Original Article

Experimental Design Of Cardio –Toxidrome Of I.V Calcium Channel Blocker Overdose In Pigeon

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Abstract

Study design and objectives:
Goal; To evaluate and assess ,the effects of verapamil((CCB) overdose on systemic toxicity in awake pigeon by experimental demonstration the signs and symptoms of verapamil via determination of the variables cardio- respiratory in the pigeon as Prospective, experimental trial model compared to control .Method : 24 healthy domestic pigeons were used, the verapamil intravenously administered in the pigeon's ulnar wing vein at 4 mg/kg . Heart rate (HR),, respiratory rate (fR), indirect systolic arterial pressure (SAP) were measured prior to verapamil iv administration in the awake pigeons state at baseline (resting 0- time) and at 5, 10 ,15 ,20 minutes interval later and toxic gastrointestinal manifestations were observed compared to control (2 pigeons). Results; the baseline cardio-respiratory variables in the pigeon , the heart rate ,systolic arterial pressure and respiratory rate were dropped to the mean ± SD HR, SAP, fR respectively, 84+/-10beats minute(-1), 66+/-12 mmHg, 17 ± 2 breaths minute(-1). The regurgitation and vomiting, watery green droppings as gastrointestinal toxic manifestations were clearly noticed along with dizziness or lightheadedness and sudden death prognosis as well ,compared control pigeon's recordings . Conclusion; In the awake pigeon ,verapamil was induced dropping up to 35% of baseline(time-0) of cardio-respiratory variables with hypotension at the moderate level is associated with disparate effects on systemic hemodynamics, and toxic gastrointestinal manifestations ,probably resulting from differential reflex autonomic activations , death prognosis due to cardiac arrest .

Keywords: pigeon ,verapamil ,calcium channel blocker, heart rate ,systolic arterial pressure , respiratory rate, cardiorespiratory

Abbreviations: Calcium channel blocker (CCB), heart rate(HR), Systolic arterial pressure (SAP) , Respiratory rate(fR) .intravenous(iv) .,Cardiovascular system(cvs)

Introduction:

The use of birds as test models in experimental and environmental toxicology as related to health effects is reviewed, and an overview of descriptive tests routinely used in experimental toxicology is provided. Toxicological research on pigeons may be applicable to human health both directly by their use as models for mechanistic a studies and indirectly as monitors of toxic quality (1&2) . Calcium channel blocker (CCB) toxicity is one of the most lethal prescription drug overdoses; therefore, understanding the emergent

management of such cases is essential. Overdoses of immediate-release CCBs are characterized by rapid progression to hypotension, bradydysrhythmia, and cardiac arrest. Nondihydropyridines Verapamil (Isoptin), a phenylalkylamine, has a higher affinity for calcium slow channels in the cardiac conducting system than in peripheral smooth muscle cells; therefore, it causes a greater negative dromotropic and inotropic effect than do other CCBs.

All existing CCBs function by binding to the L-subtype, voltage-sensitive, slow calcium channels in cell membranes. The L-type calcium channel blockers decrease the flow of calcium into the cells of the cardiac conduction pathway, which leads to an inhibition of phase 0 in cardiac pacemaker cells and slows the phase 2 plateau in Purkinje cells, cardiac myocytes, and vascular smooth muscle cells. In cardiac muscle and vascular smooth, muscle rapid calcium influx causes myosin and actin binding and contraction by inhibiting calcium influx, cause decreased myocardial contractility and peripheral arterial vasodilation.

Methodology:

Routine scientific procedures;

Design: Non blinded, controlled animal ,weighing a mean ± standard deviation (SD) of 385 ± 35 g. Research laboratory of a Baghdad college of medical sciences. Type of participants :24 healthy domestic pigeons obtained from a commercial supplier plus 2 pigeons as control..

Practice Essentials; The experimental procedures, 24 adults of both sex of pigeons weighting of average of 300- 400 gm. the test drug (verapamil) was administering in the pigeon's ulnar wing vein runs across the ventral surface of the elbow (Fig 1) which can be palpated. Here again, feathers can be parted by wetting with surgical spirit to provide a good view and uncluttered access to the vein.

