EFFECT OF PROPRANOLOL ON THE VENTRICULAR ARRHYTHMIAS INDUCED BY HYPERCARBIA DURING HALOTHANE ANAESTHESIA IN MAN

BY
KAZUAKI FUKUSHIMA, TATSUSHI FUJITA, TAKANORI FUJIWARA, HIROSHI OOSHIMA AND TETSUO SATO

SUMMARY
The effects of propranolol on arterial blood pressure, heart rate, and cardiac rhythm during ventricular arrhythmias initiated by hypercarbia were investigated in thirteen subjects during 1 per cent halothane anaesthesia. Propranolol was consistently effective in the treatment of ventricular arrhythmia induced by hypercarbia in all subjects. The successful use of propranolol suggests that the mechanism for ventricular arrhythmia produced by respiratory acidosis during halothane anaesthesia was related to beta adrenergic receptors. Blockade of these receptors by beta adrenergic agents decreased markedly the sensitization of myocardium to sympathetic stimulation.

It is well recognized that ventricular arrhythmia may be produced during anaesthesia with halogenated hydrocarbons. This phenomenon, which was first discovered by Levy and Lewis (1911), has led to considerable investigation. Several theories have been advanced concerning its cause but the subject is still controversial.

Johnstone and Nisbet (1961) concluded that carbon dioxide is one of the factors concerned in the production of ventricular arrhythmia during halothane anaesthesia in humans. Muir, Hall and Littlewort (1959) observed ventricular extrasystoles during halothane anaesthesia in underventilated cats. Price and his co-workers (1958) have demonstrated that arrhythmias associated with hypercarbia during cyclopropane anaesthesia were caused by liberation of catecholamines from sympathetic nerve endings in the myocardium.

Several investigators (Hellewell and Potts, 1965; Johnstone, 1964; Katz, 1965; Moran et al., 1962; Murray, McKnight and Davis, 1963; Payne and Senfield, 1964; Purchase, 1966; Schull, Berry and Villarreal, 1961) have successfully used beta adrenergic blocking agents, dichloroisoproterenol (DCI), pronethalol (Nethalide), or propranolol (Inderal), in the treatment of ventricular arrhythmias following administration of catecholamines during halothane anaesthesia.

The present communication describes an investigation of the value of the beta adrenergic agent propranolol (Inderal) in the treatment of ventricular arrhythmia induced by hypercarbia during halothane anaesthesia in man.

The threshold levels of arterial carbon dioxide tension and pH required to produce ventricular arrhythmias secondary to respiratory acidosis during halothane anaesthesia were determined in each study.

METHOD
Thirteen adult patients who were premedicated with moderate doses of pentobarbitone, pethidine, and atropine were studied. The operations were mainly orthopaedic, but a few were gynaecological procedures. The ages of the patients ranged from 13 to 45 years and all were otherwise considered normal on the basis of history and physical examination. In all cases sleep was induced with thiopentone 200–300 mg intravenously and the trachea intubated following the intravenous administration of suxamethonium chloride. Anaesthesia was maintained with halothane 1 per cent, nitrous oxide 4 l./min and oxygen 2 l./min, using a Fluotec placed outside the circle absorption system. A Wright respirometer (BOC) was connected to the inspiratory side of the anaesthetic system to measure ventilation. Respiration was assisted or controlled by manual compression of the reservoir bag in such

This paper was presented on September 2, 1966, at the 2nd Asian and Australasian Congress of Anesthesiology, Tokyo, Japan.
Case 10
BP 120/80, HR 110, pH 7.43, Pco₂ 35.5
CONTROL (1% FLUOTHANE)

BP 100/80, HR 120, pH 7.10, Pco₂ 32.0
CO₂ INHALATION

BP 100/80, HR 94
INDÉRAL

BP 95/65, HR 86
After CO₂ DISCONTINUANCE

Case 13
BP 120/80, HR 80, pH 7.36, Pco₂ 36.1
CONTROL (1% FLUOTHANE)

BP 125/80, HR 84, pH 7.04, Pco₂ 31.0
CO₂ INHALATION

BP 90/65, HR 64
After CO₂ DISCONTINUANCE
EFFECT OF PROPRANOLOL ON THE VENTRICULAR ARRHYTHMIAS

a way as to maintain the arterial carbon dioxide tension within normal limits. Carbon dioxide was added to the anaesthetic system at rates ranging from 800 ml/min to 1000 ml/min. Further, in order to enhance the increase in arterial carbon dioxide tension, the soda-lime canister was removed from the system.

