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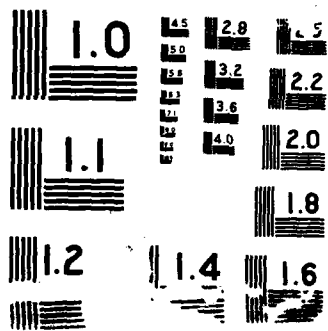
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**STUDY OF THE EFFECTS OF DRUGS UPON THE
CARDIOVASCULAR AND RESPIRATORY SYSTEM**

ANNUAL PROGRESS REPORT

by

Robert W. Caldwell

Clinton B. Nash

February 1, 1984

(January 1, 1983 ~ December 31, 1983)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

Contract No: DAMD17-83-C-3011

**University of Tennessee Center for the Health Sciences
Memphis, Tennessee 38163**

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<p>During this past year we have: 1. Performed pilot experiments to define the cardiopulmonary actions of the candidate drug, WR-6026 and re-examined the cardiopulmonary actions of primaquine. 2. Written a protocol to study the Cardiovascular and Pulmonary Effects of WR-6026. 2HC vs Primaquine. 2H₂PO₄. A copy of this protocol (originally submitted on 5 August, 1983) is attached (Section I). 3. Performed the entire experimental protocol for both drugs (WR-6026 and Primaquine). We are currently in the process of tabulating and analyzing data from these experiments. A comprehensive written report will be forwarded to our contract monitor at Walter Reed Army Institute of Research as soon as possible. A summary of our findings for these studies is attached (Section II). <i>Keywords: antimalarials; antileishmanials; blood pressure; electrocardiography</i></p>					
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Summary

During this past year we have:

1. Performed pilot experiments to define the cardiopulmonary actions of the candidate drug, WR-6026 and re-examined the cardiopulmonary actions of primaquine.
2. Written a protocol to study the Cardiovascular and Pulmonary Effects of WR-6026. 2HC vs Primaquine . 2H₃PO₄. A copy of this protocol (originally submitted on 5 August, 1983) is attached (Section I).
3. Performed the entire experimental protocol for both drugs (WR-6026 and Primaquine). We are currently in the process of tabulating and analyzing data from these experiments. A comprehensive written report will be forwarded to our contract monitor at Walter Reed Army Institute of Research as soon as possible. A summary of our findings for these studies is attached (Section II).



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FOREWARD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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Section I

PROTOCOL

Cardiovascular and Pulmonary Effects of WR-6026·2HCl vs Primaquine·2H₃PO₄

BACKGROUND

During World War II there was a great interest in developing new anti-malarial drugs. A very fruitful source of active compounds was found to be the 8-aminoquinolines. Early in the experimental studies of these agents it was noted that they had a wide variety of cardiovascular effects.

WR-6026 is an 8-aminoquinoline originally synthesized in the malarial research program during World War II. However, more recently this substance has been noted to be the most active antileishmanial compound tested in the WRAIR screening program from more than 3000 compounds. Because of its structural similarity to primaquine, one would expect similar cardiopulmonary actions between the two agents. This protocol describes experiments to make such a comparison.

The purpose of these experiments is to compare the effects of intravenous infusions of WR-6026 with those of primaquine upon the rhythm, electrical activity and the function of the heart; the pulmonary blood pressure and circulation; the systemic blood pressure and circulation; and the pulmonary ventilation, including blood oxygen, CO₂ and pH.

Previous Studies with WR-6026 -- According to Korte and Basmania (1981), the cardiopulmonary profile of WR-6026, determined following intravenous administration, was unique in that it produced urticaria and angioneurotic edema in the anesthetized dog. This response was hypothesized to be due to a non-

hypersensitive release of endogenous autocooids, such as histamine. The hypotensive effect of bolus injections of WR-6026 and the increase in hematocrit observed during a 45-minute infusion of WR-6026 were consistent with a hypothesis of histamine release. Infusion of WR-6026, 17.8 mg/kg over a 45-minute period, also produced a decrease in heart rate and prolongation of the PR, QTc and QRS intervals of the electrocardiogram similar to that observed with primaquine. WR-6026, like primaquine, may affect reflex sympathetic activity as it blunted the expected increase in pulse pressure and heart rate following carotid occlusion. However, unlike primaquine, WR-6026 did not attenuate the cardiopulmonary responses of isoproterenol.

