THE EFFECT OF KETAMINE ON TRANSMEMBRANE POTENTIALS OF PURKINJE FIBRES OF THE PIG HEART

J. T. HAMILTON AND J. S. BRYSON

SUMMARY
The action of ketamine upon spontaneously active and electrically driven Purkinje fibres of the moderator band of the pig heart has been studied using a floating micro-electrode technique. Ketamine hydrochloride altered the transmembrane potential in a dose-related and reversible manner. Concentrations of $1 \times 10^{-5}$M were subthreshold whereas $5 \times 10^{-5}$M and $1 \times 10^{-4}$M slowed the frequency and increased the action potential duration of spontaneous preparations, actions consistent with an antiarrhythmic effect. Higher concentrations of $5 \times 10^{-4}$M ketamine initially led to a shortening of the action potential duration, then failure of the original spontaneous activity. During recovery pacemaker-like activity developed associated with a loss of resting membrane potential. In electrically driven preparations $5 \times 10^{-4}$M ketamine significantly shortened the duration of the action potentials between evoked potentials and markedly augmented the response to adrenaline, actions consistent with an arrhythmogenic effect. These findings suggest a basis for isolated reports of cardiac side effects.

Several investigators have reported effects on the heart of the dissociative anaesthetic ketamine including depression (Goldberg, Keane and Phear, 1970), stimulation (Traber, Wilson and Priano, 1968) and antiarrhythmic activity (Goldberg, Keane and Phear, 1970; Dowdy and Kaya, 1968). In this laboratory we have demonstrated that ketamine potentiates and then depresses the isolated rat diaphragm preparation (Hamilton et al., 1972) and that this is a direct effect upon the muscle, as both potentiation and blockade of the directly stimulated muscle were produced in the presence of tubocurarine. It was concluded that the initial stimulant actions were possibly veratrinic in nature.

In the present investigation the actions of ketamine on the Purkinje conduction system of the mammalian heart have been studied. Intracellular recordings have been made from isolated spontaneously active and electrically-driven cells of the septomarginal trabecula (moderator band) of the pig.

The results show that ketamine can alter the electrophysiological properties of the conduction system in a dose-related and reversible manner.

METHODS
Domestic pigs (4.5 and 9.0 kg) were stunned with a captive bolt pistol, exsanguinated and the heart was removed rapidly. The moderator band with pieces of free ventricular wall and interventricular septum was dissected and placed in cold, oxygenated Krebs-Henseleit solution. The preparation was then transferred to an organ bath, held firmly by two threads placed over the pieces of myocardium at the ends of the band, and totally immersed in a continuous flow of pre-warmed (37 ± 1°C) Krebs-Henseleit solution gassed with 95% oxygen, 5% carbon dioxide.

The preparation was then rested for a period of 1–2 hours during which time it usually developed spontaneous activity. In some experiments it was stimulated orthodromically with a bipolar neurological electrode inserted into the interventricular musculature using pulses of 0.5 msec duration and up to 5 volts amplitude at source, delivered from a Grass S8 stimulator.

The Purkinje fibres were impaled with glass floating microelectrodes containing 3M KCl (resistances between 10 and 30 megohms) and the electrical activity amplified with either a WPM4 electrometer.
EFFECT OF KETAMINE ON PURKINJÉ FIBRES

A higher concentration of ketamine ($5 \times 10^{-5}$M) administered on three occasions to the same preparation elicited pronounced alterations of both frequency and contour on two occasions. This is illustrated from the mean of five action potentials (columns 3 and 5 in table I and fig. 1(a)) before and after exposure to $5 \times 10^{-5}$M ketamine. Note in fig. 1(a)B the initial transient irregularity followed by a regular but greatly reduced frequency of action potentials. However, before withdrawal of the drug, the frequency tended to return to control values (fig. 1(a)D). During the time when the maximum drug effect occurred, all action potentials retained the same pattern in phases 1 and 2 as in the control period. In columns 3 and 4 in table I the comparison of five control action potentials with five occurring during the maximum drug effect reveals that the beat interval increased by about 600 msec corresponding to a rate decrease of almost 50% ($P<0.001$). In addition, significant increases in the duration of action potential and the magnitude of diastolic depolarization in phase 4 were found. When the ketamine was removed, recovery occurred rapidly and completely. No further additions of the drug were made until control levels were regained.

