythmic action if used up to a certain dosage, beyond which they become toxic. The safety margins of lignocaine and prilocaine are wider than those of other local anaesthetics (Barile et al., 1969; Musto et al., 1969).

It follows that there is room for the synthesis and testing of new local anaesthetic compounds, in the hope of finding one showing lower cardiovascular toxicity and thus greater safety in therapeutic use.

A local anaesthetic (MY 33–7) has recently been synthesized which possesses the following chemical and physico-chemical properties.

(a) Like almost all local anaesthetics, it shows three basic constituent groups: a lipophilic, an intermediate and a hydrophilic group.

(b) Its empirical formula is C\textsubscript{18}H\textsubscript{35}NO\textsubscript{2}Cl.

(c) Molecular weight = 327.898.

(d) Melting point = 178–180°C.

(e) It is soluble in water, alcohol and chloroform but insoluble in ether.

(f) A 1 per cent aqueous solution has a pH of 5.4–5.7.

(g) It is a white, odourless crystalline powder.

Preliminary toxicological screening has revealed that:

(1) The acute toxicity of MY 33–7 is very low (on subcutaneous injection it is one-third that of lignocaine).

(2) The chronic toxicity of the product in therapeutic doses is practically nil.

(3) No teratogenic effects have been observed.

(4) Local tolerance to MY 33–7 is similar to that of lignocaine at concentrations of 0.5 or 1 per cent. Signs of irritation were seen with MY 33–7 only at concentrations of 2 per cent or over.

The effects of the drug on the cardiovascular system of rats, cats and dogs are practically identical with the changes known to be produced by lignocaine (Wiedling, 1959), i.e. (a) a hypotensive effect in doses exceeding 2 mg/kg intravenously and 20 mg/kg intramuscularly; (b) a lengthening of the P–Q interval, a widening of QRS intervals and a lengthening of the repolarization stage in the electrocardiogram.

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In animal tests the local anaesthetic action of MY 33-7 is observed at concentrations amounting to at most one-quarter of those of lignocaine. It has been shown, during clinical trials in man, that a 0.5 per cent solution MY 33-7 and a solution of 2 per cent lignocaine possess equal anaesthetic activity (Ferrero, Giudice and Guzzon, 1971). Since the local anaesthetic activity of MY 33-7 is exerted at a lower concentration than that of lignocaine, it seems rational to suppose that, in active anaesthetic dosage, MY 33-7 will have fewer side effects on the heart.

On this basis, therefore, it was decided to study the effects of MY 33-7, compared with those of lignocaine, on the cardiovascular system in man, using a system of multiple simultaneous recordings.

**METHOD**

Twenty in-patients in good cardiovascular condition were chosen; ten were treated with 0.5 per cent MY 33-7 and ten with 2 per cent lignocaine; 20-ml doses were used. Both anaesthetics were administered by subcutaneous injection. These, concentrations are equi-anaesthetic, as shown by the experiments carried out by Mascherpa at the Department of Pharmacology, University of Pavia, by the method of infiltration anaesthesia in the guineapig (after Bülbbring and Wajda, 1945), instillation on the cornea in rabbits (Régnier, 1929), and sciatic nerve conduction in the rat (Setnikar, 1966).

Each patient was studied under similar basal experimental conditions by means of a non-invasive system of multiple simultaneous recordings, both before and 30 minutes after administration of the local anaesthetic.

The electrocardiogram (Pescador's III P lead), apical phonocardiogram, carotid pulse, femoral pulse, and maximum mean and minimum arterial pressures were recorded simultaneously.

The following parameters were analyzed:

- Minute volume.
- Peripheral vascular resistances (dyne/sec/cm⁻³).
- Systolic left-ventricular work (g/cm).
- Deformation time and its two components: electromechanical latency time; electropressure latency time.
- Isometric contraction time.
- Tension time.
- Ventricular ejection time.
- Ventricular ejection time/tension time ratio, or Blumberger's haemodynamic ratio.
- Mechanical systole/electrical systole ratio, or Kühns' systolic ratio.
- Systolic arterial pressure.
- Diastolic arterial pressure.
- Heart rate.
- Atrioventricular conduction time (paper speed 100 mm/sec).
- T-wave amplitude in mm (studied in Pescador's III P lead, which we consider particularly sensitive to changes in myocardial oxygenation) (Allaria, Decio and Citro, 1968; Decio, Allaria and Bottani, 1968).

