INHIBITION OF THE CARDIOVASCULAR EFFECTS OF LYSINE ACETYSALICYLATE BY PROPRANOLOL IN DOGS DURING HALOTHANE ANAESTHESIA

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ABSTRACT

The cardiovascular effects of lysine acetylsalicylate and/or propranolol were studied in 26 dogs. All animals were maintained under anaesthesia with halothane 0.75 per cent, supplemented by the intravenous administration of succinylcholine to allow controlled ventilation during a two hour period of monitoring. Cardiac output, stroke volume, heart rate, mean arterial pressure, pulse pressure, central venous pressure, total peripheral resistance, pH, P_{aO_2} , P_{aCO_2} and base deficit were measured in each dog.

Lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$, administered alone as a single bolus, significantly ($P < 0.05$) increased the cardiac output and stroke volume and significantly decreased the heart rate, central venous pressure and total peripheral resistance in dogs under halothane anaesthesia. Propranolol hydrochloride $0.5 \text{ mg} \cdot \text{kg}^{-1}$ as a single intravenous bolus was followed by a significant decrease in cardiac output, heart rate and mean arterial pressure and a significant increase in central venous pressure and total peripheral resistance. The administration of propranolol prior to lysine acetylsalicylate resulted in a significant decrease in cardiac output and heart rate. Pretreatment with propranolol was effective in inhibiting the positive inotropic effect of lysine acetylsalicylate.

KEY WORDS: ANALGESICS, lysine acetylsalicylate; HEART, lysine acetylsalicylate, propranolol.

SODIUM SALICYLATE and acetylsalicylic acid are useful analgesic, antipyretic and anti-inflammatory drugs.¹ The effects of the salicylates on the cardiovascular system appear to be minimal in ordinary therapeutic doses. Larger doses are associated with vasodilatation of the peripheral blood vessels.¹ Significant increase in the cardiac output, stroke volume, pulse pressure, central venous pressure and significant decrease in total peripheral resistance were observed following the intravenous administration of sodium salicylate $100 \text{ mg} \cdot \text{kg}^{-1}$, in dogs under light halothane anaesthesia.² The administration of propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ twenty minutes after

the intravenous administration of sodium salicylate in this model decreased but did not reverse these effects of sodium salicylate.³ The increase in cardiac output, increase in plasma volume and decrease in haematocrit following the administration of sodium salicylate are considered to be a contraindication for large doses of salicylates in patients with acute rheumatic fever and carditis.⁴ Whether the cardiovascular effects of the salicylates are due primarily to direct peripheral vascular effects, the release of catecholamines or inhibition of the biosynthesis and release of prostaglandins awaits further clarification.¹ Large doses of salicylates are associated with central respiratory and vasomotor paralysis.¹

Sodium salicylate and acetylsalicylic acid are usually administered orally. More recently, there has been interest in other aspirin-like drugs such as lysine acetylsalicylate* which appears to be approximately one half as potent as acetylsalicylic acid and suitable for intravenous, intramuscular or intra-articular administration. The

*Aspisol®, Ampul containing 900 mg, D, L-Lysine mono acetylsalicylate and 100 mg glycine in 5 ml of water, Bayer AG, Bayerwerk, Leverkusen, NRW, D-5090, Federal Republic of Germany.

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This study was partially supported by BRS Grant 5-S01-RR-05700-10 (NIH) and the Northwestern Ohio Chapter of the American Heart Association, and as conducted in conformity with the Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiological Society.

purpose of this study is to measure the effect of lysine acetylsalicylate on the cardiovascular system and to determine whether pretreatment with a beta adrenergic blocker, propranolol, modifies these effects.