Between figure 1(a) and (b) spontaneous depolarization of this cell occurred. Nevertheless, when it was exposed to $1 \times 10^{-4}$M ketamine for 3.5 min on two occasions the effect of drug was qualitatively similar to that previously found with $5 \times 10^{-5}$M, but the development of missed beats occurred much earlier and the reduced frequency was maintained for the duration of the drug perfusion. A further depolarization of 5–6 mV occurred with ketamine but the membrane potential returned to control value after removal of the drug. Otherwise recovery from this concentration was markedly different in that the effect was still manifested for up to 90 sec and was associated with the production of extremely prolonged action potentials, the largest, shown in section E of figure 1(b), having a duration of about

### Table I. The effect of ketamine on spontaneous action potentials (mean values and SEM).

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<thead>
<tr>
<th></th>
<th>Control†</th>
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<tr>
<td>Beat interval (msec)</td>
<td>831.4 ± 2.59</td>
<td>812.4 ± 5.37</td>
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<td>Action potential duration (msec)</td>
<td>401.8 ± 0.97</td>
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<td>Resting membrane potential (mV)</td>
<td>79.2 ± 0.62</td>
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<td>Total action potential height (mV)</td>
<td>112.5 ± 0.37</td>
<td>115.0 ± 1.38</td>
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†SEM where $n=5$ action potentials measured before and during exposure to ketamine; **$P<0.001$. 

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probe or a Mentor N950 intracellular probe system. The action potentials were displayed on a Tektronix 502A oscilloscope and recorded simultaneously on a Grass Model 7 polygraph, a Mingograph spray pen galvanometer (Elema Schööoander) and a Philips tape recorder (EL-1020/70).

Stock solutions of ketamine hydrochloride (ParkeDavis) in normal saline were made. Dilutions to yield the appropriate final concentrations were then prepared with Krebs-Henseleit solution which was pre-warmed to bath temperature.

Where necessary the various parameters were measured from the Mingograph records and statistical comparisons were made using the Student $t$-test. The duration of action potential was measured as the time from the initiation of phase-0 to repolarization to $-60$ mV.

**RESULTS**

Action potentials recorded from a series of spontaneously active, non-driven preparations regularly had the characteristics summarized in table I. In a series of action potentials recorded from any one cell prior to exposure to any pharmacological agent the parameters measured were quite constant, with a distinct dome-shaped contour essentially identical to that described by Matsuda, Kamiyama and Hoshi (1967) as a "transitional" type of action potential.

There was evidence of a dose-relationship between ketamine and the frequency and configuration of spontaneous action potentials recorded from cells from two such spontaneously active moderator bands. The data in table I were derived from a single cell or a closely adjacent cell and it is believed with some certainty that columns 1 and 2, 3 and 4, 5 and 6 represent recordings from the same cell respectively before and after exposure to the concentration of ketamine indicated.

Two preparations were exposed to $1 \times 10^{-5}$M ketamine (4 penetrations) for up to 3.5 min and this concentration was observed to be subthreshold. A higher concentration of ketamine ($5 \times 10^{-5}$M) administered on three occasions to the same preparation elicited pronounced alterations of both frequency and contour on two occasions. This is illustrated from the mean of five action potentials (columns 3 and 5 in table I and fig. 1(a)) before and after exposure to $5 \times 10^{-5}$M ketamine. Note in fig. 1(a)B the initial transient irregularity followed by a regular but greatly reduced frequency of action potentials. However, before withdrawal of the drug, the frequency tended to return to control values (fig. 1(a)D). During the time when the maximum drug effect occurred, all action potentials retained the same pattern in phases 1 and 2 as in the control period. In columns 3 and 4 in table I the comparison of five control action potentials with five occurring during the maximum drug effect reveals that the beat interval increased by about 600 msec corresponding to a rate decrease of almost 50% ($P<0.001$). In addition, significant increases in the duration of action potential and the magnitude of diastolic depolarization in phase 4 were found. When the ketamine was removed, recovery occurred rapidly and completely. No further additions of the drug were made until control levels were regained.