Cardiac mechanical parameters were studied using the method of multiple simultaneous recordings described by Blumberger (1940) and Holldack (1951).

The study was carried out with a 4-channel Galileo polygraph, with simultaneous recording of the carotid and femoral piezogram, apical phonocardiogram, and lead III P of the e.c.g. after Pescador and Martin de Prados (1950); chart speed was 100 mm/sec, and the response time of the detectors was 5 msec.

The deformation time (measured from the interval between the e.c.g. Q wave and the first great vibrations of the first sound complex registered at the apex) corresponds to the phase in which the electrical stimulus diffuses itself into the ventricular myocardiogram and the heart modifies its shape (from oval to spherical).

The electromechanical latency time and the electropressure latency time are the two phases in which Cerletti and Weissel (1952) have subdivided the deformation time. The first (from the Q wave to the first vibrations of the first sound) corresponds to the time spent for the electrical stimulus to activate the ventricular mass; the second (the interval between the first vibrations of the sound and first great vibrations of it) corresponds to the time spent for the endoventricular pressure to equal and then to exceed the endoatrial in order to activate mitral closure.
**Isometric contraction time:** the time during which intraventricular pressure increases gradually until it equals the end-diastolic aortic pressure. The isometric contraction time is important for evaluation of the efficiency of myocardial contraction. Obviously, when its efficiency is reduced, the ventricle takes longer to reach and overcome the end-diastolic aortic pressure. On the polygraph tracing, this time corresponds to the interval between the first broad vibrations of the first sound and the upstroke of the carotid piezogram, from which one should subtract the short time interval needed for the blood column to reach the carotid pick-up point after opening of the aortic valves.

The **tension time** corresponds to the sum of the deformation time and the contraction time.

**Ventricular ejection time:** the interval between the carotid piezogram and the dicrotic indentation. Because this time value is influenced by cardiac frequency, it was corrected for frequency according to Hartman's tables (1962).

**RESULTS**

The results are shown in table I, which gives average percentage variations and standard errors for all the parameters which were analyzed, after MY 33–7 and lignocaine treatment, and the values obtained by analyzing the means of each parameter. These data may be summarized as follows.

(a) With both drugs the effect on stroke volume was variable, with a tendency toward reduction.

(b) After both MY 33–7 and lignocaine, peripheral resistance increased almost constantly, while left ventricular systolic work tended to be reduced.

(c) Deformation time, on average, increased after the use of either drug.

(d) The electromechanical latency time was not significantly modified.

(e) Electropressure latency time increased after both drugs.

(f) Isometric contraction time behaved variously after administration of the two anaesthetics. After MY 33–7 it was either reduced or remained unchanged in 8 out of 10 cases and slightly increased in the other two. After lignocaine it varied much more, showing (sometimes marked) increases in 5 out of 10 cases. Statistical analysis of the data referring to this parameter shows no significant difference.

(g) Ventricular ejection remained almost normal after administration of either anaesthetic.

(h) Blumberger's haemodynamic ratio exhibited a variable behaviour and was more often reduced by lignocaine, but statistical analysis failed to reveal significant differences between the two treatments in this respect.