The systolic and diastolic blood pressures were measured by the auscultatory (Riva-Rocci) method at appropriate intervals. Lead 2 electrocardiogram was monitored continuously and recordings were obtained at appropriate intervals.

Arterial blood samples were collected anaerobically on two occasions in each patient. The first sample was drawn when the patient was judged to be in a steady state of anaesthesia and the second when ventricular arrhythmia first appeared during carbon dioxide inhalation. Values for pH, \( P_{CO_2} \) and \( P_{O_2} \) were determined with an Instrumentation Laboratories Model 113 meter.

When ventricular arrhythmias appeared during carbon dioxide administration, propranolol 3–5 mg as a 0.1 per cent solution was administered intravenously.

RESULTS

During the steady state, the average arterial blood pressure was 113/75 mm Hg and the heart rate was 86 beats/min. Arterial carbon dioxide tension ranged from 25.0 to 45.2 mm Hg (average 37.1 mm Hg) and arterial oxygen tension from 115 to 245 mm Hg (average 184 mm Hg). Arterial pH ranged from 7.30 to 7.46 (average 7.41). All subjects showed normal sinus rhythm on electrocardiogram.

The inhalation of carbon dioxide produced ventricular arrhythmias in all subjects during 1 per cent halothane anaesthesia. The arrhythmias consisted of unifocal premature ventricular contractions (3), multi-focal premature ventricular contraction (6), ventricular bigeminy (3), and ventricular tachycardia (1). While the heart rate averaged 86 beats/min during the control period, it increased to 104 beats/min (13 per cent increase) during the period of ventricular arrhythmias initiated by hypercarbia. There was noted a slight elevation in both systolic and diastolic blood pressure during ventricular arrhythmias compared to the control period, each increasing about 10 per cent. The average blood pressure was 113/75 mm Hg before hypercarbia and during the period of ventricular arrhythmia it averaged 125/75 mm Hg. The time at which ventricular arrhythmias first appeared ranged from 5 to 16 minutes (average 11 minutes) from the initiation of carbon dioxide administration. The arterial carbon dioxide tension associated with ventricular arrhythmias ranged from 72.0 to 98.2 mm Hg (average 86.1 mm Hg). Carbon dioxide inhalation was associated with a marked reduction in the average arterial pH from 7.41 to 7.10. The arterial pH associated with the ventricular arrhythmias ranged from 6.88 to 7.20 (average 7.10).

The intravenous administration of propranolol 3–5 mg abolished the ventricular arrhythmias in all subjects during hypercarbia. Ventricular arrhythmias reverted to normal sinus rhythms in each case within an average of 60 seconds after injection of propranolol. The intravenous injection of propranolol was followed by a decrease both in systolic and diastolic blood pressure in twelve of thirteen subjects. The average fall in arterial blood pressure was from 125/80 to 109/74 mm Hg. The heart rate decreased in all subjects with the average falling from 104 to 80 beats/min. Figure 1 shows the effect of propranolol on carbon dioxide-induced ventricular arrhythmia during anaesthesia with 1 per cent halothane in case Nos. 10 and 13 on lead 2 electrocardiogram.

The individual results concerning the effect of propranolol on carbon dioxide-induced ventricular arrhythmia during 1 per cent halothane anaesthesia on thirteen subjects are shown in table I. The threshold levels of arterial pH and carbon dioxide tension at which ventricular arrhythmias developed during 1 per cent halothane anaesthesia with carbon dioxide inhalation are shown in table II.