In our initial studies with WR-6026 we wished to determine the range of dose-rates of the candidate drug that, in our preparation, produce either: (1) minor but perceptible changes in the cardiopulmonary variable, or (2) the most severe alterations in cardiovascular and pulmonary function short of death. Dogs were anesthetized and prepared as described in the protocol outlined later in this report. Following surgical preparation, application of monitoring instruments, and a period for stabilization of cardiopulmonary function, control values were recorded over a 30-minute period followed by intravenous infusion of drug or phosphate buffer vehicle at selected dose rates over a 20-minute period in a total volume of 80 ml.

Dose-rates initially selected for investigation were those, on a molar basis, which in our previous studies of candidate antimalarials produced definite but non-lethal cardiopulmonary effects. We have also been guided by information provided by Dr. Howard Lowensohn of WRAIR. Our results to date

indicate a much shallower dose-response curve than previously noted for primaquine (Interim Report No. 6, 10 November, 1980, contract number DAMD17-75-C-5043). A summary of findings in search of the highest tolerated dose-rate and minimum effect dose-rate follows:

A. Maximum tolerated dose-rate of WR-6026 -- Successive increases in dose-related in anesthetized dogs have 4 μ moles/kg/min is the maximum tolerated dose-rate. An infusion of 6 μ moles/kg/min produced death of both dogs so treated during the 20-minute drug infusion. An infusion rate of 5 μ mole/kg/min caused death in 3 out of 5 animals. There were progressive decreases in systemic arterial pressure, heart rate, left ventricular dP/dt max. and airway resistance with loss of effective cardiac function and arterial perfusion pressure by the end of the 20-minute period. Respiratory rate, minute volume, pulmonary wedge and pulmonary arterial pressure increased before death. Respiration ceased when arterial blood pressure was about 35/8 mm Hg.

The 4 μ mole/kg/min dose-rate of WR-6026 produced the same pattern of actions: however the 2 dogs given this dose survived the 120 minute experimental period. Alterations in ECG patterns were prominent. Marked increases in P-R and Q-T intervals have been noted.

B. Minimum Effective Dose-rate of WR-6026 -- A dose-rate of 0.5 μ moles/kg/min has been noted in two dogs to produce only minor cardiopulmonary changes. Slight rises in systolic blood pressure and LV dP/dt have been noted during the drug infusion period. Respiratory rate and minute volume have also been modestly raised during this period.

Several pilot experiments employing 1.0 $\mu\text{mole/kg/min}$ have demonstrated much more definite effects, some similar and others dissimilar. Left ventricular dP/dt is elevated (5-12%) early in the infusion period (+5 min) and then falls to values slightly below baseline by the end of the infusion. Pulmonary artery pressure and pulmonary vascular resistance are modestly elevated during the infusions. The P-R and Q-T intervals are modestly increased by the 1.0 $\mu\text{mole/kg/min}$ dose.

A dose-rate of 3.0 $\mu\text{mole/kg/min}$ of WR-6026 produced effects intermediate to the other doses tested.

Previous Studies with Primaquine -- Primaquine, when infused i.v. at dose-rates of 0.5, 1.0, and 1.5 $\mu\text{mole/kg/min}$ for 20 minutes in anesthetized dogs, produced changes in several pulmonary and cardiovascular variables. These changes occurred at a 4-fold lower dose-rate than those employed in the previous studies of mefloquine, quinine, and WR-184,806. The major effects of Primaquine at dose-rates of 1.0 to 1.5 $\mu\text{moles/kg/min}$ were: 1) increases (30-50%) in pulmonary artery pressure and vascular resistance, 2) an approximately 30% prolongation of P-R interval and P wave and QRS complex duration which waned after cessation of infusion, 3) a transient depression of airway compliance, and 4) a modest production of methemoglobin. At a 2 $\mu\text{mole/kg/min}$ dose-rate, severe ventricular arrhythmias were observed including ventricular flutter. We conclude that high doses of Primaquine have significant effects upon the pulmonary vasculature and cardiac electrical conduction. The dose-cardiopulmonary response relationships for primaquine were considerably steeper than observed for the antimalarials we had studied previously (Caldwell and Nash, 1980).