MATERIALS AND METHODS

Twenty-six experiments were done on healthy mongrel dogs weighing from 11.5 to 20 kg. An electromagnetic flow probe* was implanted around the ascending aorta as previously described² and the dogs were observed for approximately ten days to ensure that the probes were well tolerated. Anaesthesia was induced with thiopentone 15 mg · kg⁻¹, and the trachea was intubated. Anaesthesia was maintained with an inspired concentration of 0.75 per cent halothane in oxygen delivered from a Copper Kettle vaporizer. Apnoea was maintained by an intravenous drip of succinylcholine 1.0 mg · ml in isotonic saline and the lungs were ventilated mechanically with a Harvard respirator set to maintain P_{aCO_2} at 5.32 ± 0.27 kPa (40 ± 2 Torr). Halothane 0.75 per cent with a succinylcholine drip produced reliable immobilization and permitted mechanical ventilation without depressing the autonomic nervous system. Aortic flow was measured by the chronically implanted electromagnetic flow probe. The aortic flow wave was recorded and an integral of this wave was triggered by the QRS complex of the electrocardiogram to obtain a measure of stroke volume for each heart beat. The femoral vein was cannulated for the injection of succinylcholine and the femoral artery was cannulated for continuous monitoring of blood pressure through a Statham pressure transducer (P23AA). The arterial cannula was also used for the anaerobic sampling of arterial blood for the determination of $[H^+]$ (pH), P_{aO_2} and P_{aCO_2} .² The heart rate was counted from the electrocardiogram.

Measurements of the haemodynamic parameters were made every five minutes for the first 30 minutes and every 15 minutes for the ensuing 90 minutes with an Offner type RB Dynograph. Control values for each animal were determined by the average of two measurements taken 15 and 30 minutes before the administration of lysine acetylsalicylate and/or propranolol. Thus

each animal served as its own control, which is expressed as O. Oesophageal temperature was maintained at $37 \pm 1^\circ\text{C}$, as measured with a thermister probe and Yellow Springs telethermometer. A Godart Capnograph* was used to provide continual visual evidence that end tidal carbon dioxide was at a normal level. Propranolol 0.5 mg · kg⁻¹ was administered intravenously immediately before the administration of lysine acetylsalicylate 50 mg · kg⁻¹. This dose of propranolol was observed to produce a consistent effect on the cardiovascular system of dogs under halothane anaesthesia.⁵ The intravenous dose of lysine acetylsalicylate of 50 mg · kg⁻¹ was selected to maximize the cardiovascular effect of the drug.

RESULTS

Measurements of the following cardiovascular variables were made during the 120 minutes of observations: (1) cardiac output, (2) stroke volume, (3) heart rate, (4) mean arterial pressure, (5) pulse pressure, (6) central venous pressure, (7) total peripheral resistance and (8) acid-base and blood gases. The Student's 't' test was used to compare values for each parameter with its control. When values at two time-intervals were significant (five per cent level) the change was considered meaningful. The first seven parameters listed above are compared graphically (Figures 1 to 7). Since P_{aCO_2} was maintained at 5.32 ± 0.27 kPa (40 ± 2 Torr), the values for pH, P_{aCO_2} , P_{aO_2} and base deficit were not changed significantly.

Cardiac Output

The cardiac output was significantly increased following the intravenous administration of lysine acetylsalicylate and significantly decreased following the administration of propranolol alone and propranolol followed by lysine acetylsalicylate in dogs under halothane anaesthesia (Figure 1). The administration of halothane did not alter the cardiac output during the two-hour period of observation.

Stroke Volume

A significant increase in stroke volume was observed following the administration of lysine acetylsalicylate (Figure 2). No consistent changes were observed in the other three groups.

*Zepeda, non-ferrous electromagnetic flow probe, Zepeda Instruments, 1937, 25th Ave., E., Seattle, Washington 98112, U.S.A.

*Capnograph Type KK, Godart de Bilt, Holland.

FIGURE 1 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the cardiac output of dogs under halothane anaesthesia. The cardiac output is plotted as per cent change from 0. Absolute values (l/min) for 0 in the four groups are as follows: halothane alone, 2.20 ± 0.28 ; halothane-lysine acetylsalicylate, 1.96 ± 0.32 ; halothane-propranolol, 1.47 ± 0.13 ; and halothane-propranolol-lysine acetylsalicylate, 2.08 ± 0.38 . Propranolol was administered immediately before lysine acetylsalicylate.

FIGURE 2 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the stroke volume of dogs under halothane anaesthesia. The stroke volume is plotted as per cent change from 0. Absolute values (ml/beat) for 0 in the four groups are as follows: halothane alone, 15.5 ± 1.4 ; halothane-lysine acetylsalicylate, 14.1 ± 1.7 ; halothane-propranolol, 10.3 ± 1.2 ; and halothane-propranolol-lysine acetylsalicylate, 15.6 ± 2.2 .