DISCUSSION

The production of ventricular arrhythmia following an increase in the arterial carbon dioxide tension...
Table I
Values before and during 1 per cent halothane anaesthesia, and after injection of propranolol in thirteen patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Control (before CO₂ inhalation)</th>
<th>1 per cent Halothane</th>
<th>CO₂ inhalation</th>
<th>Propranolol 3-5 mg i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP</td>
<td>HR</td>
<td>e.c.g.</td>
<td>pH</td>
</tr>
<tr>
<td>1</td>
<td>130/100</td>
<td>86</td>
<td>NSR</td>
<td>7.46</td>
</tr>
<tr>
<td>2</td>
<td>120/80</td>
<td>70</td>
<td>NSR</td>
<td>7.52</td>
</tr>
<tr>
<td>3</td>
<td>108/75</td>
<td>100</td>
<td>NSR</td>
<td>7.36</td>
</tr>
<tr>
<td>4</td>
<td>105/80</td>
<td>80</td>
<td>NSR</td>
<td>7.45</td>
</tr>
<tr>
<td>5</td>
<td>110/65</td>
<td>80</td>
<td>NSR</td>
<td>7.40</td>
</tr>
<tr>
<td>6</td>
<td>120/80</td>
<td>70</td>
<td>NSR</td>
<td>7.44</td>
</tr>
<tr>
<td>7</td>
<td>115/60</td>
<td>94</td>
<td>NSR</td>
<td>7.42</td>
</tr>
<tr>
<td>8</td>
<td>140/90</td>
<td>80</td>
<td>NSR</td>
<td>7.30</td>
</tr>
<tr>
<td>9</td>
<td>95/60</td>
<td>85</td>
<td>NSR</td>
<td>7.43</td>
</tr>
<tr>
<td>10</td>
<td>120/80</td>
<td>110</td>
<td>NSR</td>
<td>7.43</td>
</tr>
<tr>
<td>11</td>
<td>90/60</td>
<td>104</td>
<td>NSR</td>
<td>7.41</td>
</tr>
<tr>
<td>12</td>
<td>95/70</td>
<td>82</td>
<td>NSR</td>
<td>7.41</td>
</tr>
<tr>
<td>13</td>
<td>120/80</td>
<td>80</td>
<td>NSR</td>
<td>7.36</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>113±13</td>
<td>86</td>
<td>NSR</td>
<td>7.41</td>
</tr>
</tbody>
</table>

NSR = Normal sinus rhythm
VA = Ventricular arrhythmia
Unifocal premature ventricular contractions
Multifocal premature ventricular contractions
Ventricular bigeminy
Ventricular tachycardia

Downloaded from https://academic.oup.com/bja/article-abstract/40/1/53/245802 by guest on 30 July 2018
EFFECT OF PROPRANOLOL ON THE VENTRICULAR ARRHYTHMIAS

TABLE II
Threshold levels of arterial pH and Pco₂ at which ventricular arrhythmias appeared during 1 per cent halothane anaesthesia and carbon dioxide inhalation.

<table>
<thead>
<tr>
<th></th>
<th>Before carbon dioxide inhalation</th>
<th>Arrhythmia during carbon dioxide inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41 ± 0.05</td>
<td>7.10 ± 0.09</td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>37.1 ± 4.87</td>
<td>86.1 ± 8.23</td>
</tr>
</tbody>
</table>

tension during halothane anaesthesia is in agreement with previous reports (Johnstone and Nisbet, 1961; Payne and Senfield, 1964). Price and others (1958) have suggested, in relation to cyclopropane anaesthesia, the possibility that increased release of endogenous catecholamines at the sympathetic nerve endings in the myocardium is a cause of cardiac irregularities during hypercarbia. Millar and Morris (1961) pointed out that the plasma concentration of noradrenaline and adrenaline increased early as the arterial carbon dioxide tension rose during an initial stage of respiratory acidosis. They also speculated that this endogenous catecholamine release might play an important role in producing cardiac arrhythmia.

Nahas, Ligou and Mehlman (1960) concluded that a reduction in arterial pH may be the more important factor in liberating increased amounts of catecholamine during hypercarbia. Tenny (1960), however, concluded that there is no way to determine the relative importance of blood carbon dioxide tension as opposed to pH in stimulating sympathoadrenal activity, but suggested that a change in intracellular pH may be the true stimulus. In the present study, ventricular arrhythmias occurred early in the period of carbon dioxide inhalation.

The release of catecholamines from sympathetic nerve endings is not as marked during halothane anaesthesia as it is during cyclopropane anaesthesia (Price et al., 1958). This may account for the higher PaO₂ recorded at the onset of arrhythmia with 1 per cent halothane. Since propranolol is a beta adrenergic blocking agent, and the myocardium is known to be supplied mainly with beta receptors, it is reasonable to postulate that the arrhythmias were due to stimulation of these receptors. Arrhythmias can also be produced during halothane anaesthesia by the administration of catecholamines and their suppression by propranolol would point to a common cause. However, it remains possible that the intracellular pH change as a consequence of high PaO₂ is an important factor.

