# EFFECT OF ANTIDYSRHYTHMIC AND ANALGESIC DRUGS ON HAEMODYNA-MICS AND FIBRILLATORY THRESHOLD

Pages with reference to book, From 141 To 145

Shahid Rashid ( Present Address: Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi-32. )


## Abstract

Ten drugs with antidysrhythmic and analgesic properties were evaluated for their ability to increase the ventricular fibrillating threshold (V.F.T.) in pentobar-bitone-anaesthetized cats by the electrically induced ventricular fibrillation method. The effects of this procedure on general haemo-dynamic parameters have already been published (Rashid, 1980).

Quinidine, pentazocine, propranolol, procainamide, pethidine and indoramin raised V.F.T. by 100% or more. These drugs had a minimal effect on haemodynamics except for propranolol and indoramin which significantly depressed these parameters. Meptazinol, D.P.H. and lignocaine raised V.F.T. by 92%,78%, 64% and34%respectively. No significant side effects of these drugs were noticed. The data indicates that the analgesics pentzaocine, pethidine and meptazinol, unlike morphine, were effective in raising the V.F.T. at doses causing minimal disturbance of cardiovascular dynamics in this experimental model. Pentazocine was shown to possess the best antidysrhythmic profile against electrically-induced ventricular fibrillation.

The mode of action of all the test drugs used in this method and the suitability of this procedure for primary screening of potential antidysrhythmic agents are discussed (JPMA.31:141, 1981).


## Introduction

The most serve disorder of cardiac rhythm is ventricular fibrillation which completely disorganized cardiac activity.

Contractions of the heart cease to be coordinated and the effectiveness of the pumping action is lost resulting in circulatory collapse. Undulating irregular waves appear in the E.C.G. in place of the characteristic rhythmic waves. The development of this condition is based on the capability of the myocardium to initiate electrical excitability simulatneously in different parts of the heart muscle which are normally regularized by the dominant impulse centre located in the sino atrial node (Szekeres and Papp, 1971), and this causes uncoordinated independent contractions at various areas of the ventricle surface.

Sudden electrical shock may precipitate ventricular fibrillation in humans (Wiggers, 1940) or the condition may arise during cardiac catheterization when preparations are belg made to electrically pace the heart (Braunwald et al., 1964). To counteract the sudden onset of ventricular fibrillation, defibrillators are commonly used in clinical practice, but it has been shown in experimental studies that drugs such as B-adreno-ceptor antagonists (Wellens and Wauters, 1972; Baum et al., 1972), UM 272 (Kniffen, et al., 1973), tyramine (Wellens and Wauters, 1973) and quinidine (Lawson and Wojciechowski, 1974), are useful either in reversing ventricular fibrillation or elevating the ventricular fibrillating thershold induced by electrical stimulation.

In this presentation 10 antidysrhythmic and analgesic drugs are evaluated in respect of their efficacy for elevating the ventricular fibrillatory threshold (V.F.T.) and their effects on general haemodynamic parameters using electrically induced ventricular fibrillation technique.

## Methods

A detailed method for this technique has already been published elsewhere (Rashid, 1980). Briefly, cats of either sex weighing 1.6-3.0 Kg were anaesthetized with pentobarbitone sodium (30 mg/kg) and prepared for general haemodynamic studies as described by Alps et al (1972). Ventricular fibrillation was produced by indirect stimulation of the left ventricular myocardium without thoracotomy (Rashid and Alps, 1973; Rashid, 1980).

Animals were left for 30 minutes after surgery for establization of cardiovascular parameters. The control threshold fibrillatory voltage was established three times in each animal before injecting the test drugs. Ten minutes after the intravenous administration the haemodynamic parameters were recorded and then the threshold electrical fibrillation stimulus was again applied. If fibrillation was not ensued at threshold voltage, the voltage was increased till fibrillation was produced. The percentage increase from threshold voltage was calculated which showed the resistance offered by the test drug.

## Results

### (a) Ventricular fibrillating threshold (V.F.T):

The effect of all test drugs on the ventricular fibrillatory threshold (V.F.T.) is shown in

Table : The Effect of 10 Test Drugs on V.F.T. and General Haemodynamic Parameters. These Results were calculated 10 Minutes after I.V. Administration of Test Drug and Approximately 30 Minutes after the dast Episode of Electrically Induced Ventricular Fibrillation. (n=4).

