VERAPAMIL IN CARDIAC DYSRHYTHMIAS DURING ANAESTHESIA

BY

G. BRICHARD AND PAULETTE E. ZIMMERMANN

SUMMARY

The antidysrhythmic action of verapamil 20 mg was studied in 383 patients lightly anaesthetized with halothane in oxygen. The drug effectively inhibited ventricular and supraventricular dysrhythmias and was without effect on sinus tachycardia of adrenergic origins. Its possible modes of action have been discussed. It is suggested that it acts by preventing the function of calcium ions, thereby causing a non-specific inhibition of the cardiac dysrhythmic reactions to sympathetic overactivity. It is concluded that verapamil may be used safely for the control of supraventricular and ventricular dysrhythmias in lightly anaesthetized patients. Its use is contraindicated in patients with atrioventricular block of any grade and in undigitized patients with heart failure.

Beta adrenergic blocking drugs have been used successfully in the treatment of the cardiac dysrhythmias which may complicate light halothane-oxygen anaesthesia (Johnstone, 1970). The hazards and complications of these drugs in conscious or anaesthetized patients have been described (Katz, 1967; Epstein and Braunwald, 1967; Katz and Epstein, 1968). This report concerns our experience with verapamil (Isoptine; Cordilox), a new antidysrhythmic agent which does not possess the inconveniences of beta adrenergic blocking drugs.

Verapamil is α-isopropyl-α [(N-methyl-N-homoveratryl)-γ-aminopropyl]-3, 4-dimethoxyphenylacetonitril hydrochloride. It was first regarded as a coronary vasodilator substance (Haas and Haerfelder, 1962; Schlepper and Witzleb, 1962; Haas, 1964) and later as an inhibitor of anaesthetic, catecholamine and ouabaine-induced cardiac arrhythmias (Melville, Shister and Huq, 1964; Schaumann, Bodem and Bartsch, 1966; Schmid and Hanna, 1967; Rodrigues-Pereira and Viana, 1968; Haas and Busch, 1968). Its antidysrhythmic action has been attributed to either what appears to be a beta adrenergic blocking effect (Haas, 1964; Haas and Busch, 1967; Fleckenstein et al., 1967) or to a quinidine-like effect (Melville, Shister and Huq, 1964; Schaumann, Bodem and Bartsch, 1966; Benfey, Greef and Heeg, 1967; Rodrigues-Pereira and Viana, 1968). Fleckenstein and associates (1967) also indicated that the drug antagonizes the effects of calcium ions on the cardiac myofibrils. In the present study we will attempt to show that verapamil is not a beta adrenergic receptor blocker and we will discuss its possible mode of action. Its clinical use appears to be safe and it may prove to be of interest to anaesthetists.

METHOD

Some of the cardiovascular effects of the drug have been studied in 383 anaesthetized patients. Their ages ranged from 18 to 82 years. Each was premedicated with a standard dose of haloperidol 5 mg and papaveretum 10–20 mg according to age. Anaesthesia was induced intravenously with propanidid 150–250 mg mixed with atropine 0.25 mg and maintained with halothane in oxygen. Special care was taken to maintain a light plane of anaesthesia and to avoid hypercapnia. All patients were monitored by electrocardiography, digital plethysmography with a crystal transducer displaying the volume pulse, and by frequent measurements of the blood pressure by classical brachial cuff sphygmomanometry. The conduction time of the pressure wave from the heart to a finger was assessed by measuring the time interval between the R wave of the electrocardiogram and the
beginning of the pulse wave of the digital plethysmogram, both of which were recorded simultaneously and continuously. Each patient was given a single dose of verapamil 20 mg by a slow intravenous injection according to the following circumstances (table I).

### Table I

**Groups of patients.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Healthy non-dysrhythmic patients</td>
<td>30</td>
</tr>
<tr>
<td>(a) Verapamil</td>
<td>20</td>
</tr>
<tr>
<td>(b) Verapamil 5 min after atropine 3 mg</td>
<td>30 — 50</td>
</tr>
<tr>
<td>Group 2</td>
<td>76</td>
</tr>
<tr>
<td>(a) Sinus tachycardia</td>
<td>72</td>
</tr>
<tr>
<td>(b) Spontaneous dysrhythmia</td>
<td>— 148</td>
</tr>
<tr>
<td>Group 3</td>
<td>175</td>
</tr>
<tr>
<td>Dysrhythmia under special conditions</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>10</td>
</tr>
<tr>
<td>Nor-adrenaline infusion</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>383</strong></td>
</tr>
</tbody>
</table>

**Group 1.** This group consisted of 50 patients with normal cardiovascular systems and who did not present cardiac dysrhythmias; 30 of them were given a full vagolytic dose of atropine 3 mg intravenously (Jones, Deutsch and Turndorf, 1961) before the administration of verapamil which was injected as soon as a steady anaesthetic state was reached and before the onset of surgery.