Between figure 1(a) and (b) spontaneous depolarization of this cell occurred. Nevertheless, when it was exposed to $1 \times 10^{-4}$M ketamine for 3.5 min on two occasions the effect of drug was qualitatively similar to that previously found with $5 \times 10^{-5}$M, but the development of missed beats occurred much earlier and the reduced frequency was maintained for the duration of the drug perfusion. A further depolarization of 5–6 mV occurred with ketamine but the membrane potential returned to control value after removal of the drug. Otherwise recovery from this concentration was markedly different in that the effect was still manifested for up to 90 sec and was associated with the production of extremely prolonged action potentials, the largest, shown in section E of figure 1(b), having a duration of about

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†SEM where $n=5$ action potentials measured before and during exposure to ketamine; **$P<0.001$. 

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FIG. 1(a). Effect of ketamine $5 \times 10^{-5}$M on spontaneous action potentials. Note in (B) and (C) the reduced frequency, prolonged phase 4 and increased action potential duration, and in (D) the return toward control values prior to cessation of ketamine.

FIG. 1(b). Effect of ketamine $1 \times 10^{-4}$M on spontaneous action potentials. Note in (B) the development of a ketamine effect characterized by irregularity in frequency and intermittent prolongation of phase 4. Note in (E) the increased action potential duration due to prolongation of phase 2 during recovery.

1500 msec. The prolongation of the action potential was associated with further or persistent depolarization. Subsequently a normal rhythm and action potential was re-established but this was preceded by a period when the frequency increased and phase 4 was greatly shortened (fig. 2, section E).

High concentrations of ketamine ($5 \times 10^{-4}$M) gave marked and complex results during exposure of the above preparation on five occasions and of another preparation on two occasions. A typical example is given in figure 2 and columns 5 and 6 of table I. Over the first 90 sec of drug infusion the frequency gradually decreased. This was related to an increase in the duration of phase 4 but not to an increase in duration of action potential (fig. 2, section B). Indeed, the duration of the action potential shortened significantly (table I, column 6). In all seven occasions on which this concentration of ketamine was used spontaneous activity suddenly ceased (fig. 2, section B). Transmembrane action potentials did return when the ketamine solution was replaced by normal Krebs-Henseleit solution but the shapes were obviously different. Thereafter, activity was lost again and it will be seen that progressive depolarization was occurring. Such a state remained for about 6 min, whereupon action potentials of a bizarre type appeared (fig. 2, section G). Phase 0 was more normal with a greater $dv/dt$ than those in figure 2, sections D and E, but phase 2 was remarkably prolonged, up to 23 sec. During the next 15 min the duration of this exaggerated phase 2 progressively shortened until eventually normal action potentials reappeared.

Experimental results from electrically driven preparations are illustrated in figure 3 and in table II. Table II gives the mean values from eight cells, two from each of four preparations driven at approximately 1 Hz. Although the mean resting potential was not significantly altered after up to 2 min of exposure to $5 \times 10^{-4}$M ketamine, four cells were depolarized and four hyperpolarized on exposure to this drug.
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The mean action potential duration was significantly (P<0.001) decreased by about 30% (table II). In addition to decreasing the duration of the action potential, ketamine caused triangularization of the action potential contour with a merging of phases 2 and 3. The spike and dome arrangement of phases 1 and 2, if present, was reduced or abolished (fig. 3, section B).