**TABLE I**

Average values (related to 100) ± standard error for each parameter, determined by the multiple simultaneous recording method, after administration of 0.5 per cent MY 33–7 and 2 per cent lignocaine to 20 patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0.5% MY 33–7 Average (±SE)</th>
<th>2% lignocaine Average (±SE)</th>
<th>Student t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic output</td>
<td>91.6 (4.7)</td>
<td>92.7 (9.9)</td>
<td>0.094</td>
<td>&lt;0.95</td>
</tr>
<tr>
<td>Minute volume</td>
<td>90.0 (5.4)</td>
<td>93.0 (10.1)</td>
<td>0.265</td>
<td>&lt;0.80</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>120.6 (7.7)</td>
<td>117.8 (10.7)</td>
<td>0.212</td>
<td>&lt;0.80</td>
</tr>
<tr>
<td>Left ventricular systolic work</td>
<td>88.4 (5.3)</td>
<td>95.7 (12.0)</td>
<td>0.550</td>
<td>&lt;0.60</td>
</tr>
<tr>
<td>Deformation time</td>
<td>103.4 (3.4)</td>
<td>115.2 (12.9)</td>
<td>0.887</td>
<td>&lt;0.50</td>
</tr>
<tr>
<td>Electromechanical latency time</td>
<td>100.1 (5.8)</td>
<td>94.2 (6.3)</td>
<td>1.54</td>
<td>&lt;0.30</td>
</tr>
<tr>
<td>Electropressure latency time</td>
<td>120.0 (14.2)</td>
<td>125.9 (21.3)</td>
<td>0.230</td>
<td>&lt;0.90</td>
</tr>
<tr>
<td>Isometric contraction time</td>
<td>96.7 (5.7)</td>
<td>111.6 (14.2)</td>
<td>0.971</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Tension time</td>
<td>100.0 (3.2)</td>
<td>102.0 (3.9)</td>
<td>0.401</td>
<td>&lt;0.70</td>
</tr>
<tr>
<td>Ventricular ejection time</td>
<td>100.9 (1.5)</td>
<td>98.5 (1.7)</td>
<td>1.032</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Blumberger's haemodynamic ratio</td>
<td>101.3 (4.8)</td>
<td>93.2 (5.3)</td>
<td>1.13</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Kühns' systolic ratio</td>
<td>102.9 (2.4)</td>
<td>100.9 (3.7)</td>
<td>0.449</td>
<td>&lt;0.70</td>
</tr>
<tr>
<td>E.C.G. T wave in Pescador's III P lead</td>
<td>105.6 (9.4)</td>
<td>81.3 (4.3)</td>
<td>2.36*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Atrioventricular conduction time</td>
<td>99.2 (1.4)</td>
<td>105.2 (2.4)</td>
<td>2.11*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic arterial pressure</td>
<td>97.4 (1.1)</td>
<td>99.3 (3.2)</td>
<td>0.55</td>
<td>&lt;0.60</td>
</tr>
<tr>
<td>Diastolic arterial pressure</td>
<td>99.2 (2.7)</td>
<td>106.7 (2.8)</td>
<td>1.88</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>Heart rate</td>
<td>98.1 (2.7)</td>
<td>103.8 (2.8)</td>
<td>1.59</td>
<td>&lt;0.20</td>
</tr>
</tbody>
</table>

*P < 0.05
(i) Kühns' systolic ratio was not, on average, reduced by either of the two anaesthetics.

(j) The atrioventricular conduction time was increased after lignocaine, while remaining practically unchanged after MY 33–7. This discrepancy is accentuated by the fact that the average increase in atrioventricular conduction time after lignocaine was accompanied by a slight increase in the heart rate, while after MY 33–7 the rate was reduced, albeit only slightly.

(k) Analysis of the T wave in Pescador's III P lead revealed a constant reduction of its amplitude only after lignocaine.

(l) Systolic pressure was not influenced particularly by either of the two anaesthetics, but diastolic pressure showed some tendency to increase after lignocaine.

**DISCUSSION**

For most of the parameters considered here, the results obtained with MY 33–7 resemble those produced by lignocaine. Significant changes were observed only in a few of them.

Deformation time, on average, was found to be increased after administration of 0.5 per cent MY 33–7 and of 2 per cent lignocaine.

Analysis of the two components of deformation time shows that the electromechanical latency time was not significantly modified by either treatment. Since this parameter is proportional to the time needed for the electrical stimulus to activate the ventricular mass, it is apparent that neither drug interfered with electrical activation of the ventricle in our experimental conditions. The electropressure latency time increased with both treatments.