**Group 2.** This group consisted of 148 patients (table II); 76 of them developed cardiac dysrhythmias spontaneously during anaesthesia and 72 had sinus tachycardia (mean rate 135 beats/min) presumably of reflex adrenergic origins. Verapamil was administered after the dysrhythmia had persisted for more than 2 minutes.

**Group 3.** This group included 175 patients who developed cardiac dysrhythmias under special conditions (table III), details of which will be reported elsewhere. Verapamil was administered when it was observed that the dysrhythmias persisted during anaesthesia.

### Table II

**Spontaneous arrhythmias.**

<table>
<thead>
<tr>
<th>Type of Arrhythmia</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia (mean: 135 beats/min)</td>
<td>72</td>
</tr>
<tr>
<td>Supraventricular and ventricular dysrhythmia:</td>
<td></td>
</tr>
<tr>
<td>auricular fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>auricular flutter</td>
<td>1</td>
</tr>
<tr>
<td>supraventricular or nodal tachycardia</td>
<td>8</td>
</tr>
<tr>
<td>ventricular ectopics, unifocal</td>
<td>4</td>
</tr>
<tr>
<td>ventricular tachycardia, bifocal</td>
<td>14</td>
</tr>
<tr>
<td>ventricular tachycardia, unifocal</td>
<td>5</td>
</tr>
<tr>
<td>ventricular tachycardia, bifocal</td>
<td>31</td>
</tr>
<tr>
<td>ventricular tachycardia, multifocal</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
</tr>
</tbody>
</table>

**Group 4.** This group consisted of 10 patients who required an intravenous infusion of noradrenaline for surgical reasons during the operations. Verapamil was given 3 minutes before the infusion of noradrenaline was started and noradrenaline was administered at a rate of 32–64 μg/min for 20–30 min in order to maintain normal or raised levels of blood pressure.

**RESULTS**

**Group 1.** In the 20 patients who were not fully atropinized verapamil caused sinus tachycardia in 8 (mean increase 30 per cent), in 10 the rate was unchanged, and in 2 slightly decreased. In all patients there were small decreases in systolic and diastolic blood pressures (mean 20 mm Hg) and their faces became flushed. In 5 patients with established sinus tachycardia verapamil increased the amplitude of the volume pulse in the finger and decreased the conduction time of the pressure wave from the heart to the finger. The amplitudes of the peripheral pulse waves and the conduction times were unaltered in the remainder. In 10 patients in whom the inspired concentration of halothane was decreased to obtain a very light anaesthetic level, a decrease in the amplitude of the volume pulse and an increase in the conduc-
tion time of the pressure wave (0.16 sec) was noticed after 15–20 minutes. Verapamil had no effect on the heart rates of the 30 fully atropinized patients.

**Group 2.** Verapamil had no effect on the heart rates of the 72 patients with sinus tachycardia caused by hyper-adrenergic reflex stimulation.

**Group 3.** The various causes of the cardiac dysrhythmias in this group are listed in table III. The dysrhythmias consisted of ventricular and supraventricular disturbances. Verapamil had a prompt effect upon them. It should be stressed that although verapamil controlled and prevented dysrhythmias due to methylphenidate and theophylline it did not inhibit the sinus tachycardia induced by these drugs. The control of sinus tachycardia in these circumstances requires the use of a beta adrenergic blocker such as practolol (fig. 3).

**Group 4.** During the period of noradrenaline infusion the sinus rate increased in most patients (mean 30 per cent), the amplitude of the volume pulse decreased and the conduction time of the pressure wave decreased in each patient (fig. 4). Ventricular and supraventricular dysrhythmias were not provoked by the catecholamine infusion for approximately 20 minutes after the administration of verapamil. Multifocal ventricular extrasystoles appeared in one patient 30 minutes after the injection of the verapamil.