In four out of eight cells studied, ketamine (5×10⁻⁴M) caused the development of phase 4 depolarization when it was absent in the pre-drug control, in three cells the magnitude of such depolarization was increased by ketamine and in one cell there was no change. Although the mean change in phase 4 depolarization was very small in millivolt value it was statistically significant (P<0.05) as was the threefold increase in mean rate of phase 4 depolarization (P<0.05) induced by ketamine.

In all cells in which impalement was retained following washout, all of the parameters described returned to their pre-drug values within approximately 10 min.

Figure 3 illustrates clearly the change in the contour of the action potential in the presence of 5×10⁻⁴M ketamine and how this change was frequency-dependent. Ketamine allowed all impulses to elicit action potentials which, although altered in configuration, became positive; whereas in the control situation incomplete potentials appeared with a classical 2:1 block or failure pattern.

During this study with electrically driven preparations the appearance of spontaneous action potentials between those which were elicited electrically was recorded. If the number of action potentials observed is divided by the number of electrical stimuli applied during the same period the value obtained (R) allows a graphical representation of the appearance of extra or spontaneous potentials (R>1) and also of the failure to follow the electrical stimuli (R<1). Figure 4 shows the value of R under different experimental conditions: a single cell driven at a drive cycle length of approximately 1 Hz and exposed to a single bolus of adrenaline, the effect of an infusion of ketamine 5×10⁻⁴M (mean of five cells from two preparations), and the effect of adrenaline given during an infusion of ketamine in two cells. There is a decrease in R during ketamine infusion, a dramatic and profound potentiating effect by ketamine on the appearance of action potentials resulting from the injection of a bolus of adrenaline. This concentration of adrenaline has been shown in

![Fig. 3. Relationship between stimulus frequency (expressed on tracing as drive cycle length in msec) on the duration and configuration of action potentials of a moderator band in normal Krebs-Henseleit solution (A) and in solution containing 5×10⁻⁴M ketamine (B). Note the ability of the preparation to follow all frequencies in (B) and the incomplete potentials at a drive cycle length of 180 msec in (A). Note the shorter duration of action potential in the presence of ketamine and that this is more marked at high frequencies. (Calibration scale 100 msec, and 10 mV per division.]

**TABLE II.** The effect of ketamine 5×10⁻⁴M on driven action potentials (mean values and SEM†).

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<th>Control</th>
<th>5×10⁻⁴M ketamine</th>
</tr>
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<tr>
<td>Beat interval (msec)</td>
<td>1009.0±4.1</td>
<td>1009.0±4.1</td>
</tr>
<tr>
<td>Action potential duration (msec)</td>
<td>374.5±15.02</td>
<td>253.6±10.92†</td>
</tr>
<tr>
<td>Resting membrane potential (mV)</td>
<td>-94.6±2.08</td>
<td>-92.5±5.89</td>
</tr>
<tr>
<td>Total action potential height (mV)</td>
<td>119.0±2.15</td>
<td>117.9±5.12</td>
</tr>
<tr>
<td>Diastolic depolarization (mV)</td>
<td>1.2±0.62</td>
<td>4.3±0.72*</td>
</tr>
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</table>

*P<0.01; †P<0.001; ‡SEM for n=8 from Student t-test.
previous work in this laboratory to have little effect by itself on such driven preparations, consistent with the cell depicted in figure 4. Occasionally it was noted that when electrically driven cells were exposed to $5 \times 10^{-4} \text{M}$ ketamine, a few spontaneous action potentials appeared between the driven potentials despite the absence of applied adrenaline (fig. 4(b)).