Heart Rate

The heart rate was significantly decreased following lysine acetylsalicylate alone, propranolol alone or both drugs (Figure 3). No significant changes were observed in dogs which were maintained under halothane anaesthesia.

Mean Arterial Pressure

The mean arterial pressure was significantly decreased after the intravenous administration of

FIGURE 3 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the heart rate of dogs under halothane anaesthesia. The heart rate is plotted as per cent change from 0. Absolute values (beats/min) for 0 in the four groups are as follows: halothane alone, 143 ± 12 ; halothane-lysine acetylsalicylate, 137 ± 12 ; halothane-propranolol, 147 ± 13 ; and halothane-propranolol-lysine acetylsalicylate, 130 ± 8 .

propranolol (Figure 4). The three other groups were without significant changes.

Pulse Pressure

Significant changes at two or more time intervals were not observed in any of the four groups (Figure 5).

Central Venous Pressure and Total Peripheral Resistance

A significant decrease in central venous pressure and total peripheral resistance occurred following the administration of lysine acetylsalicylate while propranolol alone caused a significant increase in both variables (Figure 6). No change in the central venous pressure or total peripheral resistance was observed when the

FIGURE 4 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the mean arterial pressure of dogs under halothane anaesthesia. The mean arterial pressure is plotted as per cent change from 0. Absolute values (mm Hg) for 0 in the four groups are as follows: halothane alone, 133 ± 11 ; halothane-lysine acetylsalicylate, 110 ± 9 ; halothane-propranolol, 110 ± 7 ; and halothane-propranolol-lysine acetylsalicylate, 116 ± 5 .

FIGURE 5 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the pulse pressure of dogs under halothane anaesthesia. The pulse pressure is plotted as per cent change from 0. Absolute values (mm Hg) for 0 in the four groups are as follows: halothane alone, 61 ± 9 ; halothane-lysine acetylsalicylate, 56 ± 6 ; halothane-propranolol, 70 ± 10 ; and halothane-propranolol-lysine acetylsalicylate, 69 ± 4 .

FIGURE 6 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the central venous pressure of dogs under halothane anaesthesia. The central venous pressure is plotted as per cent change from 0. Absolute values ($\text{cm H}_2\text{O}$) for 0 in the four groups are as follows: halothane alone, 5.0 ± 1.0 ; halothane-lysine acetylsalicylate, 8.3 ± 1.1 ; halothane-propranolol, 8.5 ± 1.2 ; and halothane-propranolol-lysine acetylsalicylate, 8.0 ± 0.9 .

administration of propranolol was followed by lysine acetylsalicylate or with halothane alone.

DISCUSSION

The search for non-narcotic analgesic drugs has led to a re-examination of the salicylates and in particular the recently available lysine acetylsalicylate.^{6,7} It has been reported that 1,800 mg of lysine acetylsalicylate by intramuscular injection in man is equivalent to 10 mg of morphine sulphate by the same route in controlling post-

FIGURE 7 Effect of lysine acetylsalicylate $50 \text{ mg} \cdot \text{kg}^{-1}$ and/or propranolol $0.5 \text{ mg} \cdot \text{kg}^{-1}$ on the total peripheral resistance of dogs under halothane anaesthesia. The total peripheral resistance is plotted as per cent change from 0. Absolute values ($\text{dyne} / \text{sec} / \text{cm}^{-5}$) for 0 in the four groups are as follows: halothane alone, 5200 ± 863 ; halothane-lysine acetylsalicylate, 5107 ± 686 ; halothane-propranolol, 6228 ± 758 ; and halothane-propranolol-lysine acetylsalicylate, 5332 ± 741 .

operative pain.⁷ The oral dose of 600 mg of acetylsalicylic acid (Aspirin) is also equivalent to the parenteral administration of 10 mg of morphine.⁸ Lysine acetylsalicylate (LAS) is converted to acetylsalicylic acid which is metabolized to salicylic acid, the active ingredient of all the salicylates.⁹ Although there appears to be a plateau in the analgesic effect of LAS at $25 \text{ mg} \cdot \text{kg}^{-1}$,⁹ $50 \text{ mg} \cdot \text{kg}^{-1}$ was selected for this study to ensure the maximum effect on the cardiovascular system. The major advantage of LAS over acetylsalicylic acid is that it can be administered intramuscularly, intra-articularly or intravenously. Thus, the anaesthetist has the option of administering a non-narcotic analgesic by the intramuscular route which spares it from "first pass" hydrolysis in the gut and liver. This advantage is also shared by sodium salicylate which has been administered intravenously in animals^{10,11} but it is not administered commonly by the parenteral route in man.^{1,12}