ACKNOWLEDGEMENTS

We wish to thank Dr. E. S. Siker, Director, Department of Anesthesiology, Mercy Hospital, Pittsburgh 19, Pa., U.S.A., for his help and advice on the manuscript. We are also grateful to Sumitomo Chemical Industries Ltd. for the supply of Inderal.

REFERENCES


ACTION DE PROPRANOLOL SUR LES ARRHYMIES VENTRICULAIRES, CAUSEES PAR L'HYPERCARBIE DURANT L'ANES- THESIE A L'HALOTHANE CHEZ L'HOMME

Les effets de propranolol sur la pression sanguine arterielle, la frequence des contractions et le rythme du coeur durant des arrhythmies ventriculaires, causeres par l'hypercarbie, ont ete etudies chez 13 sujets durant une anesthesie avec 1% d'halothane. Propranolol fut toujours efficace dans le traitement de l'arrhythmie ventriculaire par acidose respiratoire, est lie aux recepteurs beta adrenergiques. Le blocage de ces recepteurs par des agents adrener- giques beta a nettement reduit la sensibilisation du myocardie a la stimulation sympathique.

BOOK REVIEW


There are very few anaesthetists who, by virtue of both their practical experience and their academic interest, are fully informed of the part the specialty has to play in obstetric medicine, and who are prepared also to accept a role as teacher of obstetric analgesia and anaesthesia. Amongst this small band Dr. Bonica rightfully occupies a place of considerable esteem. His experience and enthusiasm, and his encyclopaedic knowledge of the subjects which hold his interest are proverbial in the United States, and amongst his many friends and acquaintances overseas. Accepting the fact of these qualities, it is easy to understand—although, regretfully, one cannot condone—his falling into a trap of his own making. In short, his book is much too maso- quic.

Bonica states in his Preface that the book is "intended to serve both as a textbook and a reference work" for all members of the medical and nursing professions whose work includes the care of the pregnant patient and of the newborn infant. The volume under review contains over 800 pages and the companion volume has yet to appear. Utilizing the odd half-hours from a reasonably busy life, the reviewer spent over two months reading the book from cover to cover, and he was not approaching it as a relative beginner or as a prospective examination candidate. Obstetric anaes- thesia is a very important subject (especially so in the U.S.A., where possibly as many anaesthesists are given for deliveries as are administered for all other surgical interventions), and the topic of obstetric analgesia deserves equally weighty consideration (neonatal resuscitation is not discussed in Volume 1), yet when a part shows signs of outgrowing the whole within which it has previously been contained, the resulting imbalance is surely unhealthy. In the writer's view, Bonica has allowed his enthusiasm to overshadow his sense of values.

The sheer mass of the book will probably be a deter- rent to the prospective learner in this field. This is not, however, an obstacle if the book is to be looked upon as a reference work, but herein lies a dilemma. As Bonica himself justly points out, the subject has been and is advancing at a tremendous pace. Observa- tions regarding the physio-pharmacology of pregnancy and parturition, the physiology of the perinatal period, and the response of the neonate (and foetus) to drugs and to various other stimuli, are recorded in bewildering numbers with each monthly issue of the scores of authoritative journals of obstetrics, paediatrics, anaes- thetics, physiology and laboratory medicine. Today, a book on this subject is in some measure out of date from the minute that the manuscript is despatched to the publisher, and the progress of decay is exponential down to a baseline of about one-third of the mass of data. Here, then, lies the pity of it, for Bonica states that he spent ten years evolving this book, and yet most of the data (other than the immutable one- third), whilst certainly not likely to be completely rejected, might well have to be presented from a different perspective, to emphasize fresh conclusions and to provide new guide-lines of practice, in order to satisfy the contemporary student in four or five years' time.

Some specific criticisms are, I believe, justifiable.

Firstly, and germane again to the question of size, it is surely unnecessary in a book concerned with only one branch of anaesthesia, to devote extensive space to consideration of: the uptake and distribution of general anaesthetic agents (10 pages); theories and signs of anaesthesia (5 pages); techniques of general anaesthesia, vaporizers, intubation of the adult, fire and explosion (12 pages); the pharmacological properties of systemically administered anaesthetic agents and their correct administration (93 pages); the pharmacology of local anaesthetics (7 pages); skeletal muscle relaxants (12 pages); the complications of general and local anaesthesia in the adult (19 pages); oxytocics and uterine relaxants (15 pages). Possibly a