**DISCUSSION**

Using a preparation essentially similar to that of Gettes and Surawicz (1968) and Gettes, Morehouse and Surawicz (1972) ketamine produced marked, reversible, dose-related changes in transmembrane potentials in both spontaneously active and driven conditions. It was observed that the phases of both depolarization and repolarization were affected and that the duration of the action potential was the parameter most consistently altered. The rate of repolarization was increased so that the duration of the action potential was significantly shortened in both spontaneously active and electrically driven preparations exposed to $5 \times 10^{-4} \text{M}$. In preparations driven at a slow rate of about 1 Hz, it was noted that spontaneous activity developed between the evoked potentials, signifying that either a spontaneous pacemaker was “firing” more frequently or that new ectopic foci had arisen and were sending impulses throughout the moderator band. The latter is suggested by the results from two different moderator bands exposed two and five times to $5 \times 10^{-4} \text{M}$ ketamine which suggest that this agent can allow a cell to develop pacemaker activity in a reversible and reproducible manner. The marked augmentation by ketamine of the response to a small dose of adrenaline, in which many extraneous action potentials appeared between the evoked potentials, indicates a possible predisposition to tachyarrhythmia and an arrhythmogenic potentiality (Parke-Davis Monograph, 1971; W.E.G.A. Spoerel, personal communication).

In the light of these results it is interesting to note that reports in the literature suggest that ketamine may have negative or positive inotropic and chronotropic actions (Goldberg, Keane and Phear, 1970; Traber, Wilson and Priano, 1968; Dowdy and Kaya, 1968). In addition, the drug has been claimed paradoxically as being both antiarrhythmic (Goldberg, Keane and Phear, 1970; Dowdy and Kaya, 1968) and arrhythmogenic (Parke-Davis Monograph, 1971). The ability of a preparation exposed to ketamine to follow a more rapid frequency of stimulation without the production of incomplete action potentials is consistent with it allowing a positive chronotropic response and yet being antiarrhythmic on account of an increased rate of repolarization of the cell permitting regular though increased frequency without the development of decremental conduction. However, this sign of improved rate of conduction through the Purkinje system can be taken as a warning that more impulses may be conducted per unit time to the ventricles and as evidence of the likelihood that the drug will cause arrhythmias. The development of additional ectopic foci (developing during a delayed repolarization during recovery from large doses of ketamine in spontaneous preparations) suggests, on the other hand, an explanation for isolated reports of arrhythmias.

The changes in action potential contour after ketamine are similar to those shown to occur after exposure to digitalis (Varsalle, Karis and Hoffman, 1962; Hoffman and Singer, 1964; Hoffman, 1966) and include changes in repolarization and, at higher frequencies, shortening of the action potential duration. In addition, under certain conditions, ketamine, like digitalis, encourages the development of phase 4 depolarization and may lead to multifocal pacemaker-like activity as described above.
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A sympathomimetic action of ketamine is also possible in that changes observed in the pig with ketamine and catecholamines in this study have also been observed with catecholamines in the dog (Hoffman and Cranefield, 1960). Ketamine in large concentrations, and the catecholamines, are capable of shortening the duration of the action potential, encouraging the development of phase 4 depolarization, and producing pacemaker-like activity. However, during exposure to low concentrations of ketamine phase 4 depolarization is prolonged and its rate of increase is reduced—under conditions in which the threshold for the initiation of phase 0 is significantly elevated. At these small concentrations of ketamine the duration of the action potential is prolonged initially, but even during continuing exposure the duration decreases and the frequency increases. This might suggest a delayed involvement of catecholamines. Lundy, Colhoun and Gowdey (1973) have shown that intravenous injections of ketamine in the dog can lead to a release of biogenic amines into the circulation. It is possible that a large component of the effect which we have observed, may be the result of catecholamine release. The observation in figure 2 that the initially slowed potentials returned toward normal despite the continued presence of ketamine may be taken as evidence for a delayed accumulation of catecholamine or some other positive chronotropic agent at the receptor sites. The presence of nerves in close proximity to the conduction elements in the mammalian heart were described by Wilson as early as 1909, and catecholamine-containing nerve fibres in the moderator band of the pig have been described recently (Bojsen-Moller and Tranum-Jensen, 1971).