Figure (1); intravenous route via pigeon's ulnar wing vein

Administering substance;

Pigeon's ulnar vein were receiving 4 mg/kg IV of verapamil . Dampening feathers with alcohol and parting them gives adequate access to the skin and permits the bird to preen them back into place following the procedure. Intra venous injection, Commonly used sites for intravenous injection are the ulnar wing vein after adequate restraint is vital and the smallest gauge needles possible should be used for injecting pigeons intravenously. The injected volume should be no more than 2 ml/kg for all pigeons (Morton et a l. 2001 - 3).

Observation schedules' end points of verapamil toxicity;

Time intervals; At baseline zero time , 5 ,10,15,20,minutes recording of both Cardio -dynamic parameters ,heart rate , systolic arterial pressure , respiratory rate and Gastrointestinal manifestations,; regurgitating ,vomiting and watery green droppings .The starting time of regurgitating, vomiting started was at average 5.5 – 7 .5 minutes of IV administration of verapamil. The frequent episodes of regurgitating were occurred 4- 7 times and sudden death cases were (3) pigeons.

Pigeon's heart rate recording;

Wherever possible, the use of a cardiac monitor is recommended, although an oesophageal stethoscope can be of use (Lawton 1993 -4). ??/ The heart rate should never fall below 120 bpm in one of pigeons(Doolen & Jackson 1991 -5 /???). Pulse oximeter usage is also advantageous. The pulse oximeter probe can be placed a standard `C' clamp probe across the tarsus can be used. Pigeon's pulse recording for a heartbeat by listening on either side of the keel bone a stethoscope will make this task easier.

Results:

The early signs and symptoms of cardio- respiratory toxic effect of verapamil iv ingestion ,the pigeons were experiencing between regurgitating ,vomiting and watery green droppings. The difference between the two actions lies in both the appearance of the food and the behavior of the pigeon. Unlike regurgitation when the food comes up intact, vomited food is digested or almost-digested, and will be expelled in some liquid form. The pigeon will forcefully shake its head from side to side before it spits the vomiting which, is expelling almost-digested content inside the were ventriculus or intestine in liquid form. Vomiting is not natural and causes discomfort to pigeons. A pigeon that was regurgitating will often bob its head and stretch out its neck, and the food does not look digested, e.g., whole seeds are regurgitated .Vomiting is a sign of illness and should be evaluated promptly. Lethargy ,Ruffled or "fluffed" appearance and Watery green droppings Overdoses administration of iv verapamil are characterized by rapid progression to hypotension, , cardiac arrest and sudden death. In the awake pigeons, the mean ± SD HR, SAP, fR, , respectively, 155 ± 28 beats minute(-1), 155 ± 21 mmHg, 34 ± 4 breaths minute(-1). A pigeon can show signs within five minutes after iv verapamil , Seizures are rare . End point parameters of (CVS) RECORDINGS CHANGES ARE SUMMERIZED IN TABLE (1)

TABLE (1) ENDPOINT PARAMETERS (CVS) RECODING CHANGES AS MEAN +/- SD AFER VERAPAMIL I.V INGECTION

Experiment's pigeon	Resting time(0)	5 minutes	10 minutes	15minutes	20 minutes
Heart rate(HR) BEAT/MIN.	162 ± 26	135+/-12	117+/-13	97+/-12	84+/-10
SYST0LIC AE RTERIA PREESUR (SAP)	155 ± 20 mmHg	133+/-15	99+/-13	77+/-12	66.50 +/-12
RESPIRATORY RATE (fR) BREATHS/MIN.	32 ± 4	26+/-2	21+/-2	19+/-3	17+/-2
Control pigeons	158+/-23(HR)	154+/-18 (SAP)	33+/-3(fR)		

Statistics

To verify any statistically significant effect of verapamil , a Student's t-test for paired data was applied. Data are expressed as mean values ± SE

The heart rate (HR) recorded down from 162 +/- 26 to 84+/-10 beats/min (P less than 0.001), Systolic arterial pressure (SAP) from155+/- to66+/-12 mm Hg (P less than 0.001) and respiratory rate(fR) from 32 +/- 4 to 17+/-2 ml/beat (P less than 0.01)