| No. | Drugs | Mean dose mg/kg | %+ve change in V.F.T. | Change in B.P. mmHg | % Change H.R. | % Change L.V.C. | % Change C.O. | % Change C.E.I. | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Quinidine | 5 | 253 | 0/+4 | —4 | +7 | —7 | ↓—18 | 30 mmHg |
| 2. | Pentazocine | 5 | 236 | ↓+ 9/—33 | —9 | ↓—10 | —1.6 | ↓—21 | change in dia- |
| 3. | Propranolol | 6.6 | 233 | ↓—36/—33 | ↓—28 | ↓—37 | ↓—31 | ↓—46 | diastolic blood |
| 4. | Procainamide | 10 | 169 | — 2/—3 | ↑ +20 | —2.5 | ↑—24 | ↑ +15 | pressure and |
| 5. | Pethidine | 10 | 142 | + 1/+ 17 | +5 | ↓—17 | ↑ +71 | —3 | 10% change |
| 6. | Indoramin | 1 | 100 | ↓—30/—30 | ↓—16 | ↓—16 | ↓—16 | ↓—38 | in other para- |
| 7. | Morphine | 18 | 92 | ↓—68/—75 | +3 | ↓—33 | ↑ +38 | ↓—39 | meters from |
| 8. | Metpazinol | 12 | 78 | +16/+8 | —3 | ↓—24 | ↑ +40 | +2.0 | control were |
| 9. | D.P.H. | 12 | 66 | +12/+7 | —4 | ↓—12 | ↓—15 | ↓—10 | regarded as |
| 10. | Lignocaine | 5 | 44 | —34/—22 | —6 | +4 | ↓— 20 | ↓—23 | meaningful. |

B.P. =Blood pressure (mmHg)
C.E.I. =Cardiac effort index (% of control)
C.O. =Cardiac output (% of control)
H.R. =Heart rate (% of control)
L.V.C. =Left ventricular contractility (% of control)
V.F.T. =Ventricular fibrillatory threshold (% of control)
↓ =Decrease) Arrows denotes only meaningful changes.
↑ =Increase) See remarks.

Table I Propranolol (6.6 mg/kg), quinidine (5 mg/kg) and procainamide (10 mg/kg) were effective in increasing the V.F.T. upto 233%, 253% and 169% of control values respectively. Each dose was administered at about 30 minutes interval to allow the animal to recover form the electrical shock. The maximal increase in V.F.T., with low dose produced by indoramin (1 mg/kg) was 100. D.P.H. (12 mg/kg) and lignocaine (5 mg/kg) were only slightly active.

The analgesic drugs, meptazinol (12 mg/kg), morphine (18 mg/kg), pentazocine (5 mg/kg) and pethidine (10 mg/kg) were also active in increasing V.F.T. The greatest increase in V.F.T. (236% above control) and smallest increase (78% above control) were produced by pentazoncine and meptazmol respectively.

### (b) General haemodynamics:

Mean data on the effects of these drugs on cardiovascular function is shown in Table I. Changes occurring 10 minutes after the dose injection of the test drug which was effective in increasing the

V.F.T., are also shown in this table.

**(i) Blood pressure:**

Propranolol (6 6 mg/kg), Lignocaine (5 mg/ kg) and indoramin (1 mg/kg) produced a significant decrease in systolic and diastolic blood pressure, whereas quinidine, procainamide and D.P.H. produced very little change from control values. In the analgesic group only morphine produced servere depression of both sytolic and diastolic blood pressure, whereas meptazinol and pethidine slightly increased these values. A slight increase of the systolic and a significant decrease of the diastolic blood pressure was seen after pentazoline (5 mg/kg).

**(i) Heart rale:**

Lignocaine, quinidine (5 mg/kg) and D.P.H. had no effect on the heart rate whereas propranolol (6.6 mg/kg) and indoramin (1/mg/kg) decreased the rate. Procainamide produced a 20% increase in heart rate.

Morphine and pethidine induced a small increase in heart rate but meptazinol and pento-zoline were without significant effect.

**(iii) Left ventricular contractibility (L.V.C.):**

L.V.C. was decreased by all the drugs tested except lignocaine and quinidine which showed a very slight increase. No marked changes from control values were caused by procainamide, D.P.H. and pentazocine but depression was seen after propranolol, morphine, meptazinol, indro-amin and pethidine.

**(iv) Cardiac output:**

Propranolol, lignocaine, D.P.H. and indro-ramin significantly depressed cardiac output whereas procainamide, meptazinol, morphine and pethidine significantly increased cardiac output, No appreciable changes was produced by quinidine and pentazocine.

**(v) Cardiac Effect Index (C'E'T):**

Slight decreases were recorded by pethidine and D.P.H. (3% and 10% respectively), whereas significant decreases were produced by propranolol, morphine, indoramin, lignocaine pentazocine and quinidine. Procainamide and meptazinol showed an increase in this parameter.