The prolonged action potentials seen during recovery from ketamine in the spontaneous preparation are similar to those described by Trautwein (1970) in the dog preparation exposed to small concentrations of potassium in the extracellular fluid. The same author described shortening of Purkinje action potentials caused by increased concentrations of potassium. This may mean that ketamine has a biphasic effect on potassium conductance, initially increasing then decreasing the permeability. The possible effects of ketamine on potassium flux are interesting because of the similarities between the effects of ketamine and digitalis on this preparation and the known reciprocal interaction of digitalis and potassium.

Veratrine might also produce actions on this preparation similar to those of ketamine. Veratrinic agents have been shown to alter the time-course of repolarization so that new impulses originate during greatly prolonged phases 2 and 3, and that oscillatory activity can be observed (Frank, 1958). Often during the action of or recovery from ketamine prolonged phases of repolarization were observed and, sometimes, oscillatory activity was observed (fig. 2, section F). Also, in a previous study in this laboratory (Hamilton et al., 1972) a veratrinic action was implicated in the observed potentiation by ketamine of the single maximal twitch height of a curarized skeletal muscle preparation.

This study offers an explanation for the clinical observation that tachycardia may occur in association with ketamine in the hyperthyroid patient (Kaplan and Cooperman, 1971), particularly as both ketamine and hyperthyroidism can decrease the duration of the cardiac action potential (Vaughan-Williams, 1970).

If 1% w/v intravenous solutions of ketamine are employed (equivalent to $3.6 \times 10^{-2}$M) it is possible that concentrations as great as those shown to cause the above effects may be attained. Moreover, if biogenic amines are involved in the action of ketamine, any concomitant medication which increases or decreases their availability or action might be expected to affect the cardiac action of ketamine.

ACKNOWLEDGEMENTS
This study was supported by a grant-in-aid to J.T.H. from the Medical Research Council of Canada (Term Grant MT1216) and from the Ontario Heart Foundation.

The authors wish to thank Dr D. A. McCarthy, Director of Pharmacological Research (Parke, Davis & Company), for generous supplies of ketamine hydrochloride and Dr C. W. Gowdey, Head of the Department of Pharmacology, for invaluable assistance and helpful criticism in the preparation of the manuscript.

REFERENCES


Parke-Davis (1971). Formulary Monograph, Ketalar® (Ketamine HCl).


GLASGOW AND WEST OF SCOTLAND SOCIETY OF ANAESTHETISTS

PROGRAMME 1974–75

1974

SATURDAY, OCTOBER 26. (Lister Surgical Lecture Theatre, Edinburgh Royal Infirmary, 5 p.m.) Combined meeting with Edinburgh and East of Scotland Society of Anaesthetists. Dr L. F. Prescott: "Recent Advances in the Treatment of Overdoses".

TUESDAY, DECEMBER 3. Members' Night. Division of Anaesthesia, Western Infirmary, Glasgow. (This meeting will be held in the new Phase 1 Block, at the Western Infirmary.)

1975

WEDNESDAY, JANUARY 22. Mr P. E. Ghadiali, Consultant Clinical Physiologist, Brompton Hospital. "Some Cardiovascular and Pulmonary Aspects of Shock".

THURSDAY, FEBRUARY 13. Dr P. J. F. Baskett, Consultant Anaesthetist, Frenchay Hospital, Bristol. "Immediate Care".

WEDNESDAY, MARCH 12. Dr W. Auld: Presidential Address.

TUESDAY, APRIL 15. Annual General Meeting.

Unless otherwise stated, meetings will be held at the Royal College of Physicians and Surgeons of Glasgow, 242 St. Vincent Street, at 8.15 p.m.

Honorary Secretary: Dr A. G. Macdonald, Division of Anaesthesia, Victoria Infirmary, Glasgow, G42 9TY.