In experiments performed during the winter of 1983, we noted in 2 dogs that a dose-rate of 1.75 $\mu\text{mole/kg/min}$ caused severe cardiopulmonary changes but did not result in death. Therefore, we will test primaquine at dose rates of 0.5, 1.0 and 1.75 $\mu\text{moles/kg/min}$ for 20 minutes in anesthetized dogs as a reference compound to compare the above stipulated doses of WR-6026.

PROPOSED STUDIED

We will use the following protocol and experimental scheme:

Approximately 60 minutes will be required following induction of anesthesia to perform the necessary surgery, cannulation procedures, and to establish calibrations. This will be followed by a stabilization period of 20 to 30 minutes to insure that all recordings are steady, and this, in turn, will be followed by a control period of 30 minutes during which data will be recorded at 10-minute intervals. The drug infusion is then begun and continued for 20 minutes. There will be a post-infusion period of 100 minutes for observation of recovery.

I. Observations -- 30-minute control period (-30,-20,-10, and 0 minutes)

A. Cardiovascular Measures

1. arterial blood pressure -- continuous
2. left ventricular pressure -- continuous
 - a. dP/dt -- continuous
 - b. left ventricular end diastolic pressure -- continuous
3. electrocardiogram -- at 10-minute intervals: all six limb leads will be recorded at 25 mm/sec and strips at 100 mm/sec for analysis
4. heart rate -- continuous: by cardi tachometer
5. pulmonary vascular
 - a. pulmonary artery pressure -- continuous
 - b. pulmonary wedge pressure -- at 10-minute intervals
 - c. cardiac output -- at 10-minute intervals
 - d. pulmonary vascular resistance -- calculated at 10-minute intervals

B. Pulmonary Ventilatory Measures

1. Airways differential pressures
 - a. air flow -- signal integrated by preprogrammed computer
 - b. transpulmonary pressure (bronchial vs esophageal) -- signals utilized by preprogrammed computer
2. Airways integrated measure -- tidal volume, continuous
3. Airways computer measures
 - a. compliance -- continuous = $\Delta V / \Delta P$
 - b. resistance -- continuous = $\Delta P / \Delta F$
4. Respiratory rate -- continuous

C. Hematological Measures - (-30 and 0 minutes only)

1. Blood P_{CO_2} -- arterial and venous
2. Blood P_{O_2} -- arterial and venous
3. Blood pH -- arterial and venous
4. Hematocrit -- central venous

II. Drug Infusion for 20 minutes -- Observations as described in I: A, B, and C. (Drug infusion time = 0 - +20 minutes)

- A. Measures A and B from I., plotted at +10, and +20 minutes -- expanded record (25 and 100 mm/sec)
- B. Measure C from I., plotted at +20 minutes

III. Observation period -- 100 minutes post-drug

- A. Measures A and B from I., plotted at 10 minute intervals beginning at +30 minutes (beginning of drug = 0 time) -- expanded records
- B. Measure C from I. taken at +40, +60, +80, +100, and +120 minutes

Experimental Groups

<u>Group/Drug</u>	<u>Dose-Rate</u>	<u>Number of Dogs</u>
1) WR-6026•2HCl	1.0 μ mole/kg/min	6
2) WR-6026•2HCl	2.0 μ mole/kg/min	6
3) WR-6026•2HCl	4.0 μ mole/kg/min	6
4) vehicle (control)	80 ml phosphate buffer (pH 7.4)	6
5) Primaquine•2P ₀ ₄	0.5 μ mole/kg/min	6
6) Primaquine•2P ₀ ₄	1.0 μ mole/kg/min	6
7) Primaquine•2P ₀ ₄	1.75 μ mole/kg/min	6