## Discussion

Antidysrhythmic drugs have been classified into two groups. Firstly, the agents acting indirectly on the myocardium through the autonomic nervous system. Propranolol and pronethalol (Beta receptor antagonists) seem to act more specifically in a way which is probably related to their degree of Beta adrenoceptor blockade (Willens and Wauters, 1972). Indoramin (Rashid and Alps, 1973) and peperoxane (Cookson et al., 1952) both adrenoceptor antagonists have been shown to successfully reverse ventriuclar fibrillation induced by hypothermia. In the present studies, propranolol and indoramin successfully increased the V.F.T.

These results confirm the findings that propranolol has increased the V.F.T. (Baum et al., 1972; Wellens and Wauters, 1972). Other Beta adrenocepter blocking agents like pronethalol, LB 46 and Bunolol behaved similarly. These were more potent than propranolol but exerted smaller effect in increasing the V.F.T. than propranolol (Baum et al., 1972).

Propranolol did not show any significant effect on haemodyanic function in dogs at doses which increased the V.F.T. (Baum et al., 1972). The effect of propranolol on changes in cardiac output, left ventricular contractility and cardiac effort index induced by electrical stimulation in the cat have not previously been reported in the literature. In the cat experiments described here, all of the haemodynamic parameters were significantly depressed by propranolol. Propranolol also reduced 02 consumption in these experiments as estimated indirectly by measurement of the cardiac effort index (Parratt and Wadsworth, 1970).

The second group of antidysrhythmic drugs act directly on the myocardium. Quinidine and quinidine like drugs appear to act directly on the heart muscle to produce their antifibrillating effects. Quindine was shown to increase the V.F.T. in the present studies and was the most potent of all the drugs tested. These findings are contrary to the findings of Lawson and Wojciechowski (1974) in which quindidine failed to produce a significant change in V.F.T. but are in accordance with findings of Baun et al. (1971), and Szekeres and Papp (1971).

Procainamide also increased the V.F.T. in the present studies, but was less effective than propranolol or quinidine. These results were confirmed by the findings of Baum et al (1971) that 50 mg/kg procaniamide was needed to obtain a similar effect as that of 15 mg/kg of quinidine. These results were also confirmed in isolated heart tissue preparations (Vaughan Williams and Szekeres, 1961) in which procainamide was less active than quinidine in increasing the fibrillation threshold, though the regression lines relating response and log dose were similar to quinidine.

The antifibrillatory effects of analgesics have not been recorded in the literature though analgesics such as morphine and pentazocine are commonly used in myocardial infarction. Meperidine (Pethidine) is not active in ventricular fibrillation induced by electrical stimulation (Baum et al., 1971). Pentazocine has been reported to have local anaesthetic activity and have a direct depressant action on the myocardium (Fogarty et al., 1970). These actions might explain the effectiveness of pentazocine in increasing the V.F.T. as seen in the present studies and in this respect the compound is more active than morphine, pethidine and meptazinol. Pentazocine has also been reported to increase A-V nodal and intra-ven-tricular conduction and cause modest depression of enhanced ventricular automaticaity (Hayakawa et al., 1973).

Morphine and pethidine reduce the response to sympathetic nerve stimulation (Montel and Starke, 1973). Both drugs block the noradrenaline transport system of the adrenergic neuronal membrane. During electrical stimulation nor-drenaline is released from the sympathetic nerve stores and the naroctic andalgesic drugs in low concentrations reduce the response to sympathetic nerve stimulation, probably by a depression of transmitter release. Antagonists of analgesic drug have been shown to counteract this inhibition (Trendelenburg, 1957). Perhaps uptake inhibition by these two drugs is responsible for their effect in increasing V.F.T.

It is evident from experiment on isolated ventricular tissue (Rashid and Waterfall, 1979a) that meptazinol is quite active in increasing the effective refractive period and this property may partly explain the activity of this compound. After lignocame, D.P.H. was the next most weakly active drug to cause elevation of V.F.T. in the present studies. It was found that D.P.H. was not very active in increasing the effective refractive period in isolated atrial preparations. The activity of D.P.H. (66% increase in V.F.T.) could however be explained by its action in reducing the sympathetic nervous system nerve discharge and perhaps reducing the output of transmitters from these nerves.

**Effect of Analgesic Drugs on General Haemody namics:**

All of the general ahemodynamic parameters were severely depressed by morphine except for cardiac output and heart rate which showed an increase. These findings have also been reported to be true for the clinical (Lal et al. 1969) as well as for the experimental situation (Grundy, 1971). Pentazocine, meptazinol and pethidine only slightly depressed these parameters, thus supporting the observations of Nagle and Pilcher (1972) and M ller et al, (1972) for the clinical situation and confirm the findings of Hayakawa, et al (1973) and Fogarty et al (1970) in experimental studies.