It might be recalled here that according to Holdack (1951) the electropressure latency time depends essentially on left ventricular filling during ventricular diastole, with particular regard not so much to the amount of blood passing from the atrium to the ventricle during diastole as to the filling pressure.

Since the filling pressure plays a vital role in the mitral-valve closure mechanism, because the valve closes as soon as the endoventricular pressure exceeds that of the atrium, it is obvious that any factor affecting the atrioventricular pressure gradient also affects the electropressure latency time.

We are not in a position to explain the mechanism by which the two anaesthetics modify this gradient, but it might be suggested that the change results from reduction of left ventricular muscle tone.

The T wave in the electrocardiogram was significantly flattened by lignocaine. Since it is well known that the T wave is strictly dependent on myocardial oxygenation, in addition to electrolyte balance, the most likely interpretation appears to be that lignocaine causes a transient reduction of oxygen supplies to the heart muscle.

The more salient difference of action between the two anaesthetics is to be found in their effects on atrioventricular conduction time: whereas MY 33–7 does not modify this parameter, lignocaine increases it.

The practical applications of these observations are obvious: MY 33–7 should be preferred to lignocaine for patients with first- and second-degree atrioventricular block, and generally for those with myocardial insufficiency.

**ADDENDUM**

*The method of Wesler and Böger.*

(1) The pulse wave speed is calculated by multiplying two measurable values, namely a definite length travelled by the pulse wave and a definite time interval. Since the two tracings are synchronous, one can measure the delay of the femoral piezogram relative to the carotid piezogram, which is picked up at a shorter remove from the heart and is therefore recorded before the other. This delay ($\tau$) is measured in hundredths of a second as the distance in mm on the chart between two points taken at one-third or one-fourth of the upward slopes of the sphygmograms.

The time so measured represents the added time needed for the pulse wave to travel from the aortic arch to the femoral artery minus the time needed for the same wave to reach the carotid artery. The difference between these two distances is measurable (Alexander, 1949). As the aortic arch can be marked at the level of the manubrium of the sternum, and the aorto-iliac bifurcation at the level of the umbilicus, we calculate two distances, namely:

from manubrium to carotid pickup point $= \ell'$;
from manubrium to umbilicus to femoral pickup point $= l$.

The supplementary distance $L$, travelled during time $t$, corresponds to the difference between the segments $l$ and $\ell'$:

$$L = l - \ell'$$

and the velocity of the pulse wave, $a$, is equal to the ratio of this distance to the time needed to travel it:

$$a = \frac{L}{t}$$

(2) Next, we calculate the femoral time $T$, representing the time (sec) separating the peak of the primary wave from the peak of the dicrotic wave on the femoral piezogram.
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(3) Last, we determine the coefficient \( E \) of aortic elasticity as follows:

\[
E = a/(Q \times T \text{ fem.})
\]

where \( a \) = velocity of pulse wave in cm/sec;
\( Q \) = surface of aortic section in sq. cm (shown by age in Suter's table);
\( T \text{ fem.} \) = time (sec) separating the peak of the femoral sphygmogram from the peak of its dicrotic wave.

Knowing these three factors, we can calculate the stroke volume as follows:

\[
SV (\text{ml}) = 2.67 \times 10^6 \times (dp/E)
\]

where \( dp \) = differential arterial pressure in mm Hg;
\( E \) = coefficient of aortic elasticity as defined above.

REFERENCES


Jerome et al. (1963); cited by Zuccaro et al. (1969).


ETUDE CONTROLEE DES EFFETS CARDIOVASCULAIRES DU NOUVEL ANESTHESIQUE LOCAL MY 33-7, EN UTILISANT UN SYSTEME D'ENREGISTREMENT MULTIPLES SIMULTANES