Conclusion and discussion;

Blood pressure measurement;

The pigeon's blood pressure is higher in Arterial than in mammals.
Indirect blood pressure can be obtained using a Doppler transducer and a sphygmomanometer usually placed on the wing or leg with a cuff measured at 30-40% of the limb circumference. However it has been consistently demonstrated that values obtained with this method do not agree with direct systolic blood pressure measurements and may therefore be of low clinical values as a diagnostic tool.(Acierno et al. 2008 -6; Johnston et al. 2011 -7; In general, hypotension is defined as a systolic blood pressure lower than 90 mmHg and mean lower than 60 mmHg.(Lichtenberger & Ko 2007 -8) ,

Lily of the valley (glycosides) Tachycardia, arrhythmias and Oleander (glycosides) Tachycardia, arrhythmias (Lightfoot et al. 2008;-9). Avian models have been favored by this kind of toxicological research because birds are abundant, highly visible, have diverse behaviors and habitat associations, and frequently can be studied in both the laboratory and natural environment.(10).The use of birds as models for health effects toxicology has been favored mainly although of the phylogenetic distance of birds from man and also because some mammalian species usually exists with target organ sensitivity or metabolic processes that are believed more analogous to humans. However, differences in drug metabolism between birds and mammals have been shown to be more quantitative than qualitative, and birds should not be ignored as subjects for comparative studies on mechanism of action. Birds, particularly pigeons, are regularly used as predictive models for organophosphorus-induced delayed neurotoxic syndrome, teratogenicity, and other toxicity tests where study of the isolated embryo is desired. Doppler flow apparatus can also be used to monitor heart rate and may also give an audible signal of arterial blood flow (Heard 1997 -11) . In general, hypotension is defined as a systolic blood pressure lower than 90 mmHg and mean lower than 60 mmHg.(Lichtenberger & Ko 2007 -8. CCB toxic effects are manifested predominantly by their actions on the slow calcium channel.All birds have a four-chambered heart with complete separation of the pulmonary and systemic circulation. The major anatomical differences of the avian cardiovascular system from its mammalian counterparts although the birds have a much larger heart than mammals. They also have proportionally a higher stroke volume, mean arterial blood pressure, and cardiac output than mammals to enable them to meet their higher metabolic requirements. Bird shave the fastest heart rate of any animals but it can actually be lower than mammals of

similar body weight. The avian cardiac conduction system is, similar to mammals, composed of a sinoatrial node ,atrioventricular node, right atrioventricular ring (specific to birds), and Purkinje fibers and connected to the atrioventricular node, was seen in repeated indirect blood pressure measurements with most variability attributable to individual variation and cuff placement.(8&12) The oscillometric method of indirect blood pressure measurements has been found unreliable in all studied birds.(Acierno et al. 2008 -6; Zehnder et al. 2009 -13) Select a site appropriate for the size of the bird and experimental protocol. Reduce the risk of haematoma formation by ensuring that the pigeon is carefully restrained, using a fine needle and applying pressure to stop bleeding effectively emerged in HR or respiratory rate, and significant decreases in SAP were observed. Arrhythmia was need to identified in awake pigeons . CCB toxic effects are manifested predominantly by their actions on the slow calcium channel.All birds have a four-chambered heart with complete separation of the pulmonary and systemic circulation , although the They also have proportionally a higher stroke volume, mean arterial blood pressure, and cardiac output than mammals to enable them to meet their higher metabolic requirements. Bird have the fastest heart rate of any animals but it can actually be lower than mammals of similar body weight and the oscillometric method of indirect blood pressure measurements has been found unreliable in all studied birds.(Acierno et al. 2008 -6; Zehnder et al. 2009-13 .When resting respiratory frequencies forbirds and mammals are compared, the birds appear to have rates that are much lower, the ratio of bird :mammal being about 0.3 to 0.6. (14)The ratio of heart rate to respiratory rate based on these equations is 4.2 for all birds, gives a comparable ratio of 4.5 for mammals. (15 &16). CCB caused high-grade atrioventricular block, resulting in bradycardia. (17&18).

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