METHODS

I. Drugs Preparation and Delivery

WR-6026 (mw=416.44) (BN# BK01845) 6-Methoxy-8-(6-diethylamino hexylamino) lepidine dihydrochloride, supplied by WRAIR, will be dissolved in phosphate buffer, (pH 7.4) fresh daily for each experiment. The chemical is readily soluble in the desired concentrations. Primaquine P₀₄ (AldrichChem Co., lot #2429BE with certificate of purity) has been purchased. The concentration of

the solutions will be adjusted to the weight of each dog such that a fixed intravenous volume infusion rate of 4.0 ml/min will contain the appropriate amount of drug, as the salt, in moles. The total volume infused over 20 minutes will, thus, be 80 ml.

II. Animals

Mongrel dogs of either sex, weighing between 9.0 and 14.0 kg will be supplied by the University of Tennessee Vivarium for these studies. The dogs are physically examined for disease symptoms and only animals that appear healthy and have normal ECG are accepted for the study. One ml of blood will be taken and checked for presence of microfilaria using the Knott's test before onset of the experiment. Dogs will be anesthetized with Pentobarbital Na, 30 mg/kg intravenously, and maintained with venous injections of 1.0 mg/kg as necessary to maintain a stable anesthesia. Corneal and plantar reflexes, response to pain, and respiratory rate (16-20 breaths/min) will be used in "titrating" the dog to the desired level of anesthesia.

III. Cardiovascular Measurements

N. B. 1. See Appendix of protocol for WR-228,258, Dec-1981, for details of instrument calibration procedures.

2. See Cardiovascular Measurements Section of protocol for WR-228,258, Dec-1981, for details; procedures are the same except for the following:

BLOOD SAMPLING PROCEDURE

A period will be allowed following surgical and recording instrument preparation for the dog to assume stable cardiorespiratory function. From past experience, 20-30 minutes will be necessary.

At this point, the first arterial and venous blood samples (6 ml each) will be withdrawn following evacuation of the void volume in the arterial and venous cannulas. The glass syringes used will be lubricated with mineral oil and rinsed prior with heparinized saline (500 units/ml). Syringes containing blood will be immediately capped with tight-fitting rubber nipples and put in ice until analysis. The first samples drawn will be designated as -30 minutes. At time 0, the beginning of the 20 minute i.v. infusion of pH 7.4 phosphate buffer or drug solution at 4 ml/min, another set of blood samples will be taken. Additional sets of blood samples will be taken at +20, +40, +60, +80, +100, and +120 minutes. Withdrawal of blood will be performed by a person other than the operator of the blood gas analyzer. All samples will be immediately capped, placed in ice and analyzed by Mary Rose Loftus using the Corning Model 165/2 Blood Gas Analyser within the intervening 20 minute period or as rapidly as possible. Each 6 ml sample will be analyzed in triplicate until such time when duplicates are considered adequate by Drs. Caldwell, Nash and Lowensohn.

All analyses, with the addition of microhematocrit, will be performed by Mary Rose Loftus according to the procedures published by the company for this analyzer. Calibrations will be made with standard gas mixtures and pH buffers.

IV. Pulmonary Ventilatory Measurements

For the measurement of pulmonary function while breathing room air unassisted, an endotracheal tube with a side arm will be connected directly to a mesh screen Fleish pneumotachograph and the pressure difference across the screen measured by a differential pressure transducer (Validyne transducer Model MP45-24). This signal, when calibrated against a known air flow, corresponds to tidal airflow rate and, in turn, when integrated, yields tidal volume. Also, an esophageal tube (Porter ID6.5) will be inserted into the esophagus for the assessment of intrapleural pressure. The pressure difference between the airway and esophagus, or transpulmonary pressure, will be measured by a second differential pressure transducer (Validyne transducer Model MP45-14). Dynamic airway resistance and dynamic airway compliance will be computed using a Buxco Electronics Pulmonary Mechanics Computer Model 6. Airway resistance and compliance and tidal volume will be recorded with a Grass Model 7b polygraph.