SOMMAIRE

A l'aide d'un système non-invasif d'enregistrements multiples simultanés, on a étudié chez deux groupes de 10 patients sans troubles circulatoires les effets sur le système cardiovasculaire du MY 33-7, un nouvel anesthésique local, en comparaison à ceux de la lignocaine. Les deux médicaments furent administrés par voie sous-cutanée en doses de 20 ml et en concentrations équivalentes, 0,5% pour MY 33-7 et 2% pour lignocaine. Les enregistrements multiples ont été faits avant et 30 minutes après l'administration des anesthésiques. On conclut que: (1) le volume pulmonaire est réduit par les deux anesthésiques; (2) lignocaine réduit le voltage de l'onde T de l'électrocardiogramme et déprime les mécanismes de conduction du coeur; ceci n'est pas le cas avec MY 33-7 (3) MY 33-7 pourrait donc être plus sûr que lignocaine pour l'emploi chez des patients avec des troubles de la conduction.
KONTROLLIERTE KLINISCHE UNTERSUCHUNG DER KREISLAUFWIRKUNGEN DES NEUEN LOKALANAESTHETIKUMS MY 33-7 UNTER VERWENDUNG EINES SYSTEMS VON MEHRFACH-SIMULTAN-ABLEITUNGEN

ZUSAMMENFASSUNG
Unter Verwendung eines Mehrfach-Simultan-Ableitungs-Systems, das oberflächlich angebracht wurde, wurde bei zwei Gruppen von je zehn Patienten ohne Kreislauferkrankungen eine Untersuchung durchgeführt, die die Kreislaufwirkungen des neuen Lokalanaesthetikums My 33-7 mit denen von Lignocain verglichen sollte. Die Präparate wurden in 20-ml-Dosierung und gleichaktiven Konzentrationen (0,5 % für MY 33-7 und 2 % für Lignocain) subcutan verabreicht. Vor und 30 Minuten nach Verabreichung der Anaesthetika wurden die Ableitungen abgelesen.

Ergebnisse: (1) Beide Anaesthetika verringern das Schlagvolumen. (2) Lignocain verkleinert die Amplituden der T-Welle im Elektrokardiogramm und beeinträchtigt die Reizleitungsstrukturen des Herzens. MY 33-7 zeigt diesen Effekt nicht. (3) MY 33-7 dürfte deshalb bei Patienten mit Reizleitungsstorungen risikofreier in der Anwendung sein als Lignocain.

CORRESPONDENCE

Respiratory Tract Damage in Burns

Sir,—I wish to disclaim responsibility for the statement attributed to me on the first page of the paper by Drs Lloyd and Macrae, (Brit. J. Anaesth., (1971), 43, 365). I am unable, without studying the records, to give a figure for the number of adult patients with respiratory damage associated with burning injuries admitted here under the care of the plastic surgeons, let alone to other hospitals in the South Eastern region of Scotland. While not common, this injury is not as rare as the figures given imply and more often associated with deep rather than superficial burns. The child quoted was not a patient of this hospital, and I have no personal knowledge of the treatment of the mother. The injuries of both included deep burns of the face. The second case reported was assessed on admission to this hospital as a 12½ per cent burn. The facial burn was deep and required grafting. Part of the nose was completely destroyed.

The scarcity of reports in the British literature is certainly not due to lack of awareness of the problem on the part of those involved in the care of burned patients. It is accepted as a well known and dangerous complication in any patient in whom the history or injuries suggest the exposure of the airway to heat or noxious fumes. The suspicion that damage may have been done to the respiratory tract should be enough to ensure the immediate institution of active preventive and therapeutic measures. In my own experience, admittedly limited, this has varied from a few days of general measures, to tracheostomy for the relief of upper respiratory obstruction due to thermal damage, and to 20 days IPPV for the treatment of pulmonary damage due to the inhalation of smoke and fumes.

The Fire Authorities have publicly commented on the very irritant fumes produced when some modern upholstery materials are burned. This may lead to an increased incidence of pulmonary complications in patients burned in accidents in the home.

Constance C. M. Howie
West Lothian

The following reply to Dr Howie’s letter has been received:

Sir,—We much regret that Dr Howie feels that her views have been misrepresented in our paper on Respiratory Tract Damage in Burns. That this has occurred was due to a misunderstanding and was done in good faith.

We value Dr Howie’s comments on the subject and her reasons for the scarcity of reports in the British literature.

E. LL. Lloyd
W. R. MacRae
Edinburgh