The antidysrhythmic action of verapamil seems to last for about 30 minutes. In 4 per cent of our cases it caused a widening of the PR interval (fig. 5) but had no effect on the intraventricular conduction times (Brichard and Zimmermann, 1970). It is emphasized that an intravenous dose of 20 mg is required for antidysrhythmic action as lower doses seem to have no effect.

**DISCUSSION**

These findings indicate that at least four explanations of the antidysrhythmic action of verapamil may be considered. These include beta adrenergic blockade, a “quinidine-like” action, hypotension, and interference with the activity of calcium ions.

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**Table IV**  
**Response to verapamil.**

<table>
<thead>
<tr>
<th>Arrhythmias</th>
<th>Response within 90 sec</th>
<th>Decrease ventricular rate 120 beats/min</th>
<th>Return to sinus rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>11</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Ventricle ectopics</td>
<td>143</td>
<td>143</td>
<td>102</td>
</tr>
<tr>
<td>Ventricle tachycardia</td>
<td>95</td>
<td>95</td>
<td>72</td>
</tr>
</tbody>
</table>

Totals 251 251 184 250

In the 76 patients with cardiac dysrhythmias of ventricular and supraventricular origins, the antidysrhythmic effect of verapamil was immediate (table IV). The following 2 cases are of interest.

**CASE 1.** A known cardiac patient of 74 years with atrial fibrillation, fully digitalized and in severe endotoxic shock. Verapamil immediately reduced the ventricular rate from 180 to 90 beats/min (fig. 1).

**CASE 2.** A patient of 67 years with coronary disease and atrial flutter of the 2/1 type with multiple ventricular ectopic beats. Verapamil caused an immediate reversion to the 3/1 type of flutter, followed soon by a further decrease to the 4/1 type which was followed by the development of atrial fibrillation (fig. 2) and sinus rhythm some 60 minutes later.
A. Atrial flutter, 2/1 type; ventricular rate 180 beats/min.
B. With multifocal ventricular extrasystoles.
C. 30 sec after verapamil 20 mg; flutter 2/1 type; ventricular rate 180 beats/min.
D. 90 sec after verapamil; flutter 3/1 type; ventricular rate 103 beats/min.
E. 7 minutes after the verapamil; flutter 4/1 type, 3/1 type (alternative flutter); ventricular rate 80–100 beats/min.
F. Atrial fibrillation with a mean ventricular response of 70 beats/min.

**Fig. 3**

A. Multifocal ventricular tachycardia.
B. 2 minutes after verapamil 20 mg; sinus rate 125 beats/min.
C. 30 min after verapamil and 5 min after practolol 10 mg i.v.

**Beta adrenergic blockade.**

A characteristic effect of a beta blocking drug is that it prevents the sinus tachycardia caused by atropine or by reflex adrenergic stimulation of the heart provoked by surgical stimuli in lightly anaesthetized patients (Shanks, 1965; Johnstone, 1969). Verapamil does not have this property. On the contrary, it may cause sinus tachycardia with an increase in the amplitude of the volume pulse and a decrease in the conduction time of the pressure wave from the heart, suggesting positive chronotropic and positive inotropic actions. Moreover, verapamil is a coronary vasodilator (Haas, and Haerfelder, 1962; Schlepper and Witzleb, 1962; Haas, 1964; Melville, Shister and Huq, 1964) whereas the beta blocker is not. Unlike the beta blocking drugs, verapamil fails to prevent the sinus tachycardia caused by physical exercise in patients with coronary disease (Kaltenbach and Zimmerman, 1968). It would seem that verapamil and the beta blockers have but one effect in common, namely the suppression of catecholamine-induced cardiac dysrhythmias in anaesthetized subjects. It therefore seems reasonable to conclude that verapamil is not a beta adrenergic receptor blocker.
VERAPAMIL IN CARDIAC DYSRHYTHMIAS DURING ANAESTHESIA

Electrocardio-plethysmograph tracings; recorder speed 25 mm/sec.

A. During steady state halothane anaesthesia; systolic pressure 100 mm Hg; sinus rate 92 beats/min; pulse wave amplitude 8 mm; conduction time of pressure wave 0.32 sec.

B. After pancuronium I.v.; systolic pressure 120 mm Hg; sinus rate 92 beats/min; pulse-wave amplitude 8 mm; conduction time 0.26 sec.

C. After verapamil 20 mg; systolic pressure 105 mm Hg; sinus rate 120 beats/min; pulse-wave amplitude 12 mm; conduction time 0.16 sec.