When analgesics especially pethidine are administered to anaesthetized cats the predominant effect is hypotension although it may be preceded by a pressor effect due to the release of catecholamines from the adrenal medulla (Evans et al., 1952). The initial rapid fail is chiefly due to histamine release in this species (Feldberg and Paton, 1951) and is followed by a longer period of hypotension during which the blood pressure slowly recovers. This phenomenon occurred also in the present studies with pethidine. A 10% increase in diastolic blood pressure and 15% increase in heart rate was observed with pethidine in healthy men (Tammisto et al., 1970), but a biphasic response was seen after the administration of the

drug to patients suffering from myocardial infarction (Rees et al., 1967). These findings are substantiated by the present exeri-mental studies in cats in which pethidine increased diastolic blood pressure by 17 mm Hg and heart rate by 5%. This was also true for meptazinol which increased blood pressure by 16/8 mm Hg.

Cardiac effort index is a major factor warranting close attention in the dysrhythmic condition as it reflects 02 consumption by the myocardium. A reduction in 02 consumption (reduced cardiac effort index) caused by any drug is a good sign predicting recovery. Morphine and pentazocine decreased the cardiac effort index, but morphine would not be considered as a drug of choice under the present clrcumsta ances since although it produced a 92% increase in the V.F.T., it caused severe reduction of blood pressure. Morphine is also a powerful respiratory depressant. Pentazocine and pethidine may be considered but preference should be given to pentazocine for the reason that it has less depressive effects on the cardiopulmonary system in man (Lal et al., 1969). Considering meptazinol in this regard, there is little clinical data available to judge its effect on the cardiopulmonary system of man. But as with pentzaocine in animal experiments it antagonises morphine-induced respiratory depression and produces relatively little overall effect on cardiovascular function (Rashid and Waterfall 1979b).

Whereas pentazocine showed a greater effect in raising the V.F.T. than meptazmol in the present experiments, and of the analgesics tested presented the best overall antidysrhythmic profile in this experimental model, meptazinol can be considered to be as good as pethidine and both of these are to be preferred to morphine. Pethidine, however, must again be viewed with cuation in the light of its respiratory depressant action in animals and men.

The conclude, the electrically-induced ventricular fibrillation method described here simulates the clinical condition. If a drug can be shown to have no adverse effect on general haemody-namic factors and is also capable of raising the V F.T., it is possible that this drug may stand a good chance being useful clinically in the treatment of the cardiac consequences of electrical shock.

This method also fulfills the requirements for a basic screening technique for detection of potential antidysrhythmic drugs. The experimental findings correlate well with the clinical efficacy of antidysrhythmic drugs to a greater extent than the technique of inducing dysrhythmia by ouabain (Baum et al., 1971). Szekeres and Papp (1971) also recommended this method for the routine screening of antidysrhythmic drugs and to be of clinial value for establishing the antidysrhythmic profile of the compound tested.

**Refrences**

1. Alps, J.B., Borrows, E.T., Johnson, E.S., Staniforth, M. and Wilson, A.B. (1972) A comparison of the cardiovascular actions of indoramin, propranolol, lignocaine and quinidine. Cardiovasc. Res., 4:226.
2. Baum, T., Eckfeld, D.K., Shropshire, A.T., Rowles, G. and Varner, L.L. (1971) Observation on models used for the evaluation of antiarrhythmic drugs. Archs. Int. Pharmacodyn. Ther., 193:149.
3. Baum, T., Peters, J.R., Eckfeld, D.K., Varner, L.L., Metz, N. and Shropshire, A.T. (1972) Elevation of ventricular fibrillatory threshold by beta adrenergic blocking agents. Arch. Int. Pharmacodyn. Then, 200:292.
4. Braunwald, E., Ross, J., Frommer, P.L., Williams, J.F. Jr., Sonnenblick, E.H. and Gault, J.H. (1964) Clinical observations on paired electrical stimulation of the heart. Effects on ventricular performance and heart rate. Am. J. Med., 37:700.
5. Cookson, B.A. Neptune, W.B. and Bailey, C.P. (1952) Hypothermia as a means of performing intracardiac surgery under direct vision, Dis. Chest, 22:245.
6. Evans, A.G.J., Nasmyth, P.A. and Stewart, H.C. (1952) The fall of blood pressure caused by intravenous morphine in the rat and the cat. Br. J. Pharmaca., 7:542.
7. Feldberg, W. and Paton, W.D.M. (1951) Release of histamine from skin and muscle in the cat by