N.B. 1. See Appendix of protocol of WR 228,258, Dec. 1981, for details of instrument calibration procedures. (Appendix is attached.)

2. See Pulmonary Ventilatory Measurements section of protocol for WR 228,258 for details

V. Data Presentation

All measurements called for in this protocol will be presented in tabular form using per cent change of baseline where baseline = 100% (unless otherwise indicated). Summary graphs will be constructed to show percentage change from baseline (or control) which will be considered as 100%. Variability for each measurement will be given as ± 1 S.E.M. for mean per cent of baseline (unless

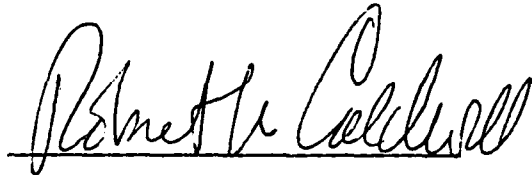
otherwise indicated). For purposes of clarification, several related variables will be plotted on a single graph. In addition, samples of actual tracings will be used to illustrate typical responses to various doses.

References

Basamania, C. and Korte, D. Cardiovascular Effects of WR-6026, WRAIR Report for IND, 1981.

Caldwell, W. and Nash, C. Cardiopulmonary Effects of Primaquine Interim Report No. 6 to WRAIR, 1980.

Caldwell, W. and Nash, C. Protocol. Cardiovascular and Pulmonary Effects of WR228,258 of 14, December, 1981.



Robert W. Caldwell, Ph.D.

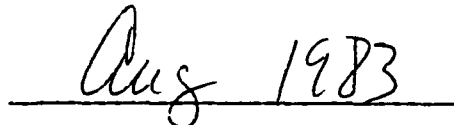


Clinton B. Nash, Ph.D.



K.U. Malik, Ph.D., D.Sc.

Quality Assurance Officer



Date

APPENDIX

INSTRUMENT CALIBRATION PROCEDURES

1. Calibration procedure for Statham Pressure Transducers (Model P23AC)

At regular intervals each transducer is connected to the channel of a model 7 B Grass recorder where it will be used and tested for maintenance of calibration. A mercury manometer is inserted in line to the transducer and a known pressure introduced. The excursion recorded is compared to the Grass internal calibration standard of 100 mm Hg = 2 cm at sensitivity 10. For each experiment, the recorder sensitivity is set to match the excursion given by 100 mm Hg pressure change.

2. Calibration procedure for Buxco Pulmonary Mechanics Computer Model 6

(further explained in instruction book provided with computer).

With power switch in "on" position enter a known flow into the system. A 50 ml/sec flow (determined by a Gilmont air flowmeter, size #3, calibration curve provided, connected to a Fleish pneumotachometer and a Validyne differential pressure transducer,¹ model MP45-24 should provide a 10 mm deflection at flow gain setting 5. With power switch in "cal" position, calibration pots are adjusted to a 20 mm deflection. Examine the calibration tidal volume signal, removing notches using fine flow zero. Set tidal volume deflection to 25 mm using TV gain.

With power switch in "on" position enter a given pressure in cm of H₂O using a H₂O manometer into a closed tube system connected to a Validyne differential pressure transducer¹, model MP45-14. A pressure of 5

¹The Validyne transducers connected through a preamplifier (Buxco) yield more stable pressure and flow signals than our previous Statham transducers. The present transducer - preamplifier - Buxco Analyzer configuration is superior to the previous arrangement in which the transducer signal went first to a Grass amplifier before being directed to the Buxco Analyzer.

H₂O = 5 mm excursion (adjust with pressure gain). With power switch in "cal" position, use "cal" pot to set a calibration signal deflection of 10 mm.