D. During noradrenaline infusion at 32 µg/min; systolic pressure 160 mm Hg; sinus rate 90 beats/min; pulse-wave amplitude 3.5 mm; conduction time 0.12 sec.

Quinidine-like action.

"Quinidine-like" is an alternative and perhaps undesirable term used to describe the effect of a drug on the activity of cell membranes (Fitzgerald, 1969), that is to say the local analgesic property of the drug. It implies an impairment in the conductivity of the specialized Purkinje tissue of the heart (fig. 6).

Verapamil is a local analgesic substance (Schmid and Hanna, 1967; Rodrigues-Pereira and Viana, 1968). In this respect it is equipotent to pronethalol (Schmid and Hanna, 1967). This fact probably explains the impairment of atrioventricular conduction which we have seen in 4 per cent of our patients immediately after the administration of verapamil (fig. 5). However, although of similar analgesic potency to pronethalol, verapamil is 6-8 times more potent than the latter in the control of hydrocarbon-adrenaline arrhythmias in dogs (Schmid and Hanna, 1967).

Moreover, the local analgesic substances are strongly cardiodepressive. Verapamil in our experience has little such effect, judging from the lack of changes in the volume pulse, pulse wave conduction time and other parameters. Drugs such as dextro-alprenolol (Lord, Katz and Eakins, 1968), procaine and propanidid (Johnstone and Barron, 1968), which are strong local analgesic substances, have a very short antidysrhythmic action when administered in single doses, whereas verapamil has a relatively long antidysrhythmic action. It may therefore be concluded that although verapamil is a local analgesic substance, its effect on membrane activity does
not appear to be sufficient to explain its mode and duration of action.

Hypotension.
A rise in blood pressure is considered by some to be a facilitating factor in the production of cardiac dysrhythmias (Katz, 1967; Katz and Epstein, 1968), the reverse being true for hypotension. Drugs such as droperidol have some antidysrhythmic action which may be related to their hypotensive action (Long, Dripps and Price, 1967).

It seems increasingly evident that the antiarrhythmic properties of some derivatives of butyrophenone, especially of droperidol, are better explained by inhibition of the membrane permeability at the whole membrane cellular level (unlike haloperidol which acts at the subcellular granular level) (Dresse and de Meyer, 1965). This membrane stabilizing process, so-called "quinidine-like", has been again recently described on the sheep Purkinje fibres (Hauswirth, 1968) when large doses of droperidol were used. Some derivatives of phenothiazine act in the same way (chlorpromazine, propiomazine, pericyazine), as do tricyclic derivatives (Collard, Dufrasne and Fraipont, 1969) largely used in psychiatry.

Verapamil causes hypotension, apparently by a papaverine-like effect (Haas and Haerfelder, 1962; Melville, Shister and Huq, 1964). This effect is of short duration (5 minutes) in contrast to its prolonged antidysrhythmic action. Maintenance of the blood pressure at normal or raised levels with noradrenaline infusion did not impair the antidysrhythmic action of the drug (fig. 4).

Calcium antagonism.
A more probable explanation of the antidysrhythmic action of verapamil seems to be that it exerts a non-specific antagonism towards the calcium ions at the cardiac myofibrillar level (Fleckenstein et al., 1967). It would thus limit the breakdown of adenosine triphosphate to cyclic adenosine monophosphate and thereby diminish the irritability of the myocardium (fig. 7). This mode of action accords with our clinical experience. The first site of action of verapamil appears to be at the periphery of the heart, like that of beta blockers and unlike that of the analgesic substances which appear to act primarily on the Purkinje tissue (fig. 6). But, unlike the beta blocker which specifically, competitively, and reversibly antagonizes the effect of catecholamines on the beta receptor site, possibly by inactivation of adenylcyclase (Himms-Hagen, 1967; Sutherland, Robison and Butcher, 1968), verapamil acts as a non-specific, non-competitive antagonist to the calcium and its action is irreversible when an overdose is given (fig. 7). As calcium ions are known to be involved in the mechanism by which cyclic adenosine monophosphate initiates the

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**Figure 7**

Difference, at the subcellular level, in the modes of action of verapamil and the beta-blockers.