opium alkaloids and other histamine liberators. J. Physiol. (Lond.), 114:409.
8. Fogarty, M., Gill, D., Hill, P. and Pettit, T. (1970) Cardiovascular effects of pentazocine in rabbits. Br. J. Pharmacol., 40:151.
9. Grundy, H.F. (1971) Cardiovascular effects of morphine, pethidine, diamorphine and nalorphine on the cat and rabbit. Br. J. Pharmacol., 42:159.
10. Hayakawa ,H., Mandel, W.J., Vyden, J.K., Parmley, W.W., Corday, E., Mccullen, A. and Allen, D. (1973) Pentazocine, haemodynamic and electrophysiological properties. J. Clin. Pharmacol., 13:313.
11. Kniffen, F.J., Schuster, D.P. and Lucchesi, B.R. (1973) Antiarrhythmic and electrophysiologic properties of UM-272, dimethyl quanternary propranolol in the canine heart. J. Pharmacol. Exp. Then, 187:260.
12. LAL, S., Savidge, R.S. and Chhabra, G.P. (1969). Cardiovascular and respiratory effects of morphine and pentazocine in patients with myocardial infarction. Lancet, 1:379. J.P.M.A. July 1981
13. Lawson, J.W. and Wojeiechowski, N.J. (1974) Interaction of quanidine and propranolol on vulnerability of the ventricle to electrical fibrillation. Arch. Int. Pharmacodvn. Ther., 207:231.
14. Miller, H.C, Mcleod, A., Kibry, B.J., Soott, D.B. and Julian, D.G. (1972) Effect of pentazocine on pulmonary circulation. Lancet, 2:1167.
15. Montel, H. and Starke, K. (1973) Effects of narcotic analgesics and their antagonists on the rabbit isolated heart and its adrenergic nerves. Br. J. Pharmacol., 49:628.
16. Nagle, R.E. and Pilcher, J. (1972) Respiratory and circulatory effect of pentazocine. Review of analgesics used after myocardial infarction. Br. Heart J., 34:244.
17. Parratt, J.R. and Wadsworth, R.M. (1970) The effect of catecholamine infusions on myocardial blood flow, metabolic heat production and on general haemodynamics, before and after alprenolol (H 56/28), in anaesthetized cats. Br. J. Pharmacol., 38:553.
18. Rashid, S. and Alps, B.J. (1973) Further observations on the experimental antidysrhythmic activity of indoramin hydrochloride. J. Pharm. Pharmacol., 25:700.
19. Rashid, S. and Waterfall, J.F. (1979) Cardiovascular actions of meptazinol in comparison with pentazocine and morphine. Gen. Pharmacol., 10:459.
20. Rashid, S. and Waterfall, J.F. (1979) Effect of antiarrhythmic and analgesic drugs on the effective refractory priod of guinea-pig isolated atria and ventricular strips. J. Pharm. Pharmacl., 31:411.
21. Rasid, S. (1980) Electrically induced ventricular fibrillation. Pakistan Heart J., 13:10.
22. REES, H.A., Muir, A.L., Mcdonald, H.R., Lawrie, D.M., Burton, J.L. and Donald, K.W. (1967) Circulatory effects of pethidine in patients with acute myocardial infarction. Lancet, 2:863.
23. Szekeres, L. and Papp, J.G. (1971) Experiencmental cardiac arrhythmias and antiarrhythmic drugs. Akademiai Kiado Budapest.
24. Tammisto, T., Takki, S. and Toikka, P. (1970) A comparison of the circulatary effects in man of the analgesics fentanyl, pentazocine and pethidine. Br. J. Anaesth., 42:317.
25. Trendelenburg, U. (1957) The action of morphine on the superior cervical ganglion and on the nictitationg membrane of the cat. Br. J. Pharmacol., 12:79.
26. Vaughan Williams, E.M. and Szekeres, L. (1961) A comparison of tests for antifibrillatory action. Br. J. Pharmacol, 17:424.
27. Wellens, D. and Wauters, E. (1972) Modification of ventricular fibrillation threshold after sympatholytic drugs in the dog. Arch. Int. Pharmacodyn. Ther., 198:355.
28. Wellens, D. and Wauters, E. (1973) Tyramine-induced modifications of ventricular fibrillation on dog. Influence of sympatholytic agents. Arch. Int. Pharmacodyn. Ther., 201:253.
29. Wiggers, C.J. (1940) The mechanism and nature of ventricular fibrillation. Am. Heart J. 20:399.