Using the given flow and pressure and employing Program 1 of the computer (see instruction book) we obtain the following:

$$\text{Flow} = \frac{100 \text{ ml/sec}}{100 \text{ ml/sec}} \frac{\text{ins}}{\text{exp}}$$



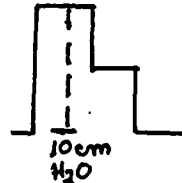
$$\text{Pressure} = \frac{5 \text{ cm H}_2\text{O}}{5 \text{ cm H}_2\text{O}} \frac{\text{1st plateau}}{\text{2nd plateau}}$$



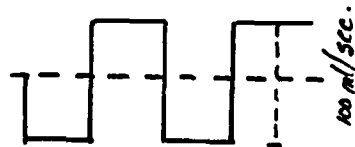
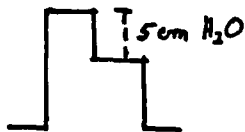
$$\text{TV} = 50 \text{ ml}/25 \text{ mm}$$



$$\text{Compliance} = 50 \text{ ml}/10 \text{ cm H}_2\text{O} \text{ or } 5 \text{ compliance units}$$



$$\text{Resistance} = 5 \text{ cm H}_2\text{O}/.1 \text{ L/sec} \text{ or } 50 \text{ resistance units}$$



Compliance and resistance calibration signals are set to a convenient deflection (20 mm)

$$5 \text{ cu} = 20 \text{ mm}$$

$$0.25 \text{ cu} = 1 \text{ mm}$$

$$50 \text{ ru} = 20 \text{ mm}$$

$$2.5 \text{ ru} = 1 \text{ mm}$$

3. Cardiac Output Computer - IL The thermal dilution method is based on the proven concept of the Fick principle wherein the dilution of temperature (or dye) is measured by a sensor located downstream and the rate of dilution is calculated. A computer determines the area of a time-temp plot and converts this to cardiac output. The instrumentation laboratories cardiac output computer is factory calibrated. The instruction booklet furnishes calibration curves for temperatures and volumes of (3 & 5 ml) saline injected. A "K" calibration value is extrapolated. The computer provides an instrument check system whereby dialing a given K factor one can check if the correct cardiac output calculation is performed. The catheter itself is fed into the jugular vein and advanced to the pulmonary artery using pressure signals obtained via a Statham P23AC transducer recorded on a Grass polygraph (Swan et al., 1970). The injection port is located 12.5 cm from the sensor tip, designed to inject the 0°C saline into the right ventricle, allowing mixing to occur.

4. Miller[®] catheter-tip pressure transducers.

On each experimental day, the transducer catheter to be used is connected through a transducer control unit (model TCB-100) to either our Gould or Grass Recorder. The reference bridge within the Control Unit is balanced to an original transducer zero pressure baseline. The calibration signal provides transducer bridge excitation voltage in 20 mm Hg steps up to 100 mm Hg. We have found the internal calibration signal is almost identical to externally applied pressures in a mercury column. At any time during a procedure, the reference position may be used to reproduce the original transducer baseline and the calibrate switch used to calibrate the recording.

5. The Corning blood gas analyzer (Model 165/2) requires a calibration sequence published by Corning using bottled reference gases of two known concentrations (one 5% CO₂, 12% O₂, balance nitrogen; one 10% CO₂ and balance nitrogen) for calibration of gas electrodes and prepared buffer solutions at two pH's (6.838 and 7.382) for calibrating blood pH electrode. At the beginning of each run of samples, a 2 point calibration of the blood gas electrodes and pH electrodes is performed with 2 gas concentrations and 2 pH's. Between each sample, a one point calibration for both gases and pH is performed.

Section II

SUMMARY OF CARDIOPULMONARY STUDIES

of WR-6026 VS Primaquine

INTRODUCTION

Seven experimental groups of six dogs each were utilized in the performance of these studies as described in the protocol (Section I). There was one control group which, after 30 min equilibration/control period, received an intravenous infusion of phosphate buffer (pH 7.4) at a volume-rate of 4 ml/min for 20 min. Cardiopulmonary variables were monitored over this 50 minute period and for an additional 100 minutes. All experimental groups were monitored indentially.