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\[ \text{Glycogen} \rightarrow \text{Glucose-1-Phosphate} \rightarrow \text{Glucose-6-Phosphate} \]

\[ \text{Phosphorylase a} \rightarrow \text{Phosphorylase b} \]

\[ \text{Ca}^{+2} \]

\[ \text{Catecholamines} \]

\[ \text{ATP} \]

\[ \text{ADENYLCYCLASE} \rightarrow \text{DIMETHYLXANTHINES} \]

\[ 3'5' \text{A.M.P.} \]

\[ \text{Specific antagonistic action of } \beta \text{ blocker at receptor site} \]

\[ \text{Non-specific antagonistic action of verapamil} \]
myocardial contraction, and since in their absence the catecholamines fail to produce a contraction (Nayler, 1967), it is suggested that, although obviously not affecting the sympathetic innervation of the heart like a beta blocker, verapamil could, on the basis of its calcium ion antagonism, moderate the dysrhythmic reaction of the heart to an overactive sympathetic system.

ACKNOWLEDGEMENTS

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REFERENCES


Haas, H., and Busch, E. (1968). Antiarrhythmische wirkungen von verapamil und seiner derivaten im vergleich zu propranolol, pronethalol, chininid, pro- 


Haas, H., and Busch, E. (1968). Antiarrhythmische wirkungen von verapamil und seiner derivaten im vergleich zu propranolol, pronethalol, chinnid, prop- 


**VERAPAMIL (ISOPTINE) DANS LES DYSRHYTHMIES CARDIAQUES DURANT L'ANESTHESIE**

**SUMMARY**

L'action antidyssrhythmique d'une dose de 20 mg de verapamil a été étudiée chez 383 patients, légèrement anesthésiés à l'halothane dans oxygène. Le médicament inhiba efficacement les dysrhythmies ventriculaires et supraventriculaires mais n'exerça aucun effet sur la tachycardie sinusale d'origine adrénergique. Le mode d'action possible est discuté. Les auteurs croient qu'il agit en empêchant la fonction des ions de calcium, causant ainsi une inhibition non-spécifique de la réaction dysrhythmique du cœur à la suractivité sympathétique. Ils concluent que verapamil peut être utilisé sans danger pour contrôler les dysrhythmies ventriculaires et supraventriculaires chez les patients légèrement anesthésiés. Son emploi est contreindiqué chez des malades avec block atrio-ventriculaire, quel

**BOOK REVIEW**


The author of this compact book is well known as Chief of the Division of Biomedical Engineering at Baylor College of Medicine in Texas. The text has apparently developed from teaching material in physiology presented over a 15-year period. There are three main sections, with numerous subheadings, dealing with direct and indirect measurement of blood pressure in man, and indirect methods in animals; also included are a brief account of the exteriorized arterial loop technique and a summary of the normal levels of arterial pressure in many animals. The author discusses and analyzes the results obtained with much old and new apparatus, but is not concerned with listing specific modern items of equipment (surprisingly, no mention of the Scala Alternans of von Recklinghausen).

The story of blood pressure recording, not too well known and far from ancient, is full of fascination, as this book reveals in ways too numerous to mention. There is something for everyone. Thus, many readers will be intrigued that Marey's tambour of 1861, providing the first faithful reproduction of intracardiac pressures, had a response time of only 5 msec; that for accurate reproduction of the sounds described by Korotkoff in 1905 a frequency spectrum of 20-300 Hz is required; and that the failure to detect arterial pressure sounds at very low pressures may be because the frequencies generated are below audibility. The exclusively practical clinician, on the other hand, can find information about optimal cuff widths (13 cm in adults, and in general about 40 per cent of the arm circumference); he will see a summarizing comment that auscultatory measurement of arterial pressure gives a systolic level about 5 mm Hg below, and a diastolic about 8 mm Hg above, the true intra-arterial reading. There is, of course, a mass of information for the research worker, who will read that the damping introduced by an intra-arterial catheter varies directly by the square root of the length and inversely by the cube of the diameter (a very small decrease in diameter means much).

The frontispiece illustrates the Rev. Stephen Hales manipulating his first-ever arterial pressure line of 1733; in series from the carotid artery of a thoroughly conscious (and well-tethered) white mare with neck laid bare, there is to be seen a brass pipe, the windpipe of a goose, and a long glass tube. Simple and direct, if damped. While the indirect techniques have obviously improved, the reader will find that a great deal is still not understood about the basis and accuracy of the oscillographic and auscultatory measurement of arterial pressure.

This book is needed, should prove its value, and is highly recommended.

R. A. Millar