The results observed in this study relative to the effects of the intravenous administration of lysine acetylsalicylate (LAS), $50 \text{ mg} \cdot \text{kg}^{-1}$ on the cardiovascular system are similar to those reported previously following the administration of sodium salicylate $100 \text{ mg} \cdot \text{kg}^{-1}$ by the same route.² Propranolol, $0.5 \text{ mg} \cdot \text{kg}^{-1}$ was effective in preventing a significant increase in stroke volume and cardiac output when administered

before LAS while, in the same dosage but administered 20 minutes after sodium salicylate(SS), it was relatively ineffective in reversing the cardiovascular effects of SS.³ The delay in the administration of propranolol was an important factor in the salicylates which have a duration of action in excess of the period of observation.¹

There has been considerable speculation relative to the role of the catecholamines in the effect of the salicylates. Early authors attributed to the catecholamines an important role in the effect of the salicylates, while their role has been minimized subsequent to the greater understanding of the prostaglandins.¹ The cardiac output was increased significantly following the administration of LAS, which favors the conclusion that the salicylates exert an inotropic effect by release of catecholamines. It has been noted that prostaglandins inhibit norepinephrine output from adrenergic nerve endings¹ and thus the inhibition of prostaglandins by the salicylates might contribute to an inotropic effect on the heart. Additional studies including determinations of the prostaglandins and catecholamine following the administration of various salicylates would be informative.

ACKNOWLEDGEMENTS

The authors wish to thank Mr. Thomas Tenney, M.S., P.E. for technical assistance, Miss Carol Perkins and Mr. Gerald Lubinski for assistance with the illustrations and Mrs. Patti Barrett for assistance in preparing the manuscript.

The halothane (Fluothane®) and propranolol (Inderal®) were generously supplied by Ayerst Laboratories, New York, New York, and the lysine acetyl-salicylate (Aspisol®) by Bayer, Leverkusen, Federal Republic of Germany.

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RÉSUMÉ

L'objet de ce travail était l'étude des effets cardiovasculaires de l'acétylsalicylate de lysine ainsi que l'étude des effets du même agent précédé de propranolol et, enfin, ceux du propranolol seul. L'étude a été effectuée chez l'animal (26 chiens). Durant toute la durée de la procédure (2 heures) les animaux ont été maintenus sous anesthésie à l'halothane (à la concentration de 0.75 pour cent) et ont reçu une perfusion de succinylcholine pour faciliter la ventilation contrôlée. Les paramètres suivants ont été mesurés: débit cardiaque, volume d'éjection, fréquence cardiaque, pression artérielle moyenne, pression différentielle, pression veineuse centrale, résistance vasculaire périphérique, pH, P_{aCO_2} , P_{aO_2} et "base excess".

L'administration en bolus intraveineux d'une dose de $50 \text{ mg} \cdot \text{kg}^{-1}$ d'acétylsalicylate de lysine aux chiens sous anesthésie à l'halothane élevait de façon significative ($p < 0.05$) le débit cardiaque et le volume d'éjection; il abaissait significativement la fréquence cardiaque, la pression veineuse centrale et la résistance vasculaire périphérique.

Une dose de propranolol ($0.5 \text{ mg} \cdot \text{kg}^{-1}$) administrée en bolus intraveineux amenait un abaissement significatif du débit et de la fréquence cardiaque et de la pression artérielle moyenne; il produisait également une élévation significative de la pression veineuse centrale et de la résistance vasculaire périphérique. Lorsque le propranolol était administré avant l'acétylsalicylate de lysine, il en résultait une diminution significative du débit et de la fréquence cardiaque. Le prétraitement au propranolol était donc efficace pour inhiber les effets inotropiques positifs de l'acétylsalicylate de lysine.