Three of the groups received either 1.0, 2.5 or 4 μ moles/kg/min of WR- 6026 \cdot 2HCl delivered as described above for the phosphate buffer vehicle. Larger dose-rates (5 and 6 μ moles/kg/min) were initially thought to be tolerated but with later experience were found to be lethal in some dogs.

The three additional groups were given primaquine \cdot 2H₃PO₄ in dose-rates of 0.5, 1.0 and 1.75 μ moles/kg/min. The high dose-rate was slightly higher than used by our laboratory in a previous study (Caldwell and Nash, 1980) but was tolerated in most preparations.

A summary of our findings for the cardiopulmonary effects of the high (maximum tolerated) and low (minimum effective) dose-rates of both WR-6026 and primaquine follows. Drug-related changes in cardiovascular and pulmonary variables are derived by comparing responses in experimental groups with those which occurred in dogs given only phosphate buffer vehicle (Control Group).

Results

1. High Dose-Rates (Maximum Tolerated)

WR-6026 - This experimental 8-aminoquinoline produced a drop in respiratory tidal volume and a sharp rise in respiratory rate; minute volume was also increased during administration of this drug and remained elevated for the entire observation period. Arterial P_{CO_2} was also reduced. Airways resistance appeared to decrease during the infusion and remained somewhat depressed.

Arterial blood pressure tended to drop during drug infusion; diastolic pressure was affected most (about 77% of control at +20 min). Cardiac output was depressed slightly by end of infusion. Left ventricular contractility (dP/dt) was markedly depressed during infusion of this drug; values were 72 and 45% of control at +10 and +20 minutes, respectively, but rose slightly throughout the remaining observation period. Pulmonary wedge pressure, pulmonary artery pressure, and pulmonary vascular resistance rose during drug infusion but returned towards baseline over the next 100 min. Marked increases in P-R and Q-T intervals have been noted in EKG.

Higher dose-rates (5 and 6 μ moles/kg/min) produced death. There were progressive decreases in systemic arterial pressure, heart rate, left ventricular dP/dt max with loss of effective cardiac function, and arterial perfusion pressure by the end of the 20-minute infusion period.

Primaquine - This clinically used 8-aminoquinoline also exhibited prominent cardiopulmonary effects when given at a dose-rate of 1.75 μ moles/kg/min. Respiratory function was affected similarly to that observed with WR-6026; respiratory rate and minute volume were elevated during drug

infusion and tidal volume was diminished. Arterial P_{CO_2} was reduced. Airways resistance and compliance were not markedly altered; both variables tended to decrease. Venous P_{O_2} did appear to be slightly elevated at the end of the drug infusion.

Cardiovascular function was not depressed as severely as with the maximum tolerated dose-rate of WR-6026. Left ventricular dP/dt dropped during drug infusion to 77% of control levels at +20 mins, but cardiac output remained fairly stable. Some increase in both pulmonary artery pressure and pulmonary vascular resistance were observed during the drug infusion. This dose-rate of primaquine did prolong P-R interval and duration of P wave and QRS complex.

At a 2 $\mu\text{mole/kg/min}$ dose-rate, severe ventricular arrhythmias occurred near the end or just following the drug infusion. These arrhythmias might be best described as ventricular flutter and rendered the heart incapable of pumping. Death followed in all cases observed.

2. Low Dose-Rates (Minimum Effective)

WR-6026 - A slight increase in respiratory rate and minute volume was produced. Additionally, slight rises in systolic blood pressure and LV dP/dt were noted.

Primaquine - This drug has no perceptible effect upon respiratory function. Left ventricular dP/dt was depressed slightly and transiently, P-R interval was modestly increased.

Summary

Our experiments for these two studies were conducted over the period from August, 1983 through January, 1984 and involved approximately 65 dogs to finally obtain 42 completed experiments (seven groups, six dogs each).

A higher dose-rate of WR-6026 was tolerated than for primaquine, 4.0 vs 1.75 μ moles/kg/min. The dose-response curves for cardiopulmonary effects were of similar slope. Death from WR-6026 resulted from gradual cardiac function depression; primaquine produced death by a primary action on heart